Previous volumes in this series


This book and all other volumes of the series can be purchased from:

International Agency for Research on Cancer (IARC) IARCPress
150 Cours Albert Thomas
69008 Lyon (France)
Tel. +33 4 72 73 85 15
Fax +33 4 72 73 83 02
press@iarc.fr

World Health Organization (WHO) WHO Marketing and Dissemination
1211 Geneva (Switzerland)
Tel. +41 22 791 2476
Fax +41 22 791 4857
bookorders@who.ch

Oxford University Press (OUP) OUP Oxford (UK)
Tel. +44 1536 454534
24 hr. Hotline:
Tel. +44 1 536 74 17 27
Fax +44 1 865 26 77 82
book.orders@oup.co.uk

WHO Blue Books on the web: www.iarc.fr/who-bluebooks
Pathology and Genetics of Tumours of the Breast and Female Genital Organs

Edited by

Fattaneh A. Tavassoli
Peter Devilee

IARCPress
Lyon, 2003
World Health Organization Classification of Tumours

Pathology and Genetics of Tumours of the Breast and Female Genital Organs

Editors Fattaneh A. Tavassoli, M.D.
Peter Devilee, Ph.D.

Coordinating Editors Lawrence M. Roth, M.D.
Rosemary Millis, M.D.

Editorial Assistants Isabelle Forcier
Christine Zorian

Layout Lauren A. Hunter
Sibylle Sölting
Pascale Dia

Illustrations Georges Mollon
Lauren A. Hunter

Printed by Druckhaus Tecklenborg
48565 Steinfurt, Germany

Publisher IARCPress
International Agency for Research on Cancer (IARC)
69008 Lyon, France
This volume was produced in collaboration with the
International Academy of Pathology (IAP)

The WHO Classification of Tumours of the Breast and Female Genital Organs presented in this book reflects the views of Working Groups that convened for Editorial and Consensus Conferences in Lyon, France, January 12-16 and March 16-20, 2002.

Members of the Working Groups are indicated in the List of Contributors on page 365

The Working Group on Gynaecological Tumours greatly appreciates the participation of, and guidance by Dr. Robert E. Scully, Harvard Medical School
Contents

1 Tumours of the breast 9
   Invasive breast carcinoma 13
   Invasive ductal carcinoma, NOS 19
   Invasive lobular carcinoma 23
   Tubular carcinoma 26
   Invasive cribriform carcinoma 27
   Medullary carcinoma 28
   Mucin producing carcinomas 30
   Neuroendocrine tumours 32
   Invasive papillary carcinoma 34
   Invasive micropapillary carcinoma 35
   Apocrine carcinoma 36
   Metaplastic carcinomas 37
   Lipid-rich carcinoma 41
   Secretory carcinoma 42
   Oncocytic carcinoma 43
   Adenoid cystic carcinoma 44
   Acinic cell carcinoma 45
   Glycogen-rich clear cell carcinoma 46
   Sebaceous carcinoma 46
   Inflammatory carcinoma 47
   Bilateral breast carcinoma 48
   Precursor lesions
     Lobular neoplasia 60
     Intrada ductal proliferative lesions 63
     Micronvasive carcinoma 74
     Intrada ductal papillary neoplasms 76
   Benign epithelial lesions 81
   Myoepithelial lesions 86
   Mesenchymal tumours 89
   Fibroepithelial tumours 99
   Tumours of the nipple 104
   Malignant lymphoma and metastatic tumours 107
   Tumours of the male breast 110

2 Tumours of the ovary and peritoneum 113
   Surface epithelial-stromal tumours 117
   Serous tumours 119
   Mucinous tumours 124
   Endometrioid tumours 130
   Clear cell tumours 137
   Transitional cell tumours 140
   Squamous cell lesions 143
   Mixed epithelial tumours 144
   Undifferentiated carcinomas 145
   Sex cord-stromal tumours 146
   Granulosa-stromal cell tumours 146
   Sertoli-stromal cell tumours 153
   Mixed sex cord-stromal tumours 158
   Steroid cell tumours 160
   Germ cell tumours 163
   Primitive germ cell tumours 163
   Biphasic or triphasic teratomas 168
   Monodermal teratomas 171
   Mixed germ cell-sex cord-stromal tumours 176
   Tumours and related lesions of the rete ovarii 180
   Miscellaneous tumours and tumour-like lesions 182
   Lymphomas and leukemias 191
   Secondary tumours of the ovary 193
   Peritoneal tumours 197

3 Tumours of the fallopian tube and uterine ligaments 203
   Tumours of the fallopian tube 206
   Tumours of the uterine ligaments 212

4 Tumours of the uterine corpus 217
   Epithelial tumours and related lesions 221
   Endometrial carcinoma 221
   Endometrial hyperplasia 228
   Endometrial polyp 230
   Mesenchymal tumours and related lesions 233
   Endometrial stromal and related tumours 233
   Smooth muscle tumours 236
   Other mesenchymal tumours 242
   Mixed epithelial and mesenchymal tumours 245
   Gestational trophoblastic disease 250
   Sex cord-like, neuroectodermal / neuroendocrine tumours, lymphomas and leukemias 255
   Secondary tumours of the uterine corpus 257

5 Tumours of the uterine cervix 259
   Epithelial tumours 262
     Squamous tumours and precursors 266
     Glandular tumours and precursors 272
     Uncommon carcinomas and neuroendocrine tumours 277
     Mesenchymal tumours 280
     Mixed epithelial and mesenchymal tumours 284
     Melanotic, germ cell, lymphoid and secondary tumours of the cervix 287

6 Tumours of the vagina 291
   Epithelial tumours 293
     Squamous tumours 293
     Glandular tumours 297
     Tumours of skin appendage origin 324
     Mesenchymal tumours 320
     Mixed epithelial and mesenchymal tumours 306
     Melanotic, neuroectodermal, lymphoid and secondary tumours 308

7 Tumours of the vulva 313
   Epithelial tumours 316
     Squamous tumours 316
     Glandular tumours 321
     Mesenchymal tumours 326
     Melanocytic tumours 331
     Germ cell, neuroectodermal, lymphoid and secondary tumours 333

8 Inherited tumour syndromes 335
   Familial aggregation of cancers of the breast and female genital organs 336
   BRCA1 syndrome 338
   BRCA2 syndrome 346
   Li-Fraumeni syndrome 351
   Cowden syndrome 355
   Hereditary non-polyposis colon cancer (HNPCC) 358
   Ataxia telangiectasia syndrome 361

Contributors 365
Source of charts and photographs 370
References 372
Subject index 425
Cancer of the breast is one of the most common human neoplasms, accounting for approximately one quarter of all cancers in females. It is associated with the Western lifestyle, and incidence rates are, therefore, highest in countries with advanced economies. Additional risk factors include early menarche and late childbirth. Breast cancer is further characterized by a marked genetic susceptibility. Early detection and advances in treatment have begun to reduce mortality rates in several countries. Through the use of cDNA expression profiles, it may become possible to predict clinical outcome in individual patients.

The typing of invasive breast cancer and its histological variants is well established. More difficult is the classification of pre-invasive breast lesions which are now increasingly detected by mammography. The WHO Working Group agreed that more clinical follow-up and genetic data are needed for a better understanding of the natural history of these lesions.
WHO histological classification of tumours of the breast

<table>
<thead>
<tr>
<th>Epithelial tumours</th>
<th>WHO classification code</th>
<th>WHO histological code</th>
<th>International Classification of Diseases for Oncology (ICD-O) code</th>
<th>Systematized Nomenclature of Medicine (SNOMED) code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma, not otherwise specified</td>
<td>8500/3</td>
<td>Adenomas</td>
<td>Tubular adenoma</td>
<td>8211/0</td>
</tr>
<tr>
<td>Mixed type carcinoma</td>
<td>8204/0</td>
<td></td>
<td>Lactating adenoma</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic carcinoma</td>
<td>8022/3</td>
<td></td>
<td>Apocrine adenoma</td>
<td>8401/0</td>
</tr>
<tr>
<td>Carcinoma with osteoclastic giant cells</td>
<td>8035/3</td>
<td></td>
<td>Pleomorphic adenoma</td>
<td>8940/0</td>
</tr>
<tr>
<td>Carcinoma with choriocarcinomatous features</td>
<td></td>
<td></td>
<td>Ductal adenoma</td>
<td>8503/0</td>
</tr>
<tr>
<td>Invasive tubular carcinoma</td>
<td>8520/3</td>
<td>Myoepithelial lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>8211/3</td>
<td></td>
<td>Myoepitheliosis</td>
<td></td>
</tr>
<tr>
<td>Invasive cribriform carcinoma</td>
<td>8201/3</td>
<td></td>
<td>Adenomyoepithelial adenosis</td>
<td>8983/0</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>8510/3</td>
<td></td>
<td>Malignant myoepitheloma</td>
<td>8982/3</td>
</tr>
<tr>
<td>Mucinous carcinoma and other tumours with abundant mucin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>8480/3</td>
<td></td>
<td>Haemangiomma</td>
<td>9120/0</td>
</tr>
<tr>
<td>Cystadenocarcinoma and columnar cell mucinous carcinoma</td>
<td>8481/0</td>
<td></td>
<td>Angiomatosis</td>
<td>8861/0</td>
</tr>
<tr>
<td>Invasive papillary carcinoma</td>
<td>8503/3</td>
<td>Mesenchymal tumours</td>
<td>Granular cell tumour</td>
<td>9580/0</td>
</tr>
<tr>
<td>Invasive micropapillary carcinoma</td>
<td>8507/3</td>
<td></td>
<td>Neurofibroma</td>
<td>9540/0</td>
</tr>
<tr>
<td>Apocrine carcinoma</td>
<td>8401/3</td>
<td></td>
<td>schwannoma</td>
<td>9560/0</td>
</tr>
<tr>
<td>Metaplastic carcinomas</td>
<td>8575/3</td>
<td></td>
<td>Angiosarcoma</td>
<td>9120/3</td>
</tr>
<tr>
<td>Pure epithelial metastatic carcinomas</td>
<td>8575/3</td>
<td></td>
<td>Liposarcoma</td>
<td>8850/3</td>
</tr>
<tr>
<td>Adenocarcinoma with spindle cell metastasis</td>
<td>8572/3</td>
<td></td>
<td>Rhabdomyosarcoma</td>
<td>8900/3</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>8430/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed epithelial/mesenchymal metastatic carcinomas</td>
<td>8575/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-rich carcinoma</td>
<td>8314/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretory carcinoma</td>
<td>8502/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncocytic carcinoma</td>
<td>8290/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>8200/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>8550/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycogen-rich clear cell carcinoma</td>
<td>8315/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sebaceous carcinoma</td>
<td>8410/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory carcinoma</td>
<td>8530/3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobular neoplasia</td>
<td>8520/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>8520/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraductal proliferative lesions</td>
<td>8500/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell atypia</td>
<td>8500/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical ductal hyperplasia</td>
<td>8500/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>8500/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microinvasive carcinoma</td>
<td>8500/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraductal papillary neoplasms</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central papilloma</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral papilloma</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical papilloma</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraductal papillary carcinoma</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracytic papillary carcinoma</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign epithelial proliferations</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosis including variants</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apocrine adenosis</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunt duct adenosis</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microglandular adenosis</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomyoepithelial adenosis</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial scar / complex sclerosing lesion</td>
<td>8502/0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org).
2. Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
TNM Clinical Classification

T – Primary Tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ
Tis (DCIS) Ductal carcinoma in situ
Tis (LCIS) Lobular carcinoma in situ
Tis (Paget) Paget disease of the nipple with no tumour

Note: Paget disease associated with a tumour is classified according to the size of the tumour.

T1 Tumour 2 cm or less in greatest dimension
T1a More than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b More than 0.5 cm but not more than 1 cm in greatest dimension
T1c More than 1 cm but not more than 2 cm in greatest dimension
T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumour more than 5 cm in greatest dimension
T4 Tumour of any size with direct extension to chest wall or skin only as described in T4a to T4d

Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

T4a Extension to chest wall
T4b Oedema (including peau d’orange), or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c Inflammatory carcinoma

Note: * Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion (Do not use the sum of all individual foci). The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

T4d Inflammatory carcinoma

N – Regional Lymph Nodes

N0 No regional lymph node metastasis
N1 Metastasis in movable ipsilateral axillary lymph node(s)
N2 Metastasis in fixed (ipsilateral axillary lymph node(s)) or clinically apparent (ipsilateral internal mammary lymph node(s)) in the absence of clinically evident axillary lymph node metastasis
N2a Metastasis in axillary lymph node(s) fixed to one another or to other structures
N2b Metastasis only in clinically apparent* internal mammary lymph node(s) and in the absence of clinically evident axillary lymph node metastasis
N3 Metastasis in ipsilateral infracavicular lymph node(s) with or without axillary lymph node involvement; or in clinically apparent* ipsilateral internal mammary lymph node(s) in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a Metastasis in infracavicular lymph node(s)
N3b Metastasis in internal mammary and axillary lymph nodes
N3c Metastasis in supraclavicular lymph node(s)

Note: * clinically apparent = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy)

M – Distant Metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

pTNM Pathological Classification

pT – Primary Tumour

The pathological classification requires the examination of the primary carcinoma with no gross tumour at the margins of resection. A case can be classified pT if there is only microscopic tumour in a margin. The pT categories correspond to the T categories.

pT0 No tumour detectable
pT1 Tumour of any size with direct extension to chest wall or skin
pT1a More than 0.1 cm but not more than 0.5 cm in greatest dimension
pT1b More than 0.5 cm but not more than 1 cm in greatest dimension
pT1c More than 1 cm but not more than 2 cm in greatest dimension
pT1d Inflammatory carcinoma
pT2 Tumour more than 2 cm but not more than 5 cm in greatest dimension
pT3 Tumour more than 5 cm in greatest dimension
pT4 Tumour of any size with direct extension to chest wall or skin
pT4a Extension to chest wall
pT4b Oedema (including peau d’orange), or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
pT4c Inflammatory carcinoma

Note: When classifying pT the tumour size is a measurement of the invasive component. If there is a large in situ component (e.g. 4 cm) and a small invasive component (e.g. 0.5 cm), the tumour is coded pT1a.

pN – Regional Lymph Nodes

pN0 No regional lymph node metastasis
pN1 Metastasis in ipsilateral axillary lymph node(s), and/or in internal mammary nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent
pN1a Metastasis in 1-3 axillary lymph node(s), including at least one larger than 2 mm in greatest dimension
pN1b Internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent
pN1c Metastasis in 1-3 axillary lymph nodes and internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent
pN2 Metastasis in 4-9 axillary lymph node(s), or in clinically apparent*** ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis
pN2a Metastasis in 4-9 axillary lymph node(s), including at least one that is larger than 2 mm
pN2b Metastasis in clinically apparent internal mammary lymph node(s), in the absence of axillary lymph node metastasis
pN3 Metastasis in 10 or more ipsilateral axillary lymph nodes, or in ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative, microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a Metastasis in 10 or more axillary lymph nodes (at least one larger than 2 mm) or metastasis in infracavicular lymph node(s)

Note: ** clinically apparent = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy)

pM – Distant Metastasis

The pM categories correspond to the M categories.
# Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0,N1,N2</td>
<td>M0</td>
</tr>
<tr>
<td>IIIIC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

1. Axillary (ipsilateral): interpectoral (Rotter) nodes and lymph nodes along the axillary vein and its tributaries, which may be divided into the following levels:
   (i) Level I (low axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle.
   (ii) Level II (mid-axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter) lymph nodes.
   (iii) Level III (apical axilla): apical lymph nodes and those medial to the medial margin of the pectoralis minor muscle, excluding those designated as subclavicular or infraclavicular.

Note: Intramammary lymph nodes are coded as axillary lymph nodes, level I.

2. Infraclavicular (subclavicular) (ipsilateral).

3. Internal mammary (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia.

4. Supraclavicular (ipsilateral).

The pathological N classification requires the resection and examination of at least the low axillary lymph nodes (level II). Examination of one or more sentinel lymph nodes may be used for pathological classification. If classification is based solely on sentinel node biopsy without subsequent axillary lymph node dissection it should be designated (sn) for sentinel node, e.g. pN1(sn).
Invasive breast carcinoma

Definition
Invasive breast carcinoma is a group of malignant epithelial tumours characterized by invasion of adjacent tissues and a marked tendency to metastasize to distant sites. The vast majority of these tumours are adenocarcinomas and are believed to be derived from the mammary parenchymal epithelium, particularly cells of the terminal duct lobular unit (TDLU). Breast carcinomas exhibit a wide range of morphological phenotypes and specific histopathological types have particular prognostic or clinical characteristics.

Epidemiology
Invasive breast cancer is the most common carcinoma in women. It accounts for 22% of all female cancers, 26% in affluent countries, which is more than twice the occurrence of cancer in women at any other site (2188). The areas of high risk are the affluent populations of North America, Europe and Australia where 6% of women develop invasive breast cancer before age 75. The risk of breast cancer is low in the less developed regions of sub-Saharan Africa and Southern and Eastern Asia, including Japan, where the probability of developing breast cancer by age 75 is one third that of rich countries. Rates are intermediate elsewhere. Japan is the only rich country that in year 2000 still showed low incidence rates.

The risk of the disease had been increasing until the early 1980s in both developed and developing countries and continues to increase in particular in the developing countries (3068). Thereafter, in developed countries, the advent of mammography and the previously mentioned improvements in survival altered both incidence and mortality; the latter no longer appropriately reflect trends in the underlying risk of the disease.

Breast cancer incidence, as with most epithelial tumours, increases rapidly with age. Figure 1.02 shows age-specific incidence rates for three selected populations representing countries with low (Japan), intermediate (Slovenia) and high incidence rates (USA), just before screening was implemented. The curves show a characteristic shape, rising steeply up to menopausal age and less rapidly or not at all afterwards. The different behaviour at older ages is due to a cohort effect in the populations of Japan and Slovenia experiencing an increase in risk that affects mainly younger generations. If current trends persist, these generations will maintain their higher risk and the age-specific curve will approach that of Americans.

Around 1990, breast cancer incidence varied 10-fold world wide, indicating important differences in the distribution of the underlying causes (2189). Geographical variations, time trends, and studies of populations migrating from low to high risk areas which show that migrant populations approach the risk of the host country in one or two generations (174,1478,3266), clearly suggest an important role of environmental factors in the aetiology of the disease.

Aetiology
The aetiology of breast cancer is multifactorial and involves diet, reproductive factors, and related hormonal imbalances. From descriptive epidemiological

I.O. Ellis C.J. Cornelisse
S.J. Schnitt A.J. Sasco
X. Sastre-Garau R. Kaaks
G. Bussolati P. Pisani
F.A. Tavassoli D.E. Goldgar
V. Eusebi P. Devilee
J.L. Peterse M.J. Cleeton-Jansen
K. Mukai A.L. Barresen-Dale
L. Tabár L. van’t Veer
J. Jacquemier A. Sapino

Fig. 1.01 Global incidence rates of breast cancer. Age-standardized rates (ASR) per 100,000 population and year. From Globocan 2000 (846).
data it has clearly emerged that breast cancer is a disease of affluent societies which have acquired the Western lifestyle, characterized by a high-caloric diet rich in animal fat and proteins, combined with a lack of physical exercise. Regions which have featured this lifestyle for a long period of time (North America, Northern Europe, Australia) have reached a plateau of an incidence rate of 70 to 90 new cases per 100,000 population/year while countries that have more recently become industrialized and affluent show a marked increase in incidence and mortality. In addition to breast cancer, the Western lifestyle carries a high risk of cancer of the prostate, colon/rectum, and endometrium. Specific environmental exposures operative in the development of breast cancer (e.g. radiation, alcohol, exogenous hormones) have been identified but carry a lower risk.

More than most other human neoplasms, breast cancer often shows familial clustering. Two high penetrance genes have been identified (BRCA1/2) which greatly increase the breast cancer risk (see Chapter 8). However, it is anticipated that multigenic traits also play a significant role in the inherited susceptibility to breast cancer.

**Reproductive lifestyle**

For almost half a century, the events of reproductive life have been considered to be risk factors for breast cancer in women. Breast cancer occurs more frequently among women who have an early menarche, remain nulliparous or, if parous, have few children with a late age at first delivery. Infertility per se appears to be a risk factor as may be lack of breast-feeding. Finally, late age at menopause also increases the risk.

Most of these factors have also been found relevant in populations at low risk of breast cancer such as the Japanese and Chinese. Although the data is limited in Africa, at least one study confirmed the negative impact of late age at first delivery, reduced number of pregnancies and shorter breast feeding time.

Recent data indicates that the age at any delivery, not just the first is associated with breast cancer risk, with deliveries occurring before the age of 30 having a protective effect.

Controversies still surround the issue of abortion, some studies, but not others, finding an increased risk for induced abortion. Similarly, the protective effect of lactation, once considered quite a strong factor, was later given less importance; its impact appears limited to long-term cumulative breast feeding, preferably exceeding two years.

**Exogenous hormones**

Two major types of hormonal compounds have been evaluated in relation to breast cancer: oral contraceptives and menopausal replacement therapy. The evidence suggests a small increase in the relative risk associated with the use of combined oral contraceptives, especially among current and recent users, which is not related to duration of use and type or dose of preparation, and may be partly linked to detection bias.

Information on the effect of postmenopausal estrogen-progestogen contraceptives shows relative risks from 1.0 to 1.3, which are not statistically significant. Yet it should be noted that, among hormone replacement therapy users, there is an over representation of tumours that, with regard to tumour stage, type and grade are associated with a more favourable prognosis.

**Nutrition**

High intakes of fruit and vegetables are probably associated with a slightly reduced risk of breast cancer.
Rapid growth and greater adult height, reflecting in part, the total food intake in early years, are associated with an increased risk [674]. Similarly a high body mass, also linked to a high total caloric intake, or intake not counterbalanced by caloric expenditure, is a risk factor for postmenopausal breast cancer. Total fat, as well as saturated animal fat, also possibly increases the risk [674, 3153].

Meat consumption is possibly associated with an increased risk. Red meat was more frequently cited as a risk factor and diets rich in poultry possibly have no links [3153]. In countries with different meat consumption levels within the population, higher risks were associated with higher total meat, red meat or processed meat intake in most studies, although this was not always statistically significant. In conclusion there is considerable consistent evidence that higher meat consumption, particularly red or fried/browned meat is associated with a higher risk of breast cancer [674].

Recent studies, however, tend to suggest that several associations, either preventive for vegetables and fruit, or risk for fat may have been overstated [804, 815, 817]. Other questions remaining unsolved include the long term cumulative effects of exposure to contaminants, either formed during cooking, such as heterocyclic amines in well-done meat or pesticide residues.

**Alcohol**
The consumption of alcohol has been relatively consistently found to be associated with a mild increase in risk of breast cancer [2729, 3153]. A dose-response was found with number of drinks per day, including a low level of consumption [1691]. Hormone use or other factors potentially including genetic polymorphism [2182] may modify the risk.

**Smoking**
The evidence on smoking and breast cancer remains inconclusive [787, 816, 784, 402]. Tobacco has been viewed as an anti-estrogen and a potential protective factor [182].

**Body weight**
It has long been known that the influence of weight on breast cancer risk depends on the menopausal status [1292]. More than 100 studies over nearly 30 years in many countries have established that higher body weight increases breast cancer risk among postmenopausal women. This is largely independent of reproductive and lifestyle risk factors and of the effect of physical activity. The association appears to increase in a stepwise fashion with advancing age after menopause.

The increase in risk with body-mass index (BMI) has been somewhat modest in the majority of studies [1292]. Above a BMI of 24 kg/m², the incidence rate increases among postmenopausal women. The greatest slope of increases in risk across higher BMI levels is in low and moderate risk countries suggesting that increases in BMI now being observed in those countries may become a major factor contributing to future increases in breast cancer rates. While risk ratios have levelled off at BMI levels near 25 kg/m² in high risk countries, this is not the case in low to moderate risk countries, where risk has continued to increase across a wider range of body weight. The association between BMI and breast cancer is stronger among women who have never used postmenopausal hormone replacement therapy, suggesting that the risk from being overweight may be mediated by the elevations in endogenous estrogen production among heavier women. Adult weight gain is a strong and consistent predictor of postmenopausal breast cancer risk particularly among women who have never used hormone replacement therapy [1292].

In populations with a high incidence of breast cancer, the overall association between BMI and breast cancer risk among premenopausal women is the inverse. The reduction in risk with excessive weight is modest and not observed until a BMI of 28 kg/m². Despite this, however, the breast cancer mortality rate is not lower among heavier premenopausal women [1292].

**Physical activity**
The association between physical activity and breast cancer risk is independent of menopausal status [1292]. The decrease in risk among the most physically active women was about 20-40%. Activity that is sustained throughout lifetime, or at a minimum performed after menopause, may be particularly beneficial. It appears that physical activity has...
similar effects within different populations. Although lifetime physical activity is desirable, beginning recreational physical activity after the menopause can probably be beneficial for both weight control and breast cancer risk reduction [1292].

**Endogenous hormones**

There is overwhelming evidence from epidemiological studies that sex steroids (androgens, estrogens, progestogens) have an important role in the development of breast tumours. Breast cancer incidence rates rise more steeply with age before menopause than after, when ovarian synthesis of estrogens and progesterone ceases and ovarian androgen production gradually diminishes [1447]. The estrogen excess hypothesis is central, stipulating that breast cancer risk depends directly on breast tissue exposure to estrogens. In vitro studies show increased breast cell proliferation and inhibition of apoptosis. Animal studies show increased rates of tumour development when estrogens are administered. The risk is higher among postmenopausal women who have elevated plasma levels of testosterone and androstenedione, reduced levels of sex hormone-binding globulin (SHBG), and increased levels of oestrone, oestradiol, and bioavailable oestradiol not bound to SHBG.

A second major theory, the estrogen plus progestogen hypothesis [255, 1446], postulates that, compared to exposure to estrogens alone (as in postmenopausal women not using exogenous hormones), risk of breast cancer is further increased in women who have elevated plasma and tissue levels of estrogens in combination with progestogens. This theory is supported by observations that proliferation of mammary epithelial cells is increased during the luteal phase of the menstrual cycle, compared to the follicular phase.

Among premenopausal women, several studies have not shown any clear association between breast cancer risk and circulating levels of androgens, estrogens, or progesterone [255,1183,2448,2613,2909].

A metabolic consequence of excess body weight and lack of physical activity is development of insulin resistance. Elevated insulin levels, may lead to increased ovarian and/or adrenal synthesis of sex steroids, particularly of androgens, and decrease the hepatic synthesis and circulating levels of SHBG [1376]. Especially in postmenopausal women, elevated plasma androgens lead to increased estrogen formation in adipose tissue, and hence to increased levels of oestrone and oestradiol. The hypothesis that chronic hyperinsulinemia might explain the observed associations of breast cancer risk with low plasma SHBG and elevated androgens and estrogens, among postmenopausal women [1376] has, however, received only limited support [661,1377]. Insulin-growth factor-I (IGF-I) and IGF-binding proteins (IGFBP) appear to be significant risk predictors [1127,1377]. Future adult cancer risk is in part set by exposures in relation to breast cancer. Some specific exposures

Only limited data is available on specific exposures in relation to breast cancer. Long-term follow-up of women exposed to the Hiroshima or Nagasaki nuclear explosions indicates an increased risk of breast cancer, in particular for women exposed around puberty [2938]. Similarly, exposure as a result of treatment and surveillance of tuberculosis is associated with risk [304]. Yet there is little evidence for a different pattern of risk as a function of fractionated versus one time only irradiation [1678]. Systematic reviews on occupation and breast cancer are few, indicating an increased risk for selected occupations and specific chemical and physical exposures. This data contrasts with the long-held view that risk of breast cancer is related to social class, with higher risk for execu-

<table>
<thead>
<tr>
<th>Table 1.01</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of symptoms of women presenting in a breast clinic (288,898).</strong></td>
</tr>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Lump</td>
</tr>
<tr>
<td>Nipple problems</td>
</tr>
<tr>
<td>Deformity</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Family history</td>
</tr>
</tbody>
</table>

**Fig. 1.07** Age distribution of benign and malignant breast lesions in patients presenting with a discrete breast lump. From Dixon and Sainsbury [787].

Another important period is adolescence, where diet may play a role either directly or possibly indirectly through a modification of growth velocity [242].
tives, administrative and clerical jobs (387). A recent hypothesis deals with circadian disruption through night work, with an increased risk in women working predominantly at night (632,2556). Over the last ten years concerns have arisen as to the potential risks of exposure to, not only hormones, but to artificial products mimicking hormonal activities. This led to the concept of xeno-estrogens. The exact role they play is unknown. Most epidemiological studies deal with various pesticides, essentially organochlorines which remain in the environment for a very long time and the residues of which may be found in adipose tissue of various species, including humans (628). Studies have produced conflicting results with some suggesting a possibly increased risk, some no risk and others showing a negative effect. For the time being, many consider these links as speculative and unfounded (1951,2503) or as markers of susceptibility (1951).

Finally, based on animal experience, a viral hypothesis has been put forward. In mice, a retrovirus, the murine mammary tumour virus, is a recognized cause of mammary tumours, transmitted with milk from mothers to daughters. Another candidate is the Epstein-Barr virus, although data from the USA are not particularly supportive (1015). Other potential viral candidates remain to be searched for.

Table 1.02
Conditions requiring referral to a specialist clinic.

<table>
<thead>
<tr>
<th>Lump</th>
<th>Any new discreet mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A new lump in pre-existing nodularity</td>
</tr>
<tr>
<td></td>
<td>Asymmetrical nodularity that persists at review after menstruation</td>
</tr>
<tr>
<td></td>
<td>Abscess on breast inflammation which does not settle after one course of antibiotics</td>
</tr>
<tr>
<td></td>
<td>Cyst persistently refilling or recurrent cyst (if the patient has recurrent multiple cysts and the GP has the necessary skills, then aspiration is acceptable)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain</th>
<th>If associated with a lump</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intractable pain that interferes with a patient’s lifestyle or sleep and which has failed to respond to reassurance, simple measures such as wearing a well supporting brassiere and common drugs</td>
</tr>
<tr>
<td></td>
<td>Unilateral persistent pain in postmenopausal women</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nipple discharge</th>
<th>All women &gt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women &lt; 50 with:</td>
</tr>
<tr>
<td></td>
<td>Bilateral discharge sufficient to stain clothes</td>
</tr>
<tr>
<td></td>
<td>Bloodstained discharge</td>
</tr>
<tr>
<td></td>
<td>Persistent single duct discharge</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nipple retraction, distortion, eczema</th>
<th>Change in skin contour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Family history of breast cancer</td>
</tr>
</tbody>
</table>

Lump

Benign and malignant disease does differ between age cohorts, benign conditions being more common in younger women and breast cancer the commonest cause of symptoms in older women. The most common findings in symptomatic women are breast lumps, which may or may not be associated with pain. Nipple abnormalities (discharge, retraction, distortion or eczema) are less common and other forms of presentation are rare. Some symptoms have a higher risk of underlying malignancy for which hospital referral is recommended. Breast abnormalities should be evaluated by triple assessment including clinical examination, imaging (mammography and ultrasound) and tissue sampling by either fine needle aspiration cytology or needle core biopsy.

Clinical features

Imaging

Imaging should include mammography except in women under age 35, where it is rarely of value, unless there is strong clinical suspicion or tissue/needle biopsy evidence of malignancy. The mammographic appearances of breast carcinoma are varied and include well defined, ill defined and spiculate

Fig. 1.08 A Mammogram of infiltrating carcinoma, clinically occult, less than 1 cm. B Mammographic detail of small, non-palpable, infiltrating carcinoma (<1 cm). C Macroscopic picture.
masses, parenchymal deformity and calcification with or without a mass lesion. By far the most common manifestation of breast cancer on the mammogram is tumour mass without calcifications. The mammographic histological correlation of 1,168 open surgical biopsies at Falun Central Hospital, Sweden, included 866 histologically proven malignancies. As seen in Table 1.03, the mammograms of these breasts cancer showed:

1) Stellate or circular tumour mass with no associated calcifications in 64% of the cases.
2) An additional 17% had both calcifications and tumour mass.
3) Only calcifications without associated tumour mass accounted for less than 20% of all malignancies detectable on the mammogram.

**Grading of invasive carcinoma**

Invasive ductal carcinomas and all other invasive tumours are routinely graded based on an assessment of tubule/gland formation, nuclear pleomorphism and mitotic counts. Many studies have demonstrated a significant association between histological grade and survival in invasive breast carcinoma. It is now recognized as a powerful prognostic factor and should be included as a component of the minimum data set for histological reporting of breast cancer (779,1190). Assessment of histological grade has become more objective with modifications of the Patley & Scarff (2195) method first by Bloom and Richardson (293) and more recently by Elston and Ellis (777,2385).

**Method of grading**

Three tumour characteristics are evaluated: tubule formation as an expression of glandular differentiation, nuclear pleomorphism and mitotic counts. A numerical scoring system of 1-3 is used to ensure that each factor is assessed individually. When evaluating tubules and glandular acini only structures exhibiting clear central lumina are counted; cut off points of 75% and 10% of glandular/tumour area are used to allocate the score. Nuclear pleomorphism is assessed by reference to the regularity of nuclear size and shape of normal epithelial cells in adjacent breast tissue. Increasing irregularity of nuclear outlines and the number and size of nucleoli are useful additional features in allocating scores for pleomorphism. Evaluation of mitotic figures requires care and observers must count only defined mitotic figures; hyperchromatic and pyknotic nuclei are ignored since they are more likely to represent apoptosis than proliferation. Mitotic counts require standardization to a fixed field area or by using a grid system (1984). The total number of mitoses per 10 high power fields. Field selection for mitotic scoring should be from the peripheral leading edge of the tumour. If there is heterogeneity, regions exhibiting a higher frequency of mitoses should be chosen. Field selection is by random meander through the chosen area. Only fields with a representative tumour cell burden should be assessed. The three values are added together to produce scores of 3 to 9, to which the grade is assigned as follows:

### Table 1.04

Spectrum of histological diagnosis corresponding to mammographic circular/oval lesions.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma, NOS</td>
<td>59%</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>8%</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>7%</td>
</tr>
<tr>
<td>Intracystic carcinoma</td>
<td>5%</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>4%</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>4%</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>13%</td>
</tr>
</tbody>
</table>
Grade 1 - well differentiated: 3-5 points
Grade 2 - moderately differentiated: 6-7 points
Grade 3 - poorly differentiated: 8-9 points

**Invasive ductal carcinoma, not otherwise specified (NOS)**

**Definition**
Invasive ductal carcinoma, not otherwise specified (ductal NOS) comprises the largest group of invasive breast cancers. It is a heterogeneous group of tumours that fail to exhibit sufficient characteristics to achieve classification as a specific histological type, such as lobular or tubular carcinoma.

**ICD-O code** 8500/3

**Synonyms and historical annotation**
Invasive ductal carcinoma, no specific type (ductal NST); infiltrating ductal carcinoma.

Many names have been used for this form of breast carcinoma including scirrhous carcinoma, carcinoma simplex and spheroidal cell carcinoma. Infiltrating ductal carcinoma is used by the Armed Forces Institute of Pathology (1832,2442) and was the nomenclature adopted in the previous WHO classification (2548,3154). This perpetuates the traditional concept that these tumours are derived exclusively from mammary ductal epithelium in distinction from lobular carcinomas, which were deemed to have arisen from within lobules for which there is no evidence. In addition it has been shown that the terminal duct-lobular unit (TDLU) should be regarded as a single entity from the point of view of the site of origin of most breast carcinomas (147,3091). Some groups (874,2325) have retained the term ductal but added the phrase ‘not otherwise specified (NOS)’, whilst others (2147) prefer to use ‘no specific type (NST)’ to emphasize their distinction from specific type tumours. This latter view is increasingly

---

**Table 1.05**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubule and gland formation</td>
<td></td>
</tr>
<tr>
<td>Majority of tumour (&gt;75%)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate degree (10-75%)</td>
<td>2</td>
</tr>
<tr>
<td>Little or none (&lt;10%)</td>
<td>3</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td></td>
</tr>
<tr>
<td>Small, regular uniform cells</td>
<td>1</td>
</tr>
<tr>
<td>Moderate increase in size and variability</td>
<td>2</td>
</tr>
<tr>
<td>Marked variation</td>
<td>3</td>
</tr>
</tbody>
</table>

**Mitotic counts**

<table>
<thead>
<tr>
<th>Field diameter (mm)</th>
<th>0.44</th>
<th>0.59</th>
<th>0.63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field area (mm²)</td>
<td>0.152</td>
<td>0.274</td>
<td>0.312</td>
</tr>
<tr>
<td>Mitotic count*</td>
<td>0-5</td>
<td>0-9</td>
<td>0-11</td>
</tr>
<tr>
<td>2 points</td>
<td>6-10</td>
<td>10-19</td>
<td>12-22</td>
</tr>
<tr>
<td>3 points</td>
<td>&gt;11</td>
<td>&gt;20</td>
<td>&gt;23</td>
</tr>
</tbody>
</table>

---

Fig. 1.10 Well differentiated infiltrating ductal carcinoma, Grade 1. **A** First screen. Intramammary lymph node and small (<5 mm), nonspecific density. **B** Second screen: 20 months later. The density has grown a little. **C** Third screen: after another 29 months. The 10 mm tumour is more obvious but still not palpable.
accepted internationally, but since ‘ductal’ is still widely used the terms invasive ductal carcinoma, ductal NOS or NST are preferred terminology options.

Epidemiology

Ductal NOS carcinoma forms a large proportion of mammary carcinomas and its epidemiological characteristics are similar to those of the group as a whole (see epidemiology). It is the most common 'type' of invasive carcinoma of the breast comprising between 40% and 75% in published series [774]. This wide range is possibly due to the lack of application of strict criteria for inclusion in the special types and also the fact that some groups do not recognize tumours with a combination of ductal NOS and special type patterns as a separate category, preferring to include them in the no special type (ductal NOS) group.

Ductal NOS tumours, like all forms of breast cancer, are rare below the age of 40 but the proportion of tumours classified as such in young breast cancer cases is in general similar to older cases [1493]. There are no well recognized differences in the frequency of breast cancer type and proportion of ductal NOS cancers related to many of the known risk factors including geographical, cultural/lifestyle, reproductive variables (see aetiology). However, carcinomas developing following diagnosis of conditions such as atypical ductal hyperplasia and lobular neoplasia, recognized to be associated with increased risk include a higher proportion of tumours of specific type specifically tubular and classical lobular carcinoma [2150]. Familial breast cancer cases associated with BRCA1 mutations are commonly of ductal NOS type but have medullary carcinoma like features, exhibiting higher mitotic counts, a greater proportion of the tumour with a continuous pushing margin, and more lymphocytic infiltration than sporadic cancers [1572]. Cancers associated with BRCA2 mutations are also often of ductal NOS type but have medullary carcinoma like features, exhibiting higher mitotic counts, a greater proportion of the tumour with a continuous pushing margin, and a lower mitotic count than sporadic cancers [1572].

Macroscopy

These tumours have no specific macroscopical features. There is a marked variation in size from under 10 mm to over 100 mm. They can have an irregular, stellate outline or nodular configuration. The tumour edge is usually moderately or ill defined and lacks sharp circumscription.

Histopathology

The morphological features vary considerably from case to case and there is frequently a lack of the regularity of structure associated with the tumours of specific type. Architecturally the tumour cells may be arranged in cords, clusters and trabeculae whilst some tumours are characterized by a predominantly solid or syncytial infiltrative pattern with little associated stroma. In a proportion of cases glandular differentiation may be apparent as tubular structures with central lumina in tumour cell groups. Occasionally, areas with single file infiltration or targetoid features are seen but these lack the cytomorphic characteristics of invasive lobular carcinoma. The carcinoma cells also have a variable appearance. The cytoplasm is often abundant and eosinophilic. Nuclei may be regular, uniform or highly pleomorphic with prominent, often multiple, nucleoli; mitotic activity may be virtually absent or extensive. In up to 80% of cases foci of associated ductal carcinoma in situ (DCIS) will be present [147,2874]. Associated DCIS is often of high grade comedo type, but all other patterns may be seen. Some recognize a subtype of ductal NOS carcinoma, infiltrating ductal carcinoma with extensive in situ component. The stromal component is extremely variable. There may be a highly cellular fibroblastic proliferation, a scanty connective tissue element or marked hyalinisation. Foci of elastosis may also be present, in a periductal or perivenous distribution. Focal necrosis may be present.

Classically, ductal NOS carcinomas are firm or even hard on palpation, and may have a curious 'gritty' feel when cut with a knife. The cut surface is usually grey-white with yellow streaks.

Fig. 1.11 Invasive ductal carcinoma, not otherwise specified. 84 year old patient, mastectomy specimen.

Fig. 1.12 A Infiltrating ductal carcinoma, grade I. B Infiltrating ductal carcinoma, grade II. C Invasive ductal NOS carcinoma, grade III with no evidence of glandular differentiation. Note the presence of numerous cells in mitosis, with some abnormal mitotic figures present.
Mixed type carcinoma

For a tumour to be typed as ductal NOS it must have a non-specialized pattern in over 50% of its mass as judged by thorough examination of representative sections. If the ductal NOS pattern comprises between 10 and 49% of the tumour, the rest being of a recognized special type, then it will fall into one of the mixed groups: mixed ductal and special type or mixed ductal and lobular carcinoma. Apart from these considerations there are very few lesions that should be confused with ductal NOS carcinomas.

Pleomorphic carcinoma

ICD-O code   8022/3

Pleomorphic carcinoma is a rare variant of high grade ductal NOS carcinoma characterized by proliferation of pleomorphic and bizarre tumour giant cells comprising >50% of the tumour cells in a background of adenocarcinoma or adenocarcinoma with spindle and squamous differentiation (2683). The patients range in age from 28 to 96 years with a median of 51. Most patients present with a palpable mass; in 12% of cases, metastatic tumour is the first manifestation of disease. The mean size of the tumours is 5.4 cm. Cavitation and necrosis occur in larger tumours.

The tumour giant cells account for more than 75% of tumour cells in most cases. Mitotic figures exceed 20 per 10 high power fields. All these tumours qualify as grade 3 carcinomas. The intraepithelial component displays a ductal arrangement and is often high grade with necrosis. Lymphovascular invasion is present in 19% of cases. Generally BCL2, ER and PR negative, two thirds of these pleomorphic carcinomas are TP53 positive, and one third are S-100 protein positive. All are positive for CAM5.2, EMA and pan-cytokeratin (AE1/AE3, CK1). A majority (68%) is aneuploid with 47% of them being triploid. A high S-phase (>10%) is found in 63%. Axillary node metastases are present in 50% of the patients with involvement of 3 or more nodes in most. Many patients present with advanced disease.

Carcinoma with osteoclastic giant cells

ICD-O code   8035/3

The common denominator of all these carcinomas is the presence of osteoclastic giant cells in the stroma [1089]. The giant cells are generally associated with an inflammatory, fibroblastic, hyper-
Tumours of the breast

vascular stroma, with extravasated red blood cells, lymphocytes, monocytes along with mononucleated and binucleated histiocytes some containing haemosiderin. The giant cells are variable in size and appear to embrace the epithelial component or are found within lumena formed by the cancer cells. The giant cells contain a variable number of nuclei. The giant cells and hypervascular reactive stroma can be observed in lymph node metastases and in recurrences (2952).

The carcinomatous part of the lesion is most frequently a well to moderately differentiated infiltrating ductal carcinoma but all the other histological types have been observed particularly invasive cribriform carcinoma (2003,2241), and also tubular, mucinous, papillary (3062), lobular (1274,2837), squamous and other metaplastic patterns (1200,2044, 3062).

About one-third of the reported cases had lymph nodes metastasis. The five year survival rate is around 70%, similar to, or better than, patients with ordinary infiltrating carcinomas [3062]. Prognosis is related to the characteristics of the associated carcinoma and does not appear to be influenced by the presence of stromal giant cells.

The giant cells show uniform expression of CD68 (as demonstrated by KP1 antibody on paraffin sections) (1200) and are negative for S100 protein, actin, and negative for cytokeratin, EMA, estrogen and progesterone receptors (2869). The giant cells are strongly positive for acid phosphatase, non-specific esterase and lysozyme, but negative for alkaline phosphatase indicative of morphological similarity to histiocytic cells and osteoclasts (2423,2869,2952,3025).

A number of ultrastructural and immunohistochemical studies have confirmed the histiocytic nature of the osteoclastic cells present in these unusual carcinomas (2632,2869,2952,3025). In vitro studies have recently shown that osteoclasts may form directly from a precursor cell population of monocytes and macrophages. Tumour associated macrophages (TAMs) are capable of differentiating into multinucleated cells, which can affect bone resorption in metastases (2313). Osteoclastic giant cells in carcinoma are probably also related to TAMs. Angiogenesis and chemotactic agents produced by the carcinoma may be responsible for the migration of histiocytes to the area involved by cancer and their ultimate transformation to osteoclastic giant cells (2638,2869).

**Carcinoma with choriocarcinomatous features**

Patients with ductal NOS carcinoma may have elevated levels of serum human β-chorionic gonadotrophin (β-HCG) (2649) and as many as 60% of ductal NOS carcinoma have been found to contain β-HCG positive cells (1243). Histological evidence of choriocarcinomatous differentiation, however, is exceptionally rare with only a few cases reported (993,1061,2508). All were in women between 50 and 70 years old.

**Carcinoma with melanotic features**

A few case reports have described exceptional tumours of the mammary parenchyma that appear to represent combinations of ductal carcinoma and malignant melanoma (2031,2146,2485) and in some of these cases, there appeared to be a transition from one cell type to the other. A recent genetic analysis of one such case showed loss of heterozygosity at the same chromosomal loci in all the components of the tumour, suggesting an origin from the same neoplastic clone (2031). The mere presence of melanin in breast cancer cells should not be construed as evidence of melanocytic differentiation, since melanin pigmentation of carcinoma cells can occur when breast cancers invade the skin and involve the dermo-epidermal junction (150). In addition, care must be taken to distinguish tumours showing melanocytic differentiation from breast carcinomas with prominent cytoplasmic lipofuscin deposition (2663).
Most melanotic tumours of the breast represent metastases from malignant melanomas originating in extra-mammary sites [2694]. Primary melanomas may arise anywhere in the skin of the breast, but an origin in the nipple-areola complex is extremely rare [2168]. The differential diagnosis of malignant melanoma arising in the nipple-areola region must include Paget disease, the cells of which may on occasion contain melanin pigment [2544]. This is discussed in the section on Paget disease.

Genetics
The genetic variation seen in breast cancer as a whole is similarly reflected in ductal NOS tumours and has until recently proved difficult to analyse or explain. The increasing accumulation of genetic alterations seen with increasing grade (decreasing degree of differentiation) has been used to support the hypothesis of a linear progression model in this type and in invasive breast cancer as a whole. The recent observation by a number of groups that specific genetic lesion or regions of alteration are associated with histological type of cancer or related to grade in the large ductal NOS group does not support this view. It implies that breast cancer of ductal NOS type includes a number of tumours of unrelated genetic evolutionary pathways [365] and that these tumours show fundamental differences when compared to some special type tumours including lobular [1085] and tubular carcinoma [2476]. Furthermore, recent cDNA microarray analysis has demonstrated that ductal NOS tumours can be classified in to subtypes on the basis of expression patterns [2218,2756].

Prognosis and predictive factors
Ductal NOS carcinoma forms the bulk (50-80%) of breast cancer cases and its prognostic characteristics and management are similar or slightly worse with a 35-50% 10 year survival [771] compared to breast cancer as a whole with around a 55% 10 year survival. Prognosis is influenced profoundly by the classical prognostic variables of histological grade, tumour size, lymph node status and vascular invasion (see general discussion of prognosis and predictive factors at the end of this chapter) and by predictors of therapeutic response such as estrogen receptor and ERBB2 status.

Approximately 70-80% of ductal NOS breast cancers are estrogen receptor positive and between 15 and 30% of cases ERBB2 positive. The management of ductal NOS carcinomas is also influenced by these prognostic and predictive characteristics of the tumour as well as focality and position in the breast.

Invasive lobular carcinoma
Definition
An invasive carcinoma usually associated with lobular carcinoma in situ is composed of non-cohesive cells individually dispersed or arranged in single-file linear pattern in a fibrous stroma.

ICD-O code 8520/3
Epidemiology
Invasive lobular carcinoma (ILC) represents 5-15% of invasive breast tumours (725,771,1780,2541,2935,3133). During the last 20 years, a steady increase in its incidence has been reported in women over 50 [1647], which might be attributable to the increased use of hormone replacement therapy [312,1648,2073]. During the last 20 years, a steady increase in its incidence has been reported in women over 50 [1647], which might be attributable to the increased use of hormone replacement therapy [312,1648,2073]. The mean diameter has been reported to be slightly larger than that of IDC in some series [2541,2696,3133].

Macroscopy
ILC frequently present as irregular and poorly delimited tumours which can be difficult to define macroscopically because of the diffuse growth pattern of the cell infiltrate [2696]. The mean diameter has been reported to be slightly larger than that of IDC in some series [2541,2696,3133].

Histopathology
The classical pattern of ILC [895,1780,3066] is characterized by a proliferation of small cells, which lack cohesion

Clinical features
The majority of women present with a palpable mass that may involve any part of the breast although centrally located tumours were found to be slightly more common in patients with ILC than with IDC [3133]. A high rate of multicentric tumours has been reported by some [699,1632] but this has not been found in other series based on clinical [2541] or radiological [1599] analysis (see bilateral breast carcinoma section). An 8-19% incidence of contralateral tumours has also been reported [699,725,834], representing an overall rate of 13.3%. This may be higher than that for IDC [1241,2696]. However, no significant difference in the rate of bilaterality was observed in other series of cases [648,1168,2186]. At mammography, architectural distortion is more commonly observed in ILC than in IDC whereas microcalcifications are less common in ILC [895,1780,3066].

Fig. 1.17 Carcinoma with choriocarcinomatous features. A,B Multinucleated tumour cells with smudged nuclei extend their irregular, elongated cytoplasmic processes around clusters of monocytic tumour cells, mimicking the biphasic growth pattern of choriocarcinoma. B Note the abnormal mitotic figures in this high grade carcinoma.

Fig. 1.18 Macroscopy of an invasive lobular carcinoma displays an ill defined lesion.
and appear individually dispersed through a fibrous connective tissue or arranged in single file linear cords that invade the stroma. These infiltrating cords frequently present a concentric pattern around normal ducts. There is often little host reaction or disturbance of the background architecture. The neoplastic cells have round or notched ovoid nuclei and a thin rim of cytoplasm with an occasional intracytoplasmic lumen (2312) often harbouring a central mucoid inclusion. Mitoses are typically infrequent. This classical form of ILC is associated with features of lobular carcinoma in situ in at least 90% of the cases (705,2001).

In addition to this common form, variant patterns of ILC have been described. The solid pattern is characterized by sheets of uniform small cells of lobular morphology (835). The cells lack cell to cell cohesion and are often more pleomorphic and have a higher frequency of mitoses than the classical type. In the alveolar variant, tumour cells are mainly arranged in globular aggregates of at least 20 cells (2668), the cell morphology and growth pattern being otherwise typical of lobular carcinoma. Pleomorphic lobular carcinoma retains the distinctive growth pattern of lobular carcinoma but exhibits a greater degree of cellular atypia and pleomorphism than the classical form (808,1859,3082). Intra-lobular lesions composed of signet ring cells or pleomorphic cells are features frequently associated with it. Pleomorphic lobular carcinoma may show apocrine (808) or histiocytoid (3047) differentiation. A mixed group is composed of cases showing an admixture of the classical type with one or more of these patterns (705). In about 5% of invasive breast cancers, both ductal and lobular features of differentiation are present (1780) (see Mixed type carcinoma, page 21). Analysis of E-cadherin expression may help to divide these cases between ductal and lobular tumours but the immunophenotype remains ambiguous in a minority of cases (34).

The admixture of tubular growth pattern and small uniform cells arranged in a linear pattern defines tubulo-lobular carcinoma (TLC) (ICD-O 8524/3) (875). LCIS is observed in about one third of TLC. Comparison of the clinical-pathological features of TLC and pure tubular carcinoma (TC) has shown that axillary metastases were more common in TLC (43%) than in TC (12%) (1062). A high rate of estrogen receptor (ER) positivity has also been reported in TLC (3141). Further analysis of TLC, especially regarding E-cadherin status, should help to determine whether TLC should be categorized as a variant of tubular or of lobular tumours. Without this data these tumours are best classified as a variant of lobular carcinoma.

Immunoprofile
About 70-95% of lobular carcinomas are ER positive, a rate higher than the 70-80% observed in IDC (2541,3235). Progesterone receptor (PR) positivity is 60-70% in either tumour type (2541,
ER was found to be expressed in the classical form and in variants (1994), but the rate of positivity was higher (100%) in alveolar (2668) and lower (10%) in pleomorphic ILC (2318) than in the classical type. The proliferation rate in ILC is generally low (2027). With the exception of pleomorphic lobular carcinoma ERBB2 overexpression in ILC (2274, 2477, 2750), is lower than reported in IDC (2358).

**Genetics**

Using flow cytometry, ILCs were found near diploid in about 50% of the cases (887). This fits with the finding that chromosomal abnormalities, assessed by cytogenetical (887) or comparative genomic hybridization (CGH) analysis (2027), are less numerous in ILC than in IDC. In ILC, the most common genetic alteration, found in 63-87% of the cases (887, 2027), is a loss of the long arm of chromosome 16.

The E (epithelial)-cadherin gene, which maps in 16q22, is implicated in maintaining coherence of adult epithelial tissues (1217), and acts as a cell differentiation and invasion suppressor factor (922, 2027). A correlation has been found between deletion of 16q and the loss of E-cadherin expression (2027). Immunohistochemical analysis has shown complete loss of E-cadherin expression in 80-100% of ILC (956, 1892, 2094, 2152, 2374). This contrasts with the mere decrease in staining intensity observed in 30-60% of IDC.

**Molecular analysis**

When the histological subtypes of ILC were analysed separately, a more favourable outcome was reported for the classical type than for variants (699, 705, 725). However, alveolar ILC has been considered as a low grade tumour (2668), whereas a poor prognosis of pleomorphic ILC has been reported in some series (808, 3082). No difference in the outcome of different subtypes has been observed in other series (2935). Furthermore, a large extent of lymph node involvement has not been found to increase significantly the risk of local relapse (2570). A link between lack of E-cadherin expression and adverse outcome of the disease has also been reported (125, 1176).
Treatment of ILC should depend on the stage of the tumour and parallel that of IDC. Conservative treatment has been shown to be appropriate for ILC [327, 2205,2269,2541,2570,2696].

**Tubular carcinoma**

**Definition**
A special type of breast carcinoma with a particularly favourable prognosis composed of distinct well differentiated tubular structures with open lumina lined by a single layer of epithelial cells.

**ICD-O code** 8211/3

**Epidemiology**
Pure tubular carcinoma accounts for under 2% of invasive breast cancer in most series. Higher frequencies of up to 7% are found in series of small T1 breast cancers. Tubular cancers are often readily detectable mammographically because of their spiculate nature and associated cellular stroma and are seen at higher frequencies of 9-19%, in mammographic screening series (1853, 2192,2322).

When compared with invasive carcinomas of no special type (ductal NOS), tubular carcinoma is more likely to occur in older patients, be smaller in size and have substantially less nodal involvement [691,1379,2166].

These tumours are recognized to occur in association with some epithelial proliferative lesions including well differentiated/low grade types of ductal carcinoma in situ (DCIS), lobular neoplasia and flat epithelial atypia [915,1034]. In addition, an association with radial scar has been proposed [1668,2725].

**Macroscopy**
There is no specific macroscopical feature which distinguishes tubular carcinoma from the more common ductal no special type (NOS) or mixed types, other than small tumour size. Tubular carcinomas usually measure between 0.2 cm and 2 cm in diameter; the majority are 1 cm or less [772,1829,2081].

Two morphological subtypes have been described, the ‘pure’ type which has a pronounced stellate configuration with radiating arms and central yellow flecks due to stromal elastosis and the sclerosing type characterized by a more diffuse, ill defined structure [410,2190].

**Histopathology**
The characteristic feature of tubular carcinoma is the presence of open tubules composed of a single layer of epithelial cells enclosing a clear lumen. These tubules are generally oval or rounded and, typically, a proportion appears angulated. The epithelial cells are small and regular with little nuclear pleomorphism and only scanty mitotic figures. Multi-layering of nuclei and marked nuclear pleomorphism are contraindications for diagnosis of pure tubular carcinoma, even when there is a dominant tubular architecture. Apical snouts are seen in as many as a third of the cases [2874], but are not pathognomonic. Myoepithelial cells are absent but some tubules may have an incomplete surrounding layer of basement membrane components.

Calcification may be present in the invasive tubular, associated in situ or the stromal components.

DCIS is found in association with tubular carcinoma in the majority of cases; this is usually of low grade type with a cribriform or micropapillary pattern. Occasionally, the in situ component is lobular in type. More recently an association has been described with flat epithelial atypia and associated micropapillary DCIS [915,1034].

There is a lack of consensus concerning the proportion of tubular structures required to establish the diagnosis of tubular carcinoma. In the previous WHO Classification (1,3154) and a number of published studies [410,1350, 1832] no specific cut-off point is indicated although there is an assumption that all the tumour is of a tubular configuration. Some authors have applied a strict 100% rule for tubular structures [409,552, 2190], some set the proportion of tubular structures at 75% [1668,1829, 2224,2442], and...
Invasive breast cancer

yet others at 90% [97,2147]. For pragmatic reasons, a 90% purity requirement offers a practical solution. Tumours exhibiting between 50 and 90% tubular growth pattern with other types should be regarded as mixed type of carcinoma (see Mixed type carcinomas).

Differential diagnosis
Sclerosing adenosis (SA) can be distinguished from tubular carcinoma by its overall lobular architecture and the marked compression and distortion of the glandular structures. Myoepithelial cells are always present in sclerosing adenosis and can be highlighted by immunostaining for actin. Similarly, a fully retained basement membrane can be shown by immunohistological staining for collagen IV and laminin in tubules of SA. Microglandular adenosis (MA) can be more difficult to differentiate because of the rather haphazard arrangement of the tubules, and lack of myoepithelial cells in the tubules. However, the tubules of MA are more rounded and regular and often contain colloid-like secretory material, at least focally, compared to the often angulated tubules of tubular carcinoma. Furthermore a ring of basement membrane is present around tubules of MA. Complex sclerosing lesions/radial scars have a typical architecture with central fibrosis and elastosis containing a few small, often distorted, tubular structures in which myoepithelial cells can be demonstrated. The surrounding glandular structures show varying degrees of dilatation and ductal epithelial hyperplasia.

Immunophenotype
Tubular carcinoma is nearly always estrogen and progesterone receptor positive, has a low growth fraction, and is ERBB2 and EGFR negative [691, 1379,2166].

Genetics
Tubular carcinomas of the breast have a low frequency of genetic alterations when compared to other types of breast carcinoma. Using LOH and CGH techniques, alterations have been found most frequently at chromosomes 16q (loss), 1q (gain), 8p (loss), 3p FHIT gene locus, and 11q ATM gene locus [1754,1779,2476, 2046]. Of particular interest is the observation that other sites of chromosomal alteration previously found at high levels in other types of breast cancer are not seen, which implies that tubular carcinoma of the breast is genetically distinct.

Prognosis and predictive factors
Pure tubular carcinoma has an excellent long term prognosis [409,410,552,771, 1829,2081,2224] which in some series is similar to age matched women without breast cancer [691]. Recurrence following mastectomy or breast conservation treatment is rare and localized tubular carcinomas are considered to be ideal candidates for breast conservation techniques. Following breast conservation, the risk of local recurrence is so low that some centres consider adjuvant radiotherapy unnecessary. Axillary node metastases occur infrequently, and when observed rarely involve more than one axillary lymph node. There is little adverse effect of node positivity in tubular carcinoma [691,1471] and the use of systemic adjuvant therapy and axillary node dissection are considered unnecessary by some groups [691,2166].

Invasive cribriform carcinoma

Definition
An invasive carcinoma with an excellent prognosis that grows in a cribriform pattern similar to that seen in intraductal cribriform carcinoma; a minor (<50%) component of tubular carcinoma may be admixed.

ICD-O code 8201/3

Epidemiology
Invasive cribriform carcinoma (ICC) accounts for 0.8-3.5% of breast carcinomas. The mean age of patients is 53-58 years [2148,2670,3017].

Clinical features
The tumour may present as a mass but is frequently clinically occult. At mammography, tumours typically form a spiculated mass frequently containing microcalcifications [2670,2806]. Multifocality is observed in 20% of the cases [2148].

Histopathology
The pure ICC consists almost entirely (>90%) of an invasive cribriform pattern. The tumour is arranged as invasive islands, often angulated, in which well defined spaces are formed by arches of cells (a sieve-like or cribriform pattern). Apical snouts are a regular feature. The tumour cells are small and show a low or moderate degree of nuclear pleomorphism. Mitoses are rare. A prominent, reactive appearing, fibroblastic stroma is present in many ICC. Intraductal carcinoma, generally of the cribriform type, is observed in as many as 80% of cases [2148]. Axillary lymph node metastases occur in 14.3% [2148], the cribriform pattern being retained at these sites. Lesions showing a predominantly cribriform arrange-
ment associated with a minor (<50%) component of tubular carcinoma are also included in the group of classic ICC (2148). Cases with a component (10-40%) of another carcinoma type, other than tubular carcinoma, should be called mixed type of carcinoma (2148,3017).

Immunoprofile

ICC is estrogen receptor positive in 100% and progesterone receptor in 69% of cases (3017).

Differential diagnosis

ICC should be differentiated from carcinoma tumour and adenoid cystic carcinoma; the former has intracytoplasmic argyrophilic granules, while the latter has a second cell population in addition to a well circumscribed and may be confused with a benign lesion.

Macroscope

MC has distinctive rounded, well defined margins and a soft consistency. Fleshy tan to grey in appearance, foci of necrosis and haemorrhage are frequent. The median diameter varies from 2.0-2.9 cm (2334,2370,3064).

Histopathology

Since the early descriptions of MC (895,1908,2367), the histological features of this tumour have been further specified (2334,2370,3064).

Clinical features

The tumour is well delineated and soft on palpation. Mammographically MC is typically well circumscribed and may be confused with a benign lesion.

Immunoprofile and ploidy

Flow cytometry and immunohistochemical analysis has shown that most MC are aneuploid and highly proliferative tumours (551,1244,1345,1766,2108,2201). A high apoptosis rate has also been observed in over 75% of the tumour mass. The tumour is well delineated and soft on palpation. Mammographically MC is typically well circumscribed and may be confused with a benign lesion.

Medullary carcinoma

Definition

A well circumscribed carcinoma composed of poorly differentiated cells arranged in large sheets, with no glandular structures, scant stroma and a prominent lymphoplasmacytic infiltrate.

Epidemiology

Medullary carcinoma (MC) represents between 1 and 7% (294,2334) of all breast carcinomas, depending on the stringency of diagnostic criteria used. The mean age of women with MC ranges from 45 to 52 years (623,2204,2334,3064).

Clinical features

The tumour is well delineated and soft on palpation. Mammographically MC is typically well circumscribed and may be confused with a benign lesion.

Prognosis and predictive factors

ICC has a remarkably favourable outcome (771,2148,3017). The ten-year overall survival was 90% (771) to 100% (2148). The outcome of mixed invasive cribriform carcinoma has been reported to be less favourable than that of the classic form, but better than that of common ductal carcinoma (2148). The biological behaviour of ICC is very similar to that of tubular carcinoma (771). It has been suggested that cribriform elements might correspond to tubules (2148). However, many ICC have no definite tubular structures and separation of this tumour as a distinct clinicopathological entity is justified.

Fig. 1.26 Medullary carcinoma. Mammogram showing a typical rounded, dense tumour without calcifications.
be reported [1386,3170]. MC typically lack estrogen receptors (ER) expression [1244,1340,2204,2272], and have a low incidence of ERBB2 overexpression [2439,2746,2750].

The cytokeratin profile is similar in typical and atypical MC, and does not differ significantly from that of common ductal tumours [610,1340,2943]. The cell cohesiveness of MC, contrasting with the poorly differentiated pattern and high mitotic index, has been characterized by the expression of the intercellular adhesion molecule-1 [156] and of E-cadherin [444]. This feature might account for the good limitation of the tumour and the late axillary lymph node extension.

Immunophenotyping of the lymphoid infiltrate of MC has shown that most cells correspond to mature T lymphocytes, a profile similar to that observed in common ductal carcinomas [214]. Evidence of polyclonality of the B-cell infiltrate has been obtained [1510]. Plasma cells were found to express IgG [1310] or IgA [1254]. The recent finding of an increased number of activated cytotoxic lymphocytes in MC may correspond to an active host versus tumour response [3169]. Expression of HLA class I and class II molecules by carcinoma cells, as a cause or a consequence of the immune response, was reported to characterize MC [840]. Although EBV-associated lymphoepithelioma shares some morphological features with MC, only a few cases were found associated with EBV, in contrast with the 31-51% rate of EBV-positive common ductal carcinomas [310,857].

**Genetics**

A high frequency of MC has been reported in patients with BRCA1 germ line mutation, whereas this observation was less common among patients with BRCA2 mutation or with no known germ line mutation. Typical MC were observed in 7.8% [1767] to 13% [8] of BRCA1-associated carcinomas, versus 2% in control populations. However, the presence of medullary features was found in 35% [1767] to 60% [121] of tumours arising in BRCA1 carriers. Reciprocally, in a population of MC, germ line mutations of BRCA1 were observed in 11% of the cases [764]. There is thus a large overlap between medullary features and the phenotype of BRCA1 germ line associated tumours, but not all BRCA1 mutations lead to medullary phenotype.

MC are also characterized by a high rate of TP53 alterations. Somatic mutations were found in 39% [1766] to 100% [643] of MC, together with protein accumulation in 61-87% of the cases [643,711,1345]. This contrasts with the 25-30% rate of TP53 alterations found in common ductal carcinomas [643,711,1345]. No specific TP53 mutation was found to characterize MC [643] but TP53 overstaining may be considered as a biological marker of MC. Both TP53 and BRCA1 are involved in the process of DNA repair and the alteration of these genes, together with a high proliferation rate, may account for the high sensitivity of MC to radio- and/or chemotherapy.

**Prognosis and predictive factors**

MC has been reported to have a better prognosis than the common IDC [1339,1740,1908,2204,2334,2352,2367,2370,3064] but this has been questioned by others [285,771,876]. The overall 10-year-survival reported for MC varies between about 50% [285,771,1740] to more than 90% [1339,2334,3064]. Differences in diagnostic criteria may account for this disparity and several reports underline that stringency in diagnostic criteria is required to preserve the anatomo-clinical identity of MC [876,2334,2370,3064] which is justified by the characteristic prognosis of this tumour. The outcome of MC associated with more than three metastatic axillary lymph nodes has been reported to be poor [285,1740,2202] or no different from that of common ductal tumours [876,2352]. However, less than 10% of MC [876,1339,2334,2352,2370] present with node metastases, and this might account in part for the relatively favourable overall prognosis of MC.

**Fig. 1.27** Medullary carcinoma. The tumour is composed of a syncytial sheet of large pleomorphic cells. There is no glandular differentiation. The adjacent stroma contains numerous plasma cells and mature lymphocytes.

**Fig. 1.28** Medullary carcinoma. Note multinucleated malignant cells with atypical mitoses.

**Table 1.06** Histological criteria required for a diagnosis of MC.

- Syncytial growth pattern (> 75%)
- Absence of glandular structures
- Diffuse lymphoplasmacytic infiltrate, moderate to marked
- Nuclear pleomorphism, moderate to marked
- Complete histological circumscription
Mucin producing carcinomas

Definition
A variety of carcinomas in the breast are characterized by production of abundant extracellular and/or intracellular mucin. Among these are mucinous (colloid) carcinoma, mucinous cystadenocarcinoma, columnar cell mucinous carcinoma and signet ring cell carcinoma.

Mucinous carcinoma
Mucinous carcinoma is characterized by a proliferation of clusters of generally small and uniform cells floating in large amounts of extracellular mucus often visible to the naked eye.

ICD-O code
8480/3

Synonyms
Colloid carcinoma, mucoid carcinoma, gelatinous carcinoma.

Epidemiology
Pure mucinous carcinoma accounts for about 2% of all breast carcinomas {2338,2590,2934}. It occurs in a wide age range, but the mean and median age of patients with mucinous carcinoma in some studies is somewhat higher than that of regular infiltrating carcinomas, being often over 60 years {2447,2590}. A notable proportion of the lesions have neuroendocrine differentiation {150,855} easily demonstrable by Grimelius stain or immunoreaction for chromogranin and synaptophysin (see also neuroendocrine carcinoma of breast).

Clinically, pure and mixed variants of mucinous carcinoma have been described {1498,2934}. A pure tumour must be composed entirely of mucinous carcinoma. The pure mucinous carcinomas are further subdivided into cellular and hypocellular variants. The former is more likely to have intracytoplasmic mucin and argyrophilic granules. As soon as another pattern becomes evident as a component of the tumour mass, the lesions qualifies as a mixed tumour (the proportion of the different components should be noted). The most common admixture is with regular invasive duct carcinoma.

Differential diagnosis
The two lesions most likely to be confused with mucinous carcinoma are myxoid fibroadenoma and mucocoele like lesion {2417}. The presence of compressed spaces lined by epithelial and readily recognizable. The tumours range in size from less than 1 cm to over 20 cm, with an average of 2.8 cm {1498,2338,2447,2934}.

Histopathology
Mucinous carcinoma is characterized by proliferation of clusters of generally uniform, round cells with minimal amounts of eosinophilic cytoplasm, floating in lakes of mucus. Delicate fibrous septae divide the mucous lake into compartments. The cell clusters are variable in size and shape; sometimes with a tubular arrangement; rarely, they assume a papillary configuration. Atypia, mitotic figures and microcalcifications are not common, but occur occasionally. An intraepithelial component characterized by a micropapillary solid pattern is present in 30-75% of the tumours. The lakes of mucin are mucicarmine positive, but intracytoplasmic mucin is rarely present. A notable proportion of the lesions have neuroendocrine differentiation {150,855} easily demonstrable by Grimelius stain or immunoreaction for chromogranin and synaptophysin (see also neuroendocrine carcinoma of breast).

Macroscopy
The typical glistening gelatinous appearance with bosselated, pushing margins and a soft consistency make the lesion readily recognizable. The tumours range in size from less than 1 cm to over 20 cm, with an average of 2.8 cm {1498,2338,2447,2934}.

Histopathology
Mucinous carcinoma is characterized by proliferation of clusters of generally uniform, round cells with minimal amounts of eosinophilic cytoplasm, floating in lakes of mucus. Delicate fibrous septae divide the mucous lake into compartments. The cell clusters are variable in size and shape; sometimes with a tubular arrangement; rarely, they assume a papillary configuration. Atypia, mitotic figures and microcalcifications are not common, but occur occasionally. An intraepithelial component characterized by a micropapillary solid pattern is present in 30-75% of the tumours. The lakes of mucin are mucicarmine positive, but intracytoplasmic mucin is rarely present. A notable proportion of the lesions have neuroendocrine differentiation {150,855} easily demonstrable by Grimelius stain or immunoreaction for chromogranin and synaptophysin (see also neuroendocrine carcinoma of breast).

The descriptive term cellular mucinous carcinoma has been used by some {1751} to differentiate the endocrine variant of mucinous carcinoma from the non-endocrine one; presence of intracytoplasmic neuroendocrine granules does not always correlate with the degree of cellularity, however. Traditionally, pure and mixed variants of mucinous carcinoma have been described {1498,2934}. A pure tumour must be composed entirely of mucinous carcinoma. The pure mucinous carcinomas are further subdivided into cellular and hypocellular variants. The former is more likely to have intracytoplasmic mucin and argyrophilic granules. As soon as another pattern becomes evident as a component of the tumour mass, the lesions qualifies as a mixed tumour (the proportion of the different components should be noted). The most common admixture is with regular invasive duct carcinoma.

Differential diagnosis
The two lesions most likely to be confused with mucinous carcinoma are myxoid fibroadenoma and mucocoele like lesion {2417}. The presence of compressed spaces lined by epithelial and
myoepithelial cells in fibroadenomas, along with mast cells within the myxoid stroma, helps in its recognition. In mucocoele-like lesions, the presence of myoepithelial cells adhering to the strips of cells floating in the lakes of mucus serves as an important clue to their benign nature; the cell clusters in mucinous carcinoma are purely epithelial. The presence of ducts variably distended by mucinous material adjacent to a mucocoele is another helpful clue in distinguishing mucocoele-like lesions from mucinous carcinomas.

**Immunoprofile and ploidy**

Typically mucinous carcinoma is estrogen receptor positive (2669), while less than 70% (691) are progesterone receptor positive. Nearly all pure mucinous carcinomas are diploid, while over 50% of the mixed variety are aneuploid (2933).

**Prognosis and predictive factors**

Prognostic factors relevant to breast carcinomas in general are also applicable to pure mucinous carcinomas. Tumour cellularity has also been implicated in that cellular tumours are associated with a worse prognosis (502). The presence or absence of argyrophilic granules had no prognostic significance in two studies (2590,2934). In general, pure mucinous carcinomas have a favourable prognosis (844,2590,2934). The ten-year survival ranges from 80% (1149) to 100% (844,2053). Pure mucinous carcinomas have a far better prognosis than the mixed variety with at least a 18% difference in survival rates noted in several studies (1498,2053,2934). About 10% of women with the pure form die of their cancer compared to 29% of those with the mixed type (1498,2053). A similar difference also exists in the incidence of axillary node metastases for pure and mixed types; only 3-15% of the pure variety show axillary node metastases compared to 33-46% of the mixed type (82,1498,2338). Late distant metastases may occur (502,2447,2934).

A rare cause of death among women with mucinous carcinoma is cerebral infarction due to mucin embolism to the cerebral arteries (2944).

**Mucinous cystadenocarcinoma and columnar cell mucinous carcinoma**

**Definition**

A carcinoma composed of generally tall, columnar cells with basally located bland nuclei and abundant intracytoplasmic mucin that appears either cystic (mucinous cystadenocarcinoma) or solid (columnar cell mucinous carcinoma) to the naked eye.

**ICD-O code**

Mucinous cystadenocarcinoma 8470/3

**Epidemiology**

Only four examples of mucinous cystadenocarcinoma and two of the solid columnar cell type have been reported (1486). They occurred in women 49 to 67 years of age.

**Clinical features**

The clinical features of mucinous cystadenocarcinomas are similar to common infiltrating ductal carcinomas.

**Macroscopy**

The tumours vary in size from 0.8 to 19 cm, are cystic and display a gelatinous appearance with abundant mucoid material simulating an ovarian mucinous tumour.

**Histopathology**

Microscopically, both of these variants, are composed of tall columnar mucinous cells with abundant intracytoplasmic mucin and basal nuclei. In the
Cystic variant numerous cysts of variable size are formed, some with papillary fronds lined by a single layer of predominately bland appearing, columnar mucinous cells. Focal atypia characterized by nuclear pleomorphism (but sparse mitotic activity), loss of polarity and eosinophilic cellular transformation is invariably present, as is invasion of surrounding stroma by most often the eosinophilic cells. Axillary node metastases occur in a quarter of mucinous cystadenocarcinomas. The columnar cell variant is composed of a compact to loose aggregation of round and convoluted glands lined by a single layer of generally tall, columnar mucinous epithelium with bland, basal nuclei and rare mitotic figures.

**Prognosis and predictive factors**

After a maximum follow-up of only 2 years, none of the patients has developed a recurrence or metastasis.

**Signet ring cell carcinoma**

**ICD-O code** 8490/3

Signet ring cell carcinomas are of two types. One type is related to lobular carcinoma and is characterized by a large intracytoplasmic lumina which compress the nuclei towards one pole of the cell (1849). Their invasive component has the targetoid pattern of classical lobular carcinoma. The other type is similar to diffuse gastric carcinoma, and is characterized by acidic mucussubstances that diffusely fill the cytoplasm and dislodge the nucleus to one pole of the cell. This type of signet ring cell carcinoma can be seen in association with the signet ring cell variant of DCIS (1143).

**Neuroendocrine tumours**

**Definition**

Primary neuroendocrine (NE) carcinomas of the breast are a group, which exhibits morphological features similar to those of NE tumours of both gastrointestinal tract and lung. They express neuroendocrine markers in more than 50% of the cell population. Breast carcinoma, not otherwise specified, with focal endocrine differentiation, revealed by immunocytochemical expression of neuroendocrine markers in scattered cells, is not included this group.

**Synonym**

Endocrine carcinoma.

**Epidemiology**

NE breast carcinomas represent about 2-5% of breast carcinomas. Most patients are in the 6th or 7th decades of life (2535). Neuroendocrine differentiation also occurs in male breast carcinoma (2591).

**Clinical features**

There are no notable or specific differences in presentation from other tumour types. Patients often present with a palpable nodule, which usually appears as a circumscribed mass on mammographic and ultrasound examination. Patients with small cell carcinoma often present at an advanced stage.

Endocrine hormone related syndromes are exceptionally rare. Of interest is the increase in the blood of neuroendocrine markers such as chromogranin A.

**Macroscopy**

NE breast carcinomas can grow as infiltrating or expansile tumours. The consistency of tumours with mucin production is soft and gelatinous.

**Histopathology**

Most NE breast carcinomas form alveolar structures or solid sheets of cells with a tendency to produce peripheral palisading. However, they may present as different subtypes, depending on the cell type, grade, degree of differentiation and presence of mucin production. The latter is observed in 26% of cases (2535).

**Solid neuroendocrine carcinoma**

These tumours consist of densely cellular, solid nests and trabeculae of cells that vary from spindle to plasmacytoid and large clear cells (2536) separated by delicate fibrovascular stroma. In some tumours, the nests are packed into a solitary, well defined to lobulated mass; the tumour cells rarely form rosette-like structures and display peripheral palisading reminiscent of carcinoid tumour. Some of these appear to originate from solitary, solid papillary intraductal carcinomas. Others form multiple, often rounded solid nests separated by a dense, collagenous stroma resembling the alveolar pattern of invasive lobular carcinoma. Mitotic activity ranges from 4 in the carcinoid-like tumour to 12 in the alveolar variant; focal necrosis may be seen. The tumour cells contain NE granules.

**Small cell / oat cell carcinoma**

**ICD-O codes**

Small cell carcinoma 8041/3

Oat cell carcinoma 8042/3

This is morphologically indistinguishable from its counterpart in the lung on the basis of histological and immunohistochemical features (2662). The tumours are composed of densely packed hyperchromatic cells with scant cytoplasm and display an infiltrative growth pattern. An in situ component with the same cytological features may

---

*Table 1.07*

Criteria for the differential diagnosis of mucin producing carcinomas.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Location of mucin</th>
<th>Growth pattern</th>
<th>In situ component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous (colloid) carcinoma</td>
<td>Extracellular</td>
<td>Clusters of cells in mucus lakes</td>
<td>Ductal</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>Intracellular and extracellular</td>
<td>Large cysts, columnar cells, epithelial stratification, papillae, solid areas</td>
<td>Ductal</td>
</tr>
<tr>
<td>Columnar mucinous carcinoma</td>
<td>Intracellular</td>
<td>Round and convoluted glands lined by a single layer of columnar cells</td>
<td>Ductal</td>
</tr>
<tr>
<td>Signet ring cell carcinoma</td>
<td>Intracellular</td>
<td>Isolated cells, cords, clusters</td>
<td>Mainly lobular</td>
</tr>
</tbody>
</table>

---

*32 Tumours of the breast*
be present. Areas of tumour necrosis containing pyknotic hyperchromatic nuclei are rarely detectable. Crush artefact and nuclear streaming occur, but are more typical of aspiration cytology samples. Lymphatic tumour emboli are frequently encountered.

**Large cell neuroendocrine carcinoma**

**ICD-O code** 8013/3

These poorly differentiated tumours are composed of crowded large clusters of cells, with moderate to abundant cytoplasm, nuclei with vesicular to finely granular chromatin and a high number of mitotic figures ranging from 18 to 65 per 10 hpf. Focal areas of necrosis are present [2535]. These tumours exhibit neuroendocrine differentiation similar to those encountered in the lung (see also below).

**Differential diagnosis**

A nodule of NE carcinoma in the breast may reflect metastatic carcinoid or small cell carcinoma from another site [2022]. Immunohistochemistry may help to distinguish between metastatic and primary small cell carcinomas. Mammary small cell carcinomas are cytokeratin 7-positive and cytokeratin 20-negative, whereas, for example, pulmonary small cell carcinomas are negative for both [2662]. The presence of DCIS with similar cytological features is supportive of breast origin. In addition, the expression of estrogen (ER) and progesterone receptors (PR) and of the apocrine marker GCDFP-15, which is frequently expressed by well and moderately differentiated endocrine breast carcinomas [2535], are supportive of a primary breast carcinoma. Mammary small cell carcinoma can be confused histologically with lobular carcinoma. The negative immunoreaction for E-cadherin in lobular carcinomas, in contrast to a positive reaction in 100% of small cell carcinomas, is useful in the differential diagnosis [2661].

It is also important to differentiate neuroendocrine breast carcinomas from carcinomas with neuroendocrine differentiation. The latter have immunexpression for neuroendocrine markers in scattered cells; this feature is noted in 10-18% of breast carcinomas of the usual type. Such focal neuroendocrine differentiation does not seem to carry a special prognostic or therapeutic significance [1876].

**Immunoprofile**

Argyrophilia demonstrated by Grimelius silver precipitation is a feature of neuroendocrine breast carcinomas. Only darkly granulated cells should be considered as argyrophilic [2536]. Expression of chromogranin proteins and/or synaptophysin also confirmed

---

**Fig. 1.33 Neuroendocrine carcinoma. A** Tumour cells are polarized around lumina; some cells show eosinophilic granules — carcinoid-like pattern. **B** IHC staining is positive for chromogranin.

**Fig. 1.34 Neuroendocrine carcinoma of the breast.** Alveolar pattern with rounded solid nests of spindle cells invading a dense collagenous stroma.
evidence of neuroendocrine differentiation [2533]. These proteins are identifiable by immunohistochemical and immunoblot analysis. Poorly and moderately differentiated endocrine breast carcinomas of the alveolar subtype, in general, express chromogranin A. The mRNA specific for chromogranin A is detectable by in situ hybridization technique [2535]. About 50% of well or moderately differentiated tumours express chromogranin B and A and only 16% express synaptophysin (2535). A monoclonal antibody against neuron-specific enolase (NSE) has also been used and is expressed in 100% of small cell carcinomas of the breast [2662], whereas chromogranin A and synaptophysin are expressed in about 50% of such cases. In addition, 20% of small cell mammary carcinomas express thyroid transcription factor-1 (TTF-1) [2661].

Immunodetection of pan-endocrine markers may fail to identify endocrine tumours, which produce but do not retain the specific antigen in the cells. Estrogen (ER) and progesterone receptors (PR) are expressed in the majority of tumour cells in well differentiated tumours [2535], and in more than 50% of small cell carcinomas [2662]. Expression of somatostatin receptors (SSR), a known feature of tumours showing neuroendocrine differentiation, has been demonstrated in endocrine breast carcinomas as well [2169].

**Ultrastructure**

Different types of dense core granules, whose neurosecretory nature is confirmed by ultrastructural immunolocalization of chromogranin A have been identified by electron microscopy in endocrine breast carcinomas [397]. The presence of clear vesicles of pre-synaptic type is correlated with the expression of synaptophysin. Both dense core granules and mucin vacuoles are present in neuroendocrine mucinous carcinomas (1265).

**Genetics**

Neuroendocrine breast carcinomas have not been correlated to specific gene mutations.

**Postulated normal counterpart**

Argyrophilic and chromogranin A-reactive cells, located between the basal myoepithelial and the luminal epithelial cells, have been demonstrated in histologically normal breast tissue surrounding infiltrating and in situ neuroendocrine breast carcinomas (382,1995, 2542,2956).

**Prognosis and predictive factors**

Histological grading is one of the most important prognostic parameters. NE breast carcinomas may be graded using classical criteria described elsewhere. Excluding the rare small cell variety, 45% of NE breast carcinomas are well differentiated, 40% are moderately differentiated, and only 15% are poorly differentiated. Small cell NE carcinomas should be considered as undifferentiated carcinomas [2535]. Mucinous differentiation is a favourable prognostic factor [2535]. The prognosis of primary small cell carcinomas of the breast depends on the stage of disease at the time of diagnosis. It has been demonstrated that low stage small cell carcinomas respond to conventional treatment without progression of the disease at a follow up of 33 to 48 months [2662].

**Invasive papillary carcinoma**

**Definition**

When papillary intraductal carcinomas invade, they generally assume the pattern of infiltrating duct carcinoma and lack a papillary architecture. Most of the published literature concerning papillary carcinomas of the breast probably include both invasive and in situ papillary lesions as they do not generally specify features of an invasive process [413, 603,969,1269,1604,1618,1834]. In this section, however, only data concerning invasive papillary carcinomas will be reviewed. Invasive papillary carcinomas comprise less than 1-2% of invasive breast cancers, and are characterized by a relatively good prognosis (879,2567).

**ICD-O code** 8503/3

**Clinical features**

Invasive papillary carcinomas are diagnosed predominantly in postmenopausal patients. Fisher et al. [879] noted a disproportionate number of cases in non-Caucasian women. Similar to medullary carcinomas, Fisher et al. noted that a significant proportion of patients with invasive papillary carcinoma exhibit axillary lymphadenopathy suggestive of metastatic disease, but which on pathological examination is due to benign reactive changes [879].

Mammographically, invasive papillary carcinoma is usually characterized by nodular densities which may be multiple, and are frequently lobulated (1880, 2567). These lesions are often hypoechoic on ultrasound [1827]. One study noted the difficulty in distinguishing between intracystic papillary carcinoma, intraductal papillary carcinoma with invasion, and invasive papillary carcinoma [1827].

**Fig. 1.35** Invasive papillary carcinoma. A Microfocus magnification image of a papillary carcinoma shows a low density rounded tumour. B Large section histology. C Ultrasonography shows a lobulated, well delineated lesion.
Macrosopy
Fisher et al. reported that invasive papillary carcinoma is grossly circumscribed in two-thirds of cases (879). Other invasive papillary carcinomas are grossly indistinguishable from invasive breast cancers of no special type.

Histopathology
Of the 1,603 breast cancers reviewed in the NSABP-B04 study, 38 had papillary features, and all but 3 of these were "pure," without an admixture of other histologic types (879). Microscopically, expansile invasive papillary carcinomas are characteristically circumscribed, show delicate or blunt papillae, and show focal solid areas of tumour growth. The cells typically show amphophilic cytoplasm, but may have apocrine features, and also may exhibit apical "snouting" of cytoplasm similar to tubular carcinoma. The nuclei of tumour cells are typically intermediate grade, and most tumours are histologic grade 2 (879). Tumour stroma is not abundant in most cases, and occasional cases show prominent extracellular mucin production. Calcifications, although not usually evident mammographically, are commonly seen histologically, but usually are present in associated DCIS. DCIS is present in more than 75% of cases, and usually, but not exclusively, has a papillary pattern. In rare lesions in which both the invasive and in situ components have papillary features, it may be difficult to determine the relative proportion of each. Lymphatic vessel invasion has been noted in one third of cases. Microscopic involvement of skin or nipple was present in 8 of 35 cases (23%), but Paget disease of the nipple was not observed (879). Estrogen receptor positivity was observed in all 5 cases of invasive papillary carcinoma examined in one study, and progesterone receptor positivity in 4 of 5 (80%) (2351). In a review of cytogenetic findings in 5 examples of invasive papillary carcinoma, 60% exhibited relatively simple cytogenetic abnormalities (40). In addition, none of the 4 examples of papillary carcinomas examined in two recent reports were associated with either TP53 protein accumulation or ERBB2 oncoprotein overexpression (2440,2750).

Clinical course and prognosis
There are only limited data on the prognostic significance of invasive papillary carcinoma (868,871,879). Among 35 patients with this tumour in the NSABP-B04 trial, after 5 years median follow-up, there were only 3 treatment failures, including 1 patient who died from metastatic papillary carcinoma. These survival data were similar to those reported in patients with pure tubular and mucinous carcinomas in this study (879). A later publication updating the NSABP-B04 results at 15 years revealed that patients with "favourable" histology tumours (including invasive papillary carcinomas) still had significantly better survival in univariate analysis, but tumour histology was not an independent predictor of survival in multivariate analysis (871). However, node-negative patients with invasive papillary carcinomas enrolled in the NSABP-B06 trial experienced improved survival after 10 years follow-up compared to patients with carcinomas of no special type, and tumour histology was an independent predictor of survival in multivariate analysis (868).

Invasive micropapillary carcinoma

Definition
A carcinoma composed of small clusters of tumour cells lying within clear stromal spaces resembling dilated vascular channels.

ICD-O code 8507/3

Epidemiology
Carcinomas with a dominant micropapillary growth pattern account for less than 2% of all invasive breast cancers (707, 1715,1982,2194,2229). The term invasive micropapillary carcinoma was coined by Siriaunkgul and Tavassoli who first described nine examples of this lesion (707). While quite rare in its pure form, focal micropapillary growth has been reported in 3-6% of more common types of invasive carcinomas [1982,2194]. It occurs in the same age range as invasive ductal carcinoma of no special type.

Clinical features
Invasive micropapillary carcinoma usually presents as a solid mass. Axillary lymph node metastases are present at first presentation in 72-77% [707,1715,1982,2194,2229,3049].

Macrosopy
Pure micropapillary carcinoma has a lobulated outline due to the expansive mode of growth.

Histopathology
Micropapillary carcinoma consists of hollow aggregates of malignant cells, which on cross section have the appearance of tubules with diminished or obliterated lumens rarely containing pyknotic nuclei. These tumour cell cluster lie within artificial stromal spaces caused by shrinkage of the surrounding tissue. The stromal spaces lack an endothelial lining and may be part of a speculated “missing lymphatic labyrinth” in mammary stroma [1152]. Nuclear pleomorphism is moderate, mitotic activity low, and there is neither necrosis nor lymphoecytic reaction. In non-pure tumours, gradual or abrupt transitions from typical invasive ductal carcinoma to the micropapillary components are found. Peritumoural angioinvasion may be present in up to 60% of cases. Intravascular tumour emboli,
lymph node metastases and malignant cells in pleural fluids all show the same arrangement found in the primary tumour.

Prognostic and predictive features
This unusual growth pattern is correlated with the presence of vascular invasion and axillary lymph node metastases. In multivariate analyses, however, a micropapillary growth pattern has no independent significance for survival {1982, 2194}.

Apocrine carcinoma

Definition
A carcinoma showing cytological and immunohistochemical features of apocrine cells in >90% of the tumour cells.

ICD-O code 8401/3

Epidemiology
The reported incidence of apocrine carcinoma depends on the method of detection. Based on light microscopy alone it is only 0.3-4% [149,910]. An ultrastructural study found a frequency of 0.4% for apocrine carcinomas in a prospective series [1926]. Immunohistochemical studies using anti GCDFP-15, a putative marker of apocrine differentiation [1800] gave conflicting data with an incidence ranging from 12% [809] to 72% [3113]. Twenty seven per cent of cases were positive with an in situ hybridization method using a mRNA probe against the sequence of the GCDFP-15 [1700]. In conclusion, carcinomas composed predominantly of apocrine cells constitute at the most 4% of all invasive carcinomas; focal apocrine cells diagnosed either by histology, immunohistochemistry or genetic techniques are frequent and occur in at least 30% of "ordinary" invasive carcinomas [1700].

Clinical features
There is no difference between the clinical or mammographic features, size and site of carcinomas among apocrine and non-apocrine lesions. Bilaterality is rare in apocrine carcinomas.

Histopathology
Any type and grade of breast carcinoma can display apocrine differentiation including ordinary invasive duct carcinomas, tubular, medullary, papillary, micropapillary and neuroendocrine types [17,569,809,1700], as well as classical and pleomorphic invasive lobular carcinomas [802,808]. However, recognition of apocrine carcinoma at present has no practical importance and is only of academic value.

Apocrine lobular in situ neoplasias [802,2534], and apocrine ductal in situ carcinomas (ADCIS) are also well recognized [17,1605,2887]. Apocrine carcinomas, whatever their origin, are usually composed by two types of cells variously intermingled [804]. Type A cell recognized first by most authors has abundant granular intensely eosinophilic cytoplasm. The granules are periodic acid-Schiff positive after diastase digestion. Their nuclei vary from globoid with prominent nucleoli to hyperchromatic. Some tumours, when constituted by a pure proliferation of type A cells, superficially mimic granular cell tumours. This type of apocrine carcinoma has sometimes been referred

Fig. 1.37 Invasive micropapillary carcinoma. Tumour cell clusters with irregular central spaces proliferate within empty stromal spaces. Some clusters have reversed polarity with an "inside out" morphology.

Fig. 1.38 Invasive micropapillary carcinoma. A Note the prominent vascular invasion and occasional pyknotic nuclei within the central spaces. B Lymph node metastasis. C EMA staining of of the peripheral cell membranes suggestive of an 'inside out' morphology.
to as myoblastomatoid [806]. Type B cell shows abundant cytoplasm in which fine empty vacuoles are seen. These latter result in foamy appearance so that the cells may resemble histiocytes and sebaceous cells. Nuclei are similar to those in type A cells. These same cells have been designated as seboeine [2876]. (See also Sebaceous carcinoma, page 46). Carcinosomas composed purely of foamy apocrine cells may superficially resemble a histiocytic proliferation or even an inflammatory reaction [806]. In difficult cases, both granular cell tumours and histiocytic proliferations can be easily distinguished by staining the tumours with keratin antibodies that are positive only in apocrine carcinomas.

**Immunoprofile**

Apocrine carcinomas are typically GCDFP-15 positive and BCL2 protein negative. Expression of GCDFP-15 is a feature common to many variants of breast carcinoma, however, and has been used to support breast origin in metastatic carcinomas of unknown primary site. Estrogen and progesterone receptors are usually negative in apocrine carcinoma by immunohistochemical assessment. Interestingly, many ER-, PR- apocrine carcinomas do have the ERαRNA, but fail to produce the protein [336]. The expression of other biological markers is in general similar to that of other carcinomas [177,1605,2425]. Androgen receptors have been reported as positive in 97% of ADCIS in one series [1605]. The expression of other biological markers is in general similar to that of other carcinomas [177,1605,2425]. Androgen receptors have been reported as positive in 97% of ADCIS in one series [1605]. The expression of other biological markers is in general similar to that of other carcinomas [177,1605,2425].

**Metaplastic carcinomas**

**Definition**

Metaplastic carcinoma is a general term referring to a heterogeneous group of neoplasms generally characterized by an intimate admixture of adenocarcinoma with dominant areas of spindle cell, squamous, and/or mesenchymal differentiation; the metaplastic spindle cell and squamous cell carcinomas may present in a pure form without any admixture with a recognizable adenocarcinoma. Metaplastic carcinomas can be classified into broad subtypes according to the phenotypic appearance of the tumour.

**ICD-O code** 8575/3

**Synonyms**

Matrix producing carcinoma, carcinosarcoma, spindle cell carcinoma.

**Epidemiology**

Metaplastic carcinomas account for less than 1% of all invasive mammary carcinomas [1273]. The average age at presentation is 55.

**Clinical features**

Clinical presentation is not different from that of infiltrating duct NOS carcinoma.

Most patients present with a well circumscribed palpable mass, with a median size of 3-4 cm, in some reports more than half of these tumours measure over 5 cm, with some massive lesions (>20 cm) which may displace the nipple and ulcerate through the skin. On mammography, most metaplastic carcinomas appear as well delineated mass densities. Microcalcifications are not a common feature, but may be present in the adenocarcinomatous areas; ossification, when present, is, of course, apparent on mammography.

**Macroscopy**

The tumours are firm, well delineated and often solid on cut surface. Squamous or chondroid differentiation is reflected as pearly white to firm glistening areas on the cut surface. One large and/or multiple small cysts may be apparent on the cut surface of larger squamous tumours.

**Table 1.08**

Classification of metaplastic carcinomas.

<table>
<thead>
<tr>
<th>Purely epithelial</th>
<th>Squamous</th>
<th>Large cell keratinizing spindle cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acantholytic</td>
<td>Adenocarcinoma with spindle cell differentiation</td>
</tr>
<tr>
<td>Mixed epithelial and Mesenchymal (specify components)</td>
<td>Carcinoma with chondroid metaplasia</td>
<td>Carcinoma with osseous metaplasia</td>
</tr>
<tr>
<td></td>
<td>Carcinosarcoma (specify components)</td>
<td></td>
</tr>
</tbody>
</table>

Invasive breast cancer 37
Squamous cell carcinoma

A breast carcinoma entirely composed of metaplastic squamous cells that may be keratinizing, non-keratinizing or spindled; they are neither derived from the overlying skin nor represent metastases from other sites.

ICD-O codes
Squamous cell carcinoma 8070/3
Large cell keratinizing variant 8071/3
Spindle cell variant 8074/3
Acantholytic variant 8075/3

Histopathology
Squamous cell carcinomas assume several phenotypes including large cell keratinizing, non-keratinizing, and less frequently spindle cell and acantholytic types; some show a combination of these patterns [752,987,1022, 1928,2520,2932,3061]. The most bland appearing and well differentiated cells often line cystic spaces; as the tumour cells emanate out to infiltrate the surrounding stroma, they become spindle shaped and lose their squamous features. A pronounced stromal reaction is often admixed with the spindled squamous carcinoma. The squamous differentiation is retained in metastatic foci. Squamous cell carcinoma can be graded based mainly on nuclear features and, to a lesser degree, cytoplasmic differentiation.

Immunoprofile
The spindle cell and acantholytic variants require immunohistochemical confirmation of their epithelial nature. The epithelial tumour cell components are positive for broad spectrum and high molecular weight cytokeratins (CK5 and CK34betaE12), but negative for vascular endothelial markers. Nearly all squamous cell carcinomas are negative for both estrogen (ER) and progesterone receptors (PR) [3059,3061].

Adenocarcinoma with spindle cell metaplasia

Definition
An invasive adenocarcinoma with abundant spindle cell transformation. The spindle cells are neither squamous, nor mesenchymal, but rather glandular in nature.

ICD-O code 8572/3

Clinical features
This tumour occurs mainly in postmenopausal women and presents as a discrete mass.

Pathologic features
Macroscopically, a well circumscribed, solid mass, the tumour is composed of tubules of adenocarcinoma admixed with neoplastic spindle cells. The spindle cells immunoreact with epithelial markers including CK7, but not with CK5,6 or other markers of squamous/myoepithelial differentiation. At the ultrastructural level, the spindle cells are neither squamous nor mesenchymal, but rather glandular, intermixed with glands.
cells contain intracytoplasmic lumens confirming a glandular cell population.

**Adenosquamous carcinoma**

**Definition**
An invasive carcinoma with areas of well developed tubule/gland formation intimately admixed with often widely dispersed solid nests of squamous differentiation.

**ICD-O code** 8560/3

**Histopathology**
While focal squamous differentiation has been observed in 3.7% of infiltrating duct carcinomas [878], a prominent admixture of invasive ductal and squamous cell carcinoma is rarely observed. The squamous component is often keratinizing, but ranges from very well differentiated keratinizing areas to poorly differentiated non-keratinizing foci.

Eight tumours described as examples of low grade mucopidermoid carcinoma, comparable to those occurring in the salivary glands, have been reported in the breast; these behave as low grade carcinomas [1130,1156,1515,1629,1709,2191,2234].

**Immunoprofile**
The squamous component is negative for both ER and PR, while the positivity of the ductal carcinoma component for ER and PR depends on its degree of differentiation.

**Low grade adenosquamous carcinoma**
Low grade adenosquamous carcinoma [2431] is a variant of metaplastic carcinoma which is morphologically similar to adenosquamous carcinoma of the skin and has been classified by some as syringomatous squamous tumour [2816]. The same lesion has been interpreted as an infiltrating syringomatous adenoma by others who prefer to avoid designation of carcinoma for a group of lesions which mainly recur after local excision.

**ICD-O code** 8560/1

**Synonym**
Infiltrating syringomatous adenoma. This entity is also discussed in Tumours of the Nipple.

**Clinical features**
The age range at presentation is wide. These lesions usually present as a small palpable mass between 5 and 80 mm in size.

**Histology**
These tumours are composed of small glandular structure and solid cords of epithelial cells haphazardly arranged in an infiltrative spindle cell stromal component [2421,2995]. The proportions of these three components is variable between cases. The solid nests of cells may contain squamous cells, squamous pearls or squamous cyst formation. The stroma is typically "fibromatosis-like" being cellular and composed of bland spindle cells. The stromal component can, however, be collagenous, hyalinized or variably cellular, and osteocartilaginous foci can occur rarely. It has been recognized that some low grade adenosquamous carcinomas may be found in association with a central sclerosing proliferation such as a radial scar, sclerosing papillary lesion or sclerosing adenosis [672,2421,2995]. The frequen-
cy of ductal carcinoma in situ in association with adenosquamous carcinomas is variable. These tumours lack estrogen receptor expression (672,3142).

Prognosis and predictive factors
The majority of cases have an excellent prognosis, but a proportion of cases can behave in a locally aggressive manner (2995), recurrence appears to be related to adequacy of local excision. Lymph node metastatic spread is extremely rare and noted in a single case that was 3.5 cm (2995).

Mixed epithelial / mesenchymal metaplastic carcinomas

ICD-O code 8575/3

Synonyms
Carcinoma with osseous metaplasia (8571/3), carcinoma with chondroid metaplasia (8571/3), matrix producing carcinoma, carcinosarcoma (8980/3).

Histopathology
This wide variety of tumours, some of which are also regarded as “matrix producing carcinomas” (1414,2953), show infiltrating carcinoma mixed with often heterologous mesenchymal elements ranging from areas of bland chondroid and osseous differentiation to frank sarcoma (chondrosarcoma, osteosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma). When the mesenchymal component is malignant, the designation of carcinosarcoma is used. Undifferentiated spindle cell elements may form part of the tumour. Grading is based mainly on nuclear features and, to a lesser degree, cytoplasmic differentiation.

Immunoprofile
The spindle cell elements may show positive reactivity for cytokeratins, albeit focally. Chondroid elements are frequently S-100 positive and may coexpress cytokeratins, but are negative for actin. Many of these tumours are negative for ER and PR both in the adenocarcinoma and the mesenchymal areas, but the adenocarcinoma component may be ER and PR positive if well to moderately differentiated. In carcinosarcomas, the mesenchymal component fails to immunoreact with any epithelial marker.

Differential diagnosis
The differential diagnosis varies for the different subtypes of metaplastic carcinoma. Angiosarcoma may be confused with the acantholytic variant of squamous cell carcinoma, but focal areas of squamous differentiation can be found when sampled thoroughly. A negative immunoreaction with vascular endothelial markers and a positive reaction with cytokeratins will support the diagnosis of an epithelial neoplasm. Fibromatosis and a variety of spindled mesenchymal tumours may be confused with spindle cell squamous carcinoma; these are all generally negative for epithelial markers. Myoepithelial carcinoma is the most difficult lesion to distinguish from spindle cell squamous carcinoma. The former often has ducts with prominent to hyperplastic myoepithelial cells at its periphery, while the latter may have clear cut focal squamous differentiation. Reactions to a variety of immunostains may be similar, with the possible exception of those myoepithelial carcinomas that are diffusely S-100 positive. Electron microscopy may be needed to distinguish some of these lesions. Squamous carcinoma cells have abundant tonofilaments and well developed desmosomes whether spindled or polygonal. Intercellular bridges are abundant in the well differentiated areas. In contrast, the spindle cell myoepithelial carcinomas often have pinocytotic vesicles, myofiibrils and basal lamina in addition to tonofilaments and desmosomes.
The squamous and adenosquamous carcinoma should be distinguished from pleomorphic carcinomas that may have either pattern admixed with a large number of bizarre tumour giant cells; this distinction is important as pleomorphic carcinomas are far more aggressive than either squamous or adenosquamous carcinoma. Adenocarcinomas with chondroid differentiation should be distinguished from pleomorphic adenomas. Pleomorphic adenomas invariably have a myoepithelial cell component (that may be dominant in some tumours) growing around spaces lined by benign epithelial cells. Myoepithelial cells are not evident in adenocarcinomas with chondroid differentiation.

**Prognosis and predictive factors of metaplastic carcinomas**

Given the tumour size of >3-4 cm in many cases, metastases to axillary nodes are relatively uncommon; approximately 10-15% of pure squamous cell carcinomas have axillary node metastases (503,1928). About 19-25% of those with chondro-osseous elements have axillary node metastases (752,1273,2259), and 21% have distant metastases (752). Axillary node metastases were more common (56%) among tumours with spindle and squamous metaplasia in Huvos’s study (239), however. When metaplastic carcinomas metastasize to the axillary nodes or beyond, they retain and often manifest their metaplastic potential. In studies combining carcinomas with chondroid and osseous metaplasia, the five year survival has ranged from 28-68% (474,1273,3060), those with spindle or squamous differentiation have a 63% 5-year survival (1273). Advanced stage and lymph node involvement is associated with a more aggressive course as anticipated. Among squamous cell carcinomas, the acantholytic variant may exhibit a more aggressive behaviour (807).

The carcinosarcomas are very aggressive tumours. Some metastasize as mixed epithelial and mesenchymal tumours, while only the epithelial or the sarcomatous component may metastasize in others. There is not much information available on the efficacy of current therapies in the management of metaplastic carcinomas.

**Lipid-rich carcinoma**

**Definition**

A breast carcinoma in which approximately 90% of neoplastic cells contain abundant cytoplasmic neutral lipids.

**ICD-O code** 8314/3

**Synonym** Lipid secreting carcinoma.

**Epidemiology**

Using conventional morphological features only (i.e. foamy to vacuolated clear cells), incidences of <1-6%, have been reported (28,2330,2988). Four cases only were seen within a 12-year period at the AFIP (2876). A frequency of 0.8% was found in a study using Sudan III on frozen sections (3158). The age of patients with putative lipid rich carcinoma ranges from 33 to 81 years. All except one were female, the exception being a 55-year-old man (1803).

**Clinical features**

Most patients have palpable nodules. One case presented as Paget disease of the nipple (28).

**Macroscopy**

The tumour size in the cases reported varies from 1.2 to 15 cm (3158).

**Histopathology**

Lipid-rich carcinoma should be distinguished from other carcinomas with vacuolated, clear cytoplasm (702). If histochemical methods are employed on frozen breast carcinomas, up to 75% contain cytoplasmic lipid droplets, but only 6% in large quantities (873); only these cases should be designated lipid-rich carcinoma. Histology shows a grade III invasive carcinoma in most cases. There may be associated in situ lobular or ductal carcinoma (28,2330). The neoplastic cells have large, clear, foamy to vacuolated cytoplasm in which neutral lipids should be demonstrable (2876). The tumour cells are devoid of mucins. Alpha lactalbumin and lactoferrin were found in five cases while fat globule membrane antigen was evident in occasional cells only (3158).
Lobular neoplasia

Definition
Characterized by a proliferation of generally small and often loosely cohesive cells, the term lobular neoplasia (LN) refers to the entire spectrum of atypical epithelial proliferations originating in the terminal duct-lobular unit (TDLU), with or without pagetoid involvement of terminal ducts. In a minority of women after long-term follow-up, LN constitutes a risk factor and a nonobligatory precursor for the subsequent development of invasive carcinoma in either breast, of either ductal or lobular type.

ICD-O code
Lobular carcinoma in situ (LCIS) 8520/2

Synonyms and historical annotation
The designations atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) have been widely used for variable degrees of the lesion. Two series published in 1978 [1100, 2438] concluded that the features generally used to subdivide the lobular changes into LCIS and ALH were not of prognostic significance. To avoid overtreatment, Haagensen suggested the designation lobular neoplasia (LN) for these lesions [1100]. To emphasize their non-invasive nature, the term lobular intraepithelial neoplasia (LIN) has been proposed. Based on morphological criteria and clinical outcome, LIN has been categorized into three grades [338].

Epidemiology
The frequency of LN ranges from less than 1% [3106,3107] to 3.8 % [1099] of all breast carcinomas. It is found in 0.5-4% of otherwise benign breast biopsies [2150]. Women with LN range in age from 15 [32] to over 90 years old [2876], but most are premenopausal.

Clinical features
The lesion is multicentric in as many as 85% of patients [2446,2876] and bilateral in 30% [1096] to 67% [2001] of women who had been treated by bilateral mastectomy. No mammographic abnormalities are recognized [2128,2273], except in the occasional variant of LN characterized by calcification developing within central necrosis [2534].

Macroscopy
LN is not associated with any grossly recognizable features.

Histopathology
The lesion is located within the terminal duct-lobular unit (TDLU1) with pagetoid involvement of the terminal ducts evident in as many as 75% of cases [86,1096]. On low power examination, while lobular architecture is maintained, the acini of one or more lobules are expanded to varying degrees by a monomorphic proliferation of loosely cohesive, usually small cells, with uniform round nuclei, indistinct nucleoli, uniform chromatin and rather indistinct cell margins with sparse cytoplasm. Necrosis and calcification are uncommon and mitoses are infrequent. Intracytoplasmic lumens are often present but are not specific to LN [89]. In some lesions, however, the proliferating cells are larger and more pleomorphic or of signet ring type. Apocrine metaplasia occurs but the existence of endocrine variant of LN [801] is disputed. Two types of LN have been recognized [1100]: Type A with the more usual morphology described above and Type B composed of larger, more atypical cells with less uniform chromatin and conspicuous nucleoli. The two cell types may be mixed. When composed of pleomorphic cells, the term pleomorphic LN has been used. The neoplastic cells either replace or displace the native epithelial cells in the TDLU. The myoepithelial cells may remain in their original basal location or they may be dislodged and admixed with the neoplastic cells. The basement membrane is generally intact although this is not always visible in all sections. Pagetoid involvement of adjacent ducts between intact overlying flattened epithelium and underlying base ment membrane is frequent and can result in several different patterns including a ‘clover leaf’ or ‘necklace’ appearance [1099]. Solid obliteration of acini may occur, sometimes with massive dis tension and central necrosis. LN may involve a variety of lesions including sclerosing adenosis, radial scars, papillary lesions, fibroadenomas and collagenous spherulosis.

Immunoprofile
LN is positive for estrogen receptor (ER) in 60-90% of cases and in a slightly lower percentage for progesterone receptor (PR) [62,369,1010,2159,2483]. The classical variety of LN is more likely to be positive than the pleomorphic variant [223,2683]. Unlike high grade DCIS, however, classic LN rarely expresses ERBB2 or TP53 protein [62,2327a,2483,2746]. Positivity is more likely with the pleomorphic variant [1859,2683]. Intra-

Fig. 1.74 Early lobular neoplasia. A The few neoplastic lobular cells are hardly apparent on a quick examination of the TDLU. B Double immunostaining with E-cadherin (brown) and CK34BE12 (purple) unmasks the few neoplastic cells (purple) proliferating in this lobule. These early lesions are often missed on H&E stained sections.
cytoplasmic immunoreactivity for casein has also been reported (1994, 2149). E-cadherin, commonly identified in ductal lesions, is generally absent from both LN and invasive lobular carcinoma (1892, 2336).

Grading
A three-tiered grading system has been suggested, based on the extent and degree of proliferation and/or cytological features. Those lesions with markedly distended acini, often with central necrosis, and those composed of either severely pleomorphic cells or pure signet ring cells with or without acinar distension, were designated LIN 3; they have been reported to be often associated with invasive carcinoma (2876). This grading system requires validation by other centres and is not endorsed at this time.

Differential diagnosis
Poor tissue preservation may give a false impression of loosely cohesive cells leading to over-diagnosis of LN. Distinction from a solid DCIS can be difficult on morphological grounds alone, particularly when DCIS remains confined to the lobule without unfolding it (so-called lobular cancerization). The presence of secondary lumina or a rosettelike arrangement of cells indicates a ductal lesion. In problematic cases, the immunoprofile may be helpful. LN is typically E-cadherin and CK 5,6 negative, but HMW CK34BE12 positive [337]. DCIS, on the other hand, is typically E-cadherin positive, but CK34BE12 negative. Occasional lesions are negative or positive for both HMWCK34BE12 and E-cadherin markers. Since, at present, it is uncertain how these morphologically and immunohistochemically hybrid lesions with ductal and lobular features would behave, it is important that they are recognized so that more can be learned about their nature in the future [337].

When LN involves sclerosing adenosis or other sclerosing lesions, it can be confused with an invasive carcinoma. The presence of a myoepithelial cell layer around the neoplastic cell clusters excludes the possibility of an invasive carcinoma; immunostaining for actin can unmask the myoepithelial cells, thus facilitating the distinction.

Molecular genetics
Loss of heterozygosity (LOH) at loci frequently observed in invasive carcinoma has also been reported in LN, ranging from 8% on chromosome 17p to 50% on 17q [1569]. LOH on chromosome 16q, the site of the E-cadherin gene, was found in approximately 30%. LOH was identified in LN associated with invasive carcinoma and in pure LN, suggesting that it may be a direct precursor of invasive lobular cancer. Further support for this hypothesis has come from a report that showed LOH in 50% of LN associated with invasive carcinoma at markers on chromosome 11q13 [1988]. LOH was seen in 10% of ALH and 41% of invasive lobular carcinomas. Using comparative genomic hybridization (CGH), loss of chromosomal material from 16p, 16q, 17p and 22q and gain of material to 6q was identified in equal frequency in 14 ALH and 31 LCIS.
Tumours of the breast

lesions [1707], suggesting that both are ‘neoplastic’ and at a similar stage of genetic evolution.

The most direct evidence for a precursor role of LN comes from mutational analysis of the E-cadherin gene [259,260]. In one study [261], 27 of 48 (56%) invasive lobular carcinomas had mutation in the E-cadherin gene, while none of 50 breast cancers of other types showed any alteration. It was subsequently demonstrated that truncating mutations identified in invasive lobular carcinoma were also present in the adjacent LN, providing direct proof that LN was a precursor lesion [3034].

Prognosis and predictive factors

The relative risk (RR) for subsequent development of invasive carcinoma among patients with LN ranges from 6.9 to about 12 times that expected in women without LN [87,88,1100].

Amongst 1174 women in 18 separate retrospective studies, diagnosed as having LN and treated by biopsy alone, 181 (15.4%) eventually developed invasive carcinoma [88,1096,1100,2150,2428, 2438]. Of these, 102 (6.7%) developed in the ipsilateral breast, and 79 (6.7%) in the contralateral breast, demonstrating an almost equal risk for either breast. However, in a prospective study of 100 cases of LN with 10 years of follow-up, 11 of 13 invasive recurrences were ipsilateral [2127].

With extended follow-up, the risk of development of invasive cancer continues to increase to 35% for those women who survive 35 years after their initial diagnosis of LN. Furthermore, the RR increases substantially from 4.9 (95% CI: 3.7–6.4) after one biopsy with LN to 16.1 (95% CI: 6.9–31.8) after a second biopsy with LN [298].

Early studies suggested that among LN lesions, there are no clinical or pathological features associated with increased risk of subsequent invasive carcinoma [2150,2438]. However, a more recent study using the three tiered grading system, but with a comparatively short follow-up of 5 years, found that LIN 3 and, to a lesser extent LIN 2, were associated with an increased risk [869], but LIN 1 was not. In another study, 86% of invasive carcinomas associated with LIN 3 were lobular in type, in contrast to 47% of those associated with LIN 2 and only 11% of those associated with LIN 1 [338].

Management of LN has evolved with increased understanding of the disease [1082]. The current consensus is that LN constitutes a risk factor and a non obligate precursor for subsequent development of invasive carcinoma in either breast, of either ductal or lobular type, but only in a minority of women after long-term follow-up. The current recommended management for LN is, therefore, life long follow-up with or without tamoxifen treatment. Re-excision should be considered in cases of massive acinar distension, and when pleomorphic, signet ring or necrotic variants are identified at or close to the margin.
Intraductal proliferative lesions

Definition
Intraductal proliferative lesions are a group of cytologically and architecturally diverse proliferations, typically originating from the terminal duct-lobular unit and confined to the mammary duct lobular system. They are associated with an increased risk, albeit of greatly different magnitudes, for the subsequent development of invasive carcinoma.

ICD-O codes
In the ICD-O classification, /2 is used for in situ carcinomas. The code 8500/2 covers all grades of ductal carcinoma in situ and ductal intraepithelial neoplasia, grade 3.

Site of origin and route of lesion progression
A vast majority of intraductal proliferative lesions originate in the terminal duct-lobular unit (TDLU) [3091]. A substantially smaller proportion originates in larger and lactiferous ducts. Segmentally distributed, ductal carcinoma in situ (DCIS) progression within the duct system is from its origin in a TDLU toward the nipple and into adjacent branches of a given segment of the duct system. The rare lesions that develop within the lactiferous ducts may progress toward the nipple resulting in Paget disease or to the adjacent branches of a reference duct [2089,2090,2093].

Terminology
Intraductal proliferative lesions of the breast have traditionally been divided into three categories: usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS). It should be noted, however, that the term “DCIS” encompasses a highly heterogeneous group of lesions that differ with regard to their mode of presentation, histopathological features, biological markers, and risk for progression to invasive cancer. In most cases, the histopathological distinction between different types of intraductal proliferation can be made on morphological grounds alone, particularly with standardization of histopathological criteria. However, even then, the distinction between some of the lesions (particularly between ADH and some low grade forms of DCIS) remains problematic. In addition, population-based mammography screening has resulted in increased detection of lesions that show cytological atypia with or without intraluminal proliferation but do not fulfill the diagnostic criteria for any of the existing categories. Those lesions lacking intraluminal projection have been described in the past as clinging carcinoma and more recently referred to under a variety of names including flat epithelial atypia, atypical cystic lobules, atypical columnar alteration with prominent apical snouts and secretions.

Progression to invasive breast cancer
Clinical follow-up studies have indicated that these intraductal proliferative lesions are associated with different levels of risk for subsequent development of invasive breast cancer, that ranges from approximately 1.5 times that of the reference population for UDH, to 4-5-fold (range, 2.4-13.0-fold) for ADH, and 8-10-fold for DCIS [886]. Recent immunophenotypic and molecular genetic studies have provided new insights into these lesions indicating that the long-held notion of a linear progression from normal epithelium through hyperplasia, atypical hyperplasia and carcinoma in situ to invasive cancer is overly simplistic; the inter-relationship between these various intraductal proliferative lesions and invasive breast cancer is far more complex. In brief, these data have suggested that: (1) UDH shares few similarities with most ADH, DCIS or invasive cancer; (2) ADH shares many similarities with low grade DCIS; (3) low grade DCIS and high grade DCIS appear to represent genetically distinct disorders leading to distinct forms of invasive breast carcinoma, further emphasizing their heterogeneity; and (4) at least some lesions with flat epithelial atypia are neoplastic. These data support the notion that ADH and all forms of DCIS represent intraepithelial neoplasias which in the WHO classification of tumours of the digestive system have been defined as ‘lesions characterized by morphological changes that include altered architecture and abnormalities in cytology and differentiation, they result from clonal alterations in genes and carry a predisposition, albeit of variable magnitude, for invasion and metastasis’ [1114]. The WHO Working Group felt that UDH is not a significant risk factor and that at the time of the meeting, there was insufficient genetic evidence to classify it as a precursor lesion. However, a recent CGH study suggests that a subset of UDH can be a precursor of ADH [1037].

Classification and grading
These emerging genetic data and the increasingly frequent detection of ADH and low grade DCIS by mammography have raised important questions about the manner in which intraductal proliferative lesions are currently classified. Although used by pathology laboratories worldwide, the traditional classification system suffers from high interobserver variability, in particular, in distinguishing between atypical ductal hyperplasia (ADH) and some types of low grade ductal carcinoma in situ (DCIS). Some members of the Working Group proposed that the traditional terminology be replaced by ductal intraepithelial neoplasia (DIN), reserving the term carcinoma for invasive tumours. This would help to avoid the possibility of overtreatment, particularly in the framework of population-based mammography screening programmes. In several other organ sites, the shift in terminology has already occurred e.g. cervix (CIN), prostate (PIN) and in the recent WHO classification of tumours of the digestive system [1114]. The majority of participants in the WHO Working Group was in favour of maintaining the traditional terminology which in Table 1.11 is shown next to the corresponding terms of the DIN classification. For purposes of clinical management and tumour registry coding, when the
Diagnostic reproducibility
Multiple studies have assessed reproducibility in diagnosing the range of intraductal proliferative lesions, some with emphasis on the borderline lesions (299, 503, 2155, 2157, 2411, 2571, 2723, 2724). These studies have clearly indicated that interobserver agreement is poor when no standardized criteria are used (2411). Although diagnostic reproducibility is improved with the use of standardized criteria (2571) discrepancies in diagnosis persist in some cases, particularly in the distinction between ADH and limited forms of low grade DCIS. In one study, consistency in diagnosis and classification did not change significantly when interpretation was confined to specific images as compared with assessment of the entire tissue section on a slide, reflecting inconsistencies secondary to differences in morphological interpretation (780). While clinical follow-up studies have generally demonstrated increasing levels of breast cancer risk associated with UD, ADH and DCIS respectively, concerns about diagnostic reproducibility have led some to question the practice of utilizing these risk estimates at the individual level (299).

Aetiology
In general, the factors that are associated with the development of invasive breast carcinoma are also associated with increased risk for the development of intraductal proliferative lesions (1439a, 1551a, 2536a). (See section on epidemiology of breast carcinoma).

Genetics of precursor lesions
To date, several genetic analyses have been performed on potential precursor lesions of carcinoma of the breast. The sometimes contradictory results (see below) may be due to: (i) small number of cases analysed, (ii) the use of different histological classification criteria, (iii) histomorphological heterogeneity of both the normal and neoplastic breast tissue and (iv) genetic heterogeneity, as identified by either conventional cytogenetics (1175) or by fluorescence in situ hybridization (FISH) analysis (1949). Further evidence for genetic heterogeneity comes from comparative genomic hybridization (CGH) data of microdissected tissue in usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH) (135) and DCIS (194, 366). There has been a tendency to interpret loss of heterozygosity as evidence for clonal evolution and neoplastic transformation. However, histologically normal ductal epithelium closely adjacent to invasive ductal carcinoma may share an LOH pattern with the carcinoma, while normal ducts further away in the breast do not (671). LOH has also been identified in the stromal component of in situ (1889) and invasive breast carcinoma (1545, 1889), in non-neoplastic tissue from reduction mammoplasty specimens (1568), and in normal-appearing breast ducts (1586). The biological significance of these alterations are still poorly understood, but the available data suggest that genetic alterations may occur very early in breast tumorigenesis prior to detectable morphological changes and that epithelial/stromal interactions play a role in progression of mammary carcinoma.

Clinical features
The age range of women with intraductal proliferative lesions is wide, spanning 7 to 8 decades post adolescence. All these lesions are extremely rare prior to puberty; when they do occur among infants and children, they are generally a reflection of exogenous or abnormal endogenous hormonal stimulation. The mean age for DCIS is between 50-59 years. Though most often unilateral, about 22% of women with DCIS in one breast develop either in situ or invasive carcinoma in the contralateral breast (3055).

Macroscopy
A vast majority of intraductal proliferative lesions, particularly those detected mammographically, are not evident on macroscopic inspection of the specimen. A small proportion of high grade DCIS may be extensive enough and with such an abundance of intraluminal necrosis or associated stromal reaction that it would present as multiple areas of round, pale comedo necrosis or a firm, gritty mass.

**Usual ductal hyperplasia (UDH)**

**Definition**
A benign ductal proliferative lesion typically characterized by secondary lumens, and streaming of the central proliferating cells. Although not considered a precursor lesion, long-term follow-up of patients with UDH suggests a slightly elevated risk for the subsequent development of invasive carcinoma.
In some cases, the proliferation has a solid pattern and no secondary lumens are evident. Cytologically, the lesion is composed of cells with indistinct cell margins, variation in the tinctorial features of the cytoplasm and variation in shape and size of nuclei. Admixture of epithelial, myoepithelial or metaplastic apocrine cells is not uncommon. The presence or absence of either microcalcifications or necrosis does not impact the diagnosis. UDH with necrosis, a rare event, may be mistaken for DCIS; the diagnosis should be based on the cytological features and not the presence of necrotic debris. UDH generally displays either diffuse or a mosaic pattern of positivity with high molecular weight cytokeratins (1963, 2126) such as CK5, CK1/5/10/14 (clone CK34betaE12 or clone D5/16 B4); it is also positive for E-cadherin. In UDH, the percentage of ER-positive cells was found slightly increased compared to the normal breast (2667). Increased levels of cyclin D1 expression were recently described in 11-19% of UDH cases (1172,3264).

**Genetic alterations**
Approximately 7% of UDH show some degree of aneuploidy. Loss of heterozygosity (LOH) for at least one locus, has been noted in one-third of UDH (2071). On chromosome 1p, LOH was present in 10-20% of UDH cases (72,2071). Losses on 16q and 17p were identified in UDH lesions without evidence of adjacent carcinoma (1037) whereas no alterations were reported by others (301). In UDH adjacent to carcinoma, polysomy of chromosome 1 as well as increased signal frequencies for the 20q13 region (typically present in DCIS) were identified by FISH (593,3100). By CGH, UDH lesions adjacent to carcinoma showed gain on chromosome 20q and loss on 13q in 4 of 5 cases (136), although no alteration was reported in another study (301). Some recent CGH studies suggest that a proportion of UDH lesions is monoclonal (1037,1558), and that a subset shows alterations similar to those observed in ADH (1037); however, the frequency of genetic alterations seen in UDH using LOH and CGH is much lower than in ADH. TP53 protein expression has not been demonstrated in UDH or in any other benign proliferative lesions (1567). Mutations of the TP53 gene are also absent, except as inherited mutations in Li-Fraumeni patients (72).

**Flat epithelial atypia**

**Definition**
A presumably neoplastic intraductal alteration characterized by replacement of the native epithelial cells by a single or 3-5 layers of mildly atypical cells.

---

**Table 1.12**

Usual ductal hyperplasia.

<table>
<thead>
<tr>
<th>Architectural features</th>
<th>Cellular features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Irregular fenestrations</td>
<td>1. Multiple cell types</td>
</tr>
<tr>
<td>2. Peripheral fenestrations</td>
<td>2. Variation in appearance of epithelial cells</td>
</tr>
<tr>
<td>3. Stretched or twisted epithelial bridges</td>
<td>3. Indistinct cell margins and deviation from a round contour</td>
</tr>
<tr>
<td>4. Streaming</td>
<td>4. Variation in the appearance of nuclei</td>
</tr>
<tr>
<td>5. Uneven distribution of nuclei and overlapped nuclei</td>
<td>One of the most important indicators of UDH is the presence of admixture of two or more cell types (epithelial, myoepithelial and/or metaplastic apocrine cells).</td>
</tr>
</tbody>
</table>

---

**Synonyms**
Intraductal hyperplasia, hyperplasia of the usual type, epitheliosis, ordinary intraductal hyperplasia.

**Mammography**
UDH does not have a mammographic presentation, except in rare cases with microcalcification.

**Risk of progression**
Long-term follow up of patients with UDH in one study showed that 2.6% develop subsequent invasive carcinoma after an average interval of over 14 years, compared to 8.3 years for those with ADH (2886). In another study, the absolute risk of a woman with UDH developing breast cancer within 15 years was 4% (732). The Cancer Committee of the College of American Pathologists has assigned UDH a slightly increased risk (RR of 1.5-2.0) for subsequent development of invasive carcinoma (885).

**Histopathology**
UDH is characterized by irregularly shaped and sized secondary lumens, often peripherally distributed, and streaming of the central bulus of proliferating cells. Epithelial bridges are thin and stretched; nuclei are unevenly distributed.

---

**Fig. 1.80** Usual ductal hyperplasia. A Florid type. The peripheral distribution of irregularly sized spaces is a characteristic of UDH readily apparent at low magnification. B The proliferating cells may form epithelial bridges, but the bridges are delicate and formed by spindled stretched cells. C Intensive, predominantly solid intraductal proliferation of a heterogeneous cell population. Note spindling of the cells. Several irregular peripheral luminal spaces. D Intraductal proliferation with many CK5-positive and occasional CK5-negative cells.
Synonyms
Ductal intraepithelial neoplasia 1A (DIN 1A); clinging carcinoma, monomorphic type; atypical cystic lobules; atypical lobules, type A; atypical columnar change.

Risk of progression
Some cases of flat epithelial atypia may progress to invasive breast cancer but no quantitative epidemiological data are currently available for risk estimation.

Histopathology
A flat type of epithelial atypia, this change is characterized by replacement of the native epithelial cells by a single layer of mildly atypical cells often with apical snouts, proliferation of a monotonous atypical cell population in the form of stratification of uniform, cuboidal to columnar cells generally up to 3-5 cell layers with occasional mounding. Arcades and micropapillary formations are absent or very rare. The TDLUs involved are variably distended and may contain secretory or floccular material that often contains microcalcifications.

Genetic alterations
Data on genetic alterations in flat epithelial atypia are limited. LOH has been found in at least one locus in 70% of cases in a study evaluating eight loci in thirteen lesions [1889]. LOH on 11q (D11S1311) was the most commonly noted in 50% of the pure flat atypia, while among seven flat atypias associated with infiltrating carcinomas, the frequency of LOH on 11q (D11S1311) was 57% [1889].

Atypical ductal hyperplasia (ADH)
Definition
A neoplastic intraductal lesion characterized by proliferation of evenly distributed, monomorphic cells and associated with a moderately elevated risk for progression to invasive breast cancer.

Synonyms
Ductal intraepithelial neoplasia 1B (DIN 1B), atypical intraductal hyperplasia.

Risk of progression
The Cancer Committee of the College of American Pathologists has assigned ADH a moderately increased risk (RR of 4.0:5.0) for subsequent development of invasive breast cancer [885]. Following a breast biopsy diagnosis of ADH, 3.7-22% of the women develop invasive carcinomas [299,733,1520,2886]. On the other hand, ADH has also been present in 2.2% [2158] to 10.5% [1688] of controls who did not develop subsequent carcinoma. The average interval to the subsequent development of invasive carcinoma is 8.3 years compared to 14.3 years for women with UDH [2886]. However, drastically different relative risk (RR) estimations have been reported for ADH, ranging from a low of 2.4 to a high of 13 [412,732,1688,1775,1830,2155,2158]. The upper values are even higher than the RR of 8-11 suggested for DCIS [732,885]. On the other hand, the RR of 2.4 for ADH reported in one study [1775] is much closer to the RR of 1.9 associated with UDH.

Histopathology
The most distinctive feature of this lesion is the proliferation of evenly distributed, monomorphic cells with generally ovoid nuclei. The cells may grow in micropapillae, tufts, fronds, arcades, rigid bridges, solid and cribriform patterns. Cytologically, ADH corresponds to low grade DCIS. ADH is diagnosed when characteristic cells coexist with patterns of UDH, and/or there is partial involvement of TDLU by classic morphology. There is currently no general agreement on whether quantitative criteria should be applied to separate ADH from low grade DCIS. Some define the upper limit of ADH as one or more completely involved duct/ductular cross sections measuring ≤2 mm in aggregate, while others require that the characteristic cytology and architecture be present completely in two spaces. Microcalcifications may be absent, focal or extensive within the lumen of involved ducts; its presence does not impact diagnosis.

Immunoprofile
ERBB2 protein overexpression is rare in ADH [72,1172], in contrast to high amplification rates in high grade DCIS, suggesting that ERBB2 alterations are either
not an early event in malignant transformation or that they are largely restricted to high grade DCIS. Increased levels of cyclin D1 expression were recently described in 27-57% of ADH [1172, 3264]. Nuclear accumulation of the TP53 protein is absent in ADH and low grade DCIS [1567]. Nearly 90% of ADH are negative for high molecular weight cytokeratins 1/5/10/14 (clones CK34BetaE12 and D5/16 B4), an important feature in separating ADH from UDH [1963, 2126].

Genetic alterations
Fifty percent of ADH cases share their LOH patterns with invasive carcinomas from the same breast, strongly supporting a precursor relationship between these lesions [1567]. LOH has been identified frequently on chromosomes 16q, 17p, and 11q13 [1567, 1570]. TP53 mutations are restricted to affected members of Li-Fraumeni families.

Epidemiology
A striking increase in the detection of DCIS has been noted with the introduction of widespread screening mammography and increasing awareness of breast cancer in the general population since 1983. The average annual increase in the incidence rate of DCIS in the decade of 1973 to 1983 was 3.9% compared to 17.5% annually in the decade between 1983 to 1992, increasing from 2.4 per 100,000 women in 1973 to 15.8 per 100,000 in 1992 for women of all races, an overall increase of 557% [794]. In the US, data from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) program noted that the proportion of breast carcinomas diagnosed as DCIS increased from 2.8% in 1973 to 14.4% in 1995 [794]. While close to 90% of pre-mammographic DCIS were of the high grade comedo type, nearly 60% of mammographically detected lesions are non-comedo and this percentage is increasing. Interestingly, despite the more limited surgical excisions, mortality from “DCIS” has declined. Of women with DCIS diagnosed between 1978 and 1983 (pre-mammographic era), 3.4% died of breast cancer at 10 years, despite having been treated by mastectomy in the vast majority of cases. On the other hand, only 1.9% of women diagnosed with DCIS between 1984 and 1989 died of breast cancer at 10 years, despite the increasing trend toward lumpectomy [794]. Judging from the 10-year follow-

**Ductal carcinoma in situ (DCIS)**

**Definition**
A neoplastic intraductal lesion characterized by increased epithelial proliferation, subtle to marked cellular atypia and an inherent but not necessarily obligate tendency for progression to invasive breast cancer.

**ICD-O code**
8500/2

**Synonyms**
Intraductal carcinoma, ductal intraepithelial neoplasia (DIN 1C to DIN 3).

**Risk of progression**
DCIS is considered a precursor lesion (obligate or non-obligate), with a relative risk (RR) of 8-11 for the development of invasive breast cancer [732, 885]. However, there is evidence that conservative treatment (complete local eradication) is usually curative (see below).
up period currently available for these women, it appears as if "DCIS per se is not a life threatening disease" [794]. The deaths that do occur are related to an undetected invasive carcinoma present at the time of the initial diagnosis of DCIS, progression of residual incompletely excised DCIS to invasive carcinoma, or development of a de novo invasive carcinoma elsewhere in the breast [794].

**Clinical features**

In countries where population screening is performed, the vast majority of DCIS (>85%) are detected by imaging alone. Only approximately 10% of DCIS are associated with some clinical findings and up to 5% is detected incidentally in surgical specimens, obtained for other reasons. Clinical findings, which may be associated with DCIS include (i) palpable abnormality, (ii) pathological nipple discharge and (iii) nipple alterations associated with Paget disease.

**Imaging**

Mammography constitutes by far the most important method for the detection of DCIS. In current screening programs, 10-30% of all detected ‘malignancies’ are DCIS [810,1280]. In the majority of cases, mammographic detection is based on the presence of significant microcalcifications that are associated with most of these lesions [1206, 1231, 2796].

Calcifications associated with well differentiated DCIS are usually of the laminated, crystalline type resembling psammoma bodies. They often develop as pearl-like particles in the luminal spaces within the secretion of the tumour and appear on the mammogram as multiple clusters of granular microcalcifications that are usually fine. These multiple clusters reflect the frequent lobular arrangement of this type of DCIS. Calcifications associated with poorly differentiated DCIS, are, histologically, almost exclusively of the amorphous type developing in the necrotic areas of the tumour. They appear on the mammogram as either linear, often branching, or as coarse, granular microcalcifications. Calcifications associated with the immediately differentiated DCIS may be of either the amorphous or the laminated type.

About 17% of the lesions lack histologic evidence of microcalcifications; they are either mammographically occult or manifest as an architectural distortion, a nodular mass or nonspecific density [1206].

**Size, extent and distribution**

Size/extent is an important factor in the management of DCIS. The assessment of extent of DCIS is complex and needs in optimal conditions the correlation of the
mammogram, the specimen X-ray and the histologic slides. Since the majority of DCIS is non palpable, the mammographic estimate is the sole guide for resection. Therefore, data on the mammographic pathological correlation of the tumour size are essential for guiding the extent of surgery. The mammographic extent of a DCIS is defined as the greatest distance between the most peripherally located clusters of suspicious microcalcifications, and the histologic extent as the greatest distance between the most peripherally located, histologically verified, DCIS foci. Histologic evaluation supported by correlation with the X-ray of the sliced specimen allows a precise and reproducible assessment of the extent of any DCIS present. Whole organ studies have shown that mammography, on the basis of significant microcalcifications, generally underestimates the histologic or "real" size of DCIS by an average of 1-2 cm. In a series of DCIS cases with mammographic sizes up to 3 cm, the size difference was less than 2 cm in more than 80% of the cases (1231). DCIS may appear as a multifocal process due to the presence of multiple tumour foci on two-dimensional plane sections. However, these tumour spots may not necessarily represent separate foci. Intraductal tumour growth on three-dimensional studies appears to be continuous rather than discontinuous (831).

More specifically, whereas poorly differentiated DCIS shows a predominantly continuous growth, the well differentiated DCIS, in contrast, may present a more discontinuous (multifocal) distribution. These results have a direct implication on the reliability of the margin assessment of surgical specimens. In cases of poorly differentiated DCIS, margin assessment should, theoretically, be more reliable than well differentiated DCIS. In a multifocal process with discontinuous growth, the surgical margin may lie between the tumour foci, giving the false impression of a free margin. The distribution of DCIS in the breast is typically not multicentric, defined as tumour involvement in two or more remote areas separated by uninvolved glandular tissue of 5 cm. On the contrary, DCIS is typically "segmental" in distribution (1230). In practical terms, this implies that two apparently separate areas of "malignant" mammographic microcalcifications usually do not represent separate fields of DCIS but rather a larger tumour in which the two mammographically identified fields are connected by DCIS, which is mammographically invisible due to the lack of detectable size of microcalcifications. One should be aware that single microscopic calcium particles smaller than about 80µ cannot be seen on conventional mammograms.

Grading
Although there is currently no universal agreement on classification of DCIS, there has been a move away from traditional architectural classification. Most modern systems use cytonuclear grade alone or in combination with necrosis and or cell polarization. Recent international consensus conferences held on this subject endorsed this change and recommended that, until more data emerges on clinical outcome related to pathology variables, grading of DCIS should form the basis of classification and that grading should be based primarily on cytonuclear features [6,7,1565;2346]. Pathologists are encouraged to include additional information on necrosis, architecture, polarization, margin status, size and calcification in their reports. Depending primarily on the degree of nuclear atypia, intraluminal necrosis and, to a lesser extent, on mitotic activity and calcification, DCIS is generally divided into three grades; the first two features constitute the major criteria in the majority of grading systems. It is not uncommon to find admixture of various grades of DCIS as well as various cytotological variants of DCIS within the same biopsy or even within the same ductal space. When more than one grade of DCIS is present, the proportion (percentage) of various grades should be noted in the diagnosis (2876). It is important to note that a three tiered grading system does not necessarily imply progression from grade 1 or well differentiated to grade 3 or poorly differentiated DCIS.

Histopathology

**Low grade DCIS**
Low grade DCIS is composed of small, monomorphic cells, growing in arcades, micropapillae, cribriform or solid patterns. The nuclei are of uniform size and have a regular chromatin pattern with inconspicuous nucleoli; mitotic figures

### Table 1.13
**Features of DCIS to be documented for the surgical pathology report.**

<table>
<thead>
<tr>
<th>Major lesion characteristics</th>
<th>Associated features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nuclear grade</td>
<td>1. Margins</td>
</tr>
<tr>
<td>2. Necrosis</td>
<td>If positive, note focal or diffuse involvement. Distance from any margin to the nearest focus of DCIS.</td>
</tr>
<tr>
<td>3. Architectural patterns</td>
<td>2. Size (either extent or distribution)</td>
</tr>
<tr>
<td></td>
<td>3. Microcalcifications (specify within DCIS or elsewhere)</td>
</tr>
<tr>
<td></td>
<td>4. Correlate morphological findings with specimen imaging and mammographic findings</td>
</tr>
</tbody>
</table>

### Table 1.14
**Minimal criteria for low grade DCIS.**

<table>
<thead>
<tr>
<th>Cytological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Monotonous, uniform rounded cell population</td>
</tr>
<tr>
<td>2. Subtle increase in nuclear-cytoplasmic ratio</td>
</tr>
<tr>
<td>3. Equidistant or highly organized nuclear distribution</td>
</tr>
<tr>
<td>4. Round nuclei</td>
</tr>
<tr>
<td>5. Hyperchromasia may or may not be present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Architectural features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arcades, cribriform, solid and/or micropapillary pattern</td>
</tr>
</tbody>
</table>
are rare. Some require complete involvement of a single duct cross section by characteristic cells and architecture, while others require either involvement of two spaces or one or more duct cross sections exceeding 2 mm in diameter. Microcalcifications are generally of the psammomatous type. There may be occasional desquamated cells within the ductal lumen but the presence of necrosis and comedo histology are unacceptable within low grade DCIS.

DCIS with micropapillary pattern may be associated with a more extensive distribution in multiple quadrants of the breast compared to other variants (2584). The working group’s minimal criteria for diagnosis of low grade DCIS are shown in Table 1.14.

**Intermediate grade DCIS**

Intermediate grade DCIS lesions are often composed of cells cytologically similar to those of low grade DCIS, forming solid, cribriform or micropapillary patterns, but with some ducts containing intraluminal necrosis. Others display nuclei of intermediate grade with occasional nucleoli and coarse chromatin; necrosis may or may not be present. The distribution of amorphous or laminated microcalcifications is generally similar to that of low grade DCIS or it may display characteristics of both low grade and high grade patterns of microcalcification.

**High grade DCIS**

High grade DCIS is usually larger than 5 mm but even a single <1 mm ductule with the typical morphological features is sufficient for diagnosis. It is composed of highly atypical cells proliferating as one layer, forming micropapillae, cribriform or solid patterns. Nuclei are high grade, markedly pleomorphic, poorly polarized, with irregular contour and distribution, coarse, clumped chromatin and prominent nucleoli. Mitotic figures are usually common but their presence is not required. Characteristic is the comedo necrosis with abundant necrotic debris in duct lumens surrounded by a generally solid proliferation of large pleomorphic tumour cells. However, intraluminal necrosis is not obligatory. Even a single layer of highly anaplastic cells lining the duct in a flat fashion is sufficient. Amorphous microcalcifications are common.

**Unusual variants**

A minority of the DCIS lesions is composed of spindled (827), apocrine (2887), signet ring, neuroendocrine, squamous or clear cells. There is no consensus or uniform approach to grading of these unusual variants. Some believe assessment of nuclear features and necrosis can be applied to grading of the

---

**Fig. 1.89** Low grade ductal carcinoma in situ. **A** Micropapillary type showing the longitudinal segment of a duct with numerous micropapillae characteristic of this variant. **B** Micropapillary type. The micropapillae lack a fibrovascular core and are composed of a piling of uniform cells with rounded nuclei. **C** Cribriform type. Multiple adjacent ducts are distended by a sieve-like proliferation of monotonous uniform cells. The multiple spaces are rounded and distributed in an organized fashion. **D** Cribriform type. A highly uniform population of cells with round nuclei distributed equidistant from one another grow in a cribriform pattern.
unusual variants as well. Using this approach many apocrine DCIS lesions qualify as high grade, while a minority would qualify as intermediate or, rarely, high grade DCIS. The clear and spindle cell DCIS are sometimes found coexistent and continuous with typical low grade DCIS, but often the nuclei are moderately atypical qualifying the lesions as intermediate grade DCIS. High nuclear grade spindle or clear cell DCIS is extremely rare. A vast majority of apocrine carcinomas are ER, PR and BCL2 negative, but androgen receptor positive [2888].

Proliferation
In vivo labeling with bromodeoxyuridine (BrdU) has found no significant differences between proliferating cell fraction among UDH and ADH, but the proliferating cell fraction is significantly increased in DCIS [412]. With the Ki67 antibody, the highest proliferating index (PI) of 13% has been noted among the comedo DCIS, while the PI for low grade DCIS, cribriform type is 4.5% and for micropapillary type, it is 0% [61]. DNA Ploidy: Aneuploidy has been found in 7% of UDH, 13-36% of ADH, and 30-72% of low to high grade DCIS respectively [468,579,792].

Hormone receptor expression
Estrogen plays a central role in regulating the growth and differentiation of breast epithelium as well as in the expression of other genes including the progesterone receptor (PR) [72]. The presence and concentration of the two receptors are used, not only as a clinical index of potential therapeutic response, but also as markers of prognosis for invasive breast carcinomas [196]. Only a few studies have evaluated estrogen receptor (ER) in intraductal proliferative breast lesions. Among DCIS, about 75% of the cases show ER expression [72,1399], and an association between ER positivity and the degree of differentiation has been described [1399]. There is agreement that nearly all examples of ADH express high levels of ER in nearly all the cells [72,1301,2667]. The relationship between ER positive cell numbers and patient age, as found in normal breast epithelium, is lost in these ADH lesions, indicating autonomy of ER expression or of the cells expressing the receptor [2667].

Differential diagnosis
The solid variant of low grade DCIS may be misinterpreted as lobular neoplasia (LN). Immunohistochemistry for E-cadherin and CK1/5/10/14 (clone CK34BetaE12) are helpful in separating the two. Low grade DCIS is E-cadherin positive in 100% of cases [337, 1090,3034] and CK34BetaE12 negative in 92% of cases [337,1890], whereas lobular neoplasia (LN) is E-cadherin negative [337,1033] and CK34BetaE12 positive in nearly all cases [337]. The presence of individual or clusters of cells invading the stroma (microinvasion) around a duct with DCIS is a frequent source of diagnostic problems. The difficulty is compounded by the frequent presence of dense lymphoplasmacytic infiltrate around the involved ducts. Immunostains for an epithelial and myoepithelial marker are helpful optimally in the form of double immunostaining; the epithelial cell marker can unmask the haphazard distribution of the cells, while the absence of a myoepithelial cell layer would generally ascertain the invasive nature of the cells in question. Despite all

![Image](379x609 to 528x709)

**Fig. 1.90** Intermediate grade ductal carcinoma in situ. A Micropapillary type. The micropapillae are varied in shape and composed of cells with moderately atypical, pleomorphic nuclei. A few apoptotic cells are present in the lumen. B Flat type, approaching high grade DCIS. Two adjacent ductal spaces are lined by atypical cells, rare mitotic figures and a few apoptotic nuclei. C, D Duct/duct of a duct with micropapillary atypical epithelial proliferation. Note secretory material in the lumen that should not be mixed up with comedo-type necrosis. E Clear cell type. The neoplastic cells have clear cytoplasm with moderate nuclear pleomorphism. F Apocrine type with moderate nuclear size variation. The abundant pink, granular cytoplasm suggests an apocrine cell type.

![Image](66x182 to 377x481)

**Fig. 1.91** DCIS, intermediate grade (DCIS grade 2). This typical and most common intermediate grade DCIS is characterized by a cribriform growth pattern and intraluminal necrosis.
these added studies, the distinction can remain impossible in some cases. An unknown, but relatively small, proportion of intraepithelial neoplasias cannot be easily separated into ductal or lobular subtypes on the basis of pure H&E morphology. Using immunostains for E-cadherin and CK34[BE12], some of these will qualify as ductal (E-cadherin+, CK34BetaE12-), some as lobular (E-cadherin-, CK34[BE12+), while others are either negative for both markers (negative hybrid) or positive for both (positive hybrid) [337]. This important group requires further evaluation as it may reflect a neoplasm of mammary stem cells or the immediate post-stem cells with plasticity and potential to evolve into either ductal or lobular lesions [338].

Expression profiling
Gene expression profiling has become a powerful tool in the molecular classification of cancer. Recently, the feasibility and reproducibility of array technology in DCIS was demonstrated [1721]. More than 100 changes in gene expression in DCIS were identified in comparison with control transcripts. Several genes, previously implicated in human breast cancer progression, demonstrated differential expression in DCIS versus non-malignant breast epithelium, e.g. up-regulation of lactoferrin (a marker of estrogen stimulation), PS2 (an estrogen-responsive marker), and SIX1 (a homeobox protein frequently up-regulated in metastatic breast cancer), and down-regulation of oxytocin receptor [3148].

Genetic alterations
Most studies on somatic gene alterations in premalignant breast lesions are based on small sample numbers and have not been validated by larger series [72], with the exceptions of the TP53 tumour suppressor gene and the oncogenes ERBB2 and CCND1 [72,196]. Other genes, not discussed here (e.g. oncogenes c-myc, fos, c-met, and tumour suppressor gene RB1) may also play an important role in breast carcinogenesis (for review see [3048]).

Cytogenetics
Conventional cytogenetic analysis of premalignant lesions of the breast has been carried out in only a small number of cases, and, as with invasive ductal carcinoma, abnormalities of chromosomes 1 and 16 have been identified in DCIS [1146,1567]. FISH-analyses using DNA probes to centromeric sequences of almost all chromosomes frequently identified polysomy of chromosome 3, 10, and 17 and loss of chromosome 1, 16, and 18 in DCIS [1949].

Chromosomal imbalance
CGH studies of DCIS have demonstrated a large number of chromosomal alterations including frequent gains on 1q, 6q, 8q, 17q, 19q, 20q, and Xq, and losses on 8p, 13q, 16q, 17p, and 22q [134,301,365,366,1333,1548,3045]. Most of these chromosomal imbalances
In DCIS, loss of heterozygosity (LOH) was frequently identified at several loci on chromosomes 1 (1942), 3p21 (1743), and chromosomes 8p, 12q, 16q, 17p, 17q, and 18q (924,2317,3036). The highest reported rates of LOH in DCIS are between 50% and 80% and involve loci on chromosomes 16q, 17p, and 17q, suggesting that altered genes in these regions may be important in the development of DCIS (72,924,3036). Among more than 100 genetic loci studied so far on chromosome 17, nearly all DCIS lesions showed at least one LOH (72,301,924,2071,2317,2475). By CGH and FISH, low and some intermediate grade DCIS and invasive tubular carcinoma (G1) show loss of 16q, harbouring one of the cadherin gene clusters, whereas some intermediate grade and high grade DCIS and nearly all G2 and G3 invasive ductal carcinomas show no loss of genetic material on this locus but have alterations of other chromosomes (-15q, +17p, +20q). Based upon this data, a genetic progression model was proposed (301).

ERBB2

The ERBB2 (Her2/neu) oncogene has received attention because of its association with lymph node metastases, short relapse free time, poor survival, and decreased response to endocrine and chemotherapy in breast cancer patients (72,1567). Studies of ER B2 have used mainly FISH technique to identify amplification and immunohistochemistry (IHC) to detect over expression of the oncogene, which are highly correlated (72). Amplification and/or over expression was observed on average in 30% of DCIS, correlating directly with differentiation (72); it was detected in a high proportion of DCIS of high nuclear grade (60-80%) but was not common in low nuclear grade DCIS (196). Patients with ERBB2 positive tumours may benefit from adjuvant treatment with monoclonal antibody (Herceptin).

Cyclin D1

This protein plays an important part in regulating the progress of the cell during the G1 phase of the cell cycle. The gene (CCND1) is considered a potential oncogene, but in clinical studies of invasive breast cancer, overexpression of cyclin D1 was found to be associated with estrogen receptor expression and low histological grade, both markers of good prognosis (1007). Amplification of CCND1 occurs in about 20% of DCIS and is more commonly found in high grade than in low grade DCIS (32% versus 8%) (2700). The cyclin D1 protein was detected in 50% of cases, and high levels were more likely in low grade than in the intermediate and high grade DCIS (2700). Although so far no oncogene has been identified on chromosome 20q13, amplification of this region was frequently found in DCIS (134,856).

TP53 mutations

The TP53 protein is a transcription factor involved in the control of cell proliferation, response to DNA damage, apoptosis and several other signaling pathways. It is the most commonly mutated tumour suppressor gene in sporadic breast cancer (196) and this is generally associated with aggressive biological features and poor clinical outcome. Most TP53 mutations are missense point mutations resulting in an inactivated protein that accumulates in the cell nucleus (72,712). In DCIS, TP53 mutations were found with different frequency among the three histological grades, ranging from rare in low grade DCIS, 5% in intermediate-grade, and common (40%) in high grade DCIS (712,3048).

Prognosis and predictive factors

The most important factor influencing the possibility of recurrence is persistence of neoplastic cells post-excision; primary and recurrent DCIS generally have the same LOH pattern, with acquisition of additional alterations in the latter (1670). The significance of margins is mainly to ascertain complete excision. In randomized clinical trials, comedo necrosis was found to be an important predictor of local recurrence in the NSABP-B17 trial (2843), while solid and cribriform growth patterns along with involved margin of excision were found to be predictive of local recurrence in EORTC-10853 trial (270,271). In retrospective trials, on the other hand, high nuclear grade, larger lesion size, comedo necrosis and involved margins of excision were all found to be predictive of local recurrence following breast conserving treatment for DCIS.

Although mastectomy has long been the traditional treatment for this disease, it likely represents over-treatment for many patients, particularly those with small, mammographically detected lesions. Careful mammographic and pathologic evaluation are essential to help assess patient suitability for breast conserving treatment. While excision and radiation therapy of DCIS (with or without Tamoxifen) have significantly reduced the chances of recurrence (866,870), some patients with small, low grade lesions appear to be adequately treated with excision alone, whereas those with extensive lesions may be better served by mastectomy. Better prognostic markers are needed to help determine which DCIS lesions are likely to recur or to progress to invasive cancer following breast conserving treatment. The optimal management is evolving as data accumulates from a variety of prospective studies.
Microinvasive carcinoma

Definition
A tumour in which the dominant lesion is non-invasive, but in which there are one or more clearly separate small, microscopic foci of infiltration into non-specialized interlobular stroma. If there is doubt about the presence of invasion, the case should be classified as an in situ carcinoma.

ICD-O code
Microinvasive carcinoma is not generally accepted as a tumour entity and does not have an ICD-O code.

Epidemiology
Microinvasive carcinomas are rare and occur mostly in association with an in situ carcinoma. They account for far less than 1% of breast carcinomas even in pure consultation practices where the largest number of microinvasive carcinoma is reviewed [2680].

Clinical features
There are no specific clinical features associated with microinvasive carcinoma. These lesions are typically associated with ductal carcinoma in situ which is often extensive. The features associated with the associated in situ component are responsible for detection as a mass lesion, mammographic calcification or a nipple discharge. (See clinical features of ductal and lobular carcinoma in situ).

Histopathology
There is no generally accepted agreement on the definition of microinvasive carcinoma. This is particularly true for the maximum diameter compatible with the diagnosis of microinvasive carcinoma.

Size limits
Microinvasive carcinoma has been defined as having a size limit of 1 mm (1984,2425,2739,2905). Consequently, diagnosis of microinvasive carcinoma is rare in routine practice, in contrast to larger (>1 mm) foci of invasion. Alternatively, it has also been defined as a single focus no larger than 2 mm in maximum dimension or 2-3 foci, none exceeding 1 mm in maximum dimension. Some studies have provided no maximum size (2579,3140) or criteria (1467,2703). Others have defined the microinvasive component as a percentage of the surface of the histologic sections (2583). Some have described subtypes separating those purely composed of single cells and those also containing cell clusters and/or tubules of non-gradable tumour without providing information about maximum size, extent, or number of microinvasive foci (656). More precise definitions accept an unlimited number of clearly separate foci of infiltration into the stroma with none exceeding 1 mm in diameter (80), 1 or 2 foci of microinvasion with none exceeding 1 mm (2695), a single focus not exceeding 2 mm or three foci, none exceeding 2 mm in maximum diameter (2680).

Some authors propose that the definition of microinvasive carcinoma requires extension of the invasive tumour cells beyond the specialized lobular stroma (774,2905) despite the definitive presence of vascular channels both within
the specialized lobular stroma and immediately surrounding the basement membrane that invests the ducts.

**Associated lesions**

Typically, microinvasive carcinoma occurs in larger areas of high grade DCIS in which the tumour cell population extends to involve lobular units or areas of benign disease. Microinvasion occurs in association not only with all grades of DCIS, including papillary DCIS, but also with other precursor lesions of invasive breast cancer, e.g. lobular neoplasia (LN) [1226,1249,1993], indicating that at least some forms of lobular neoplasia behave as true precursors of invasive lesions.

**Stromal reaction**

Microinvasion is most often present in a background of significant peri ductal / perilobular lymphocytic infiltrate or an altered desmoplastic stroma, features often present in cases of comedo DCIS. Angulation of mesenchymal structures may be emphasized by the plane of sectioning and can produce features reminiscent of invasive carcinoma. Basement membrane structures in such foci may be discontinuous but it is unusual to lose the entire basement membrane around such a lesion. Similarly myoepithelial cells may be scarce but are rarely totally absent in such areas.

**Change in morphology**

When true invasion extends into non-specialized stroma, the islands of tumour cells frequently adopt a different morphological character which is more typical of well established invasive mammary carcinoma of ductal NOS type and is distinct from the patterns seen with cancerization of lobules.

**Differential diagnosis**

When there is doubt about the presence of invasion and particularly, if uncertainty persists even after recuts and immunostains for detection of myoepithelial cells, the case should be diagnosed as an in situ carcinoma. Similarly, suspicious lesions which disappear on deeper levels should be regarded as unproven, with no definite evidence of established invasion. Invasion is associated with a loss of immunoreactivity to myoepithelial cells. A variety of markers is available for the identification of myoepithelial cells (3181). The most helpful include smooth muscle actin, calponin, and smooth muscle myosin (heavy chain); the latter in particular shows the least cross-reactivity with myofibroblasts that may mimic a myoepithelial cell layer when apposed to the invasive cells.

**Prognosis and predictive factors**

In true microinvasive carcinomas of the breast, the incidence of metastatic disease in axillary lymph nodes is very low and the condition is generally managed clinically as a form of DCIS. However, given the lack of a generally accepted standardized definition of microinvasive carcinoma, there is little evidence on the behaviour of microinvasive carcinoma. A recent detailed review of the literature [2425] concluded that a variety of different diagnostic criteria and definitions have been used and as a consequence it is difficult to draw any definitive conclusions. There are studies that have found no evidence of axillary node metastases associated with a finite number of invasive foci <1 mm in maximum dimension or a single invasive focus <2 mm [2680, 2695]. Others have shown a small percentage (up to 5%) with axillary node metastases [2453,2744] or have described up to 20% axillary node metastases [656,1472,2282,2579,2583]. Of 38 women who had undergone mastectomy for their minimally invasive carcinomas (a single focus <2 mm or up to 3 invasive foci, none exceeding 1 mm, with no axillary node metastases), developed recurrences or metastases [2680]. The few other studies with comparable, but not exactly the same definition, and follow-up data support the excellent prognosis for these tumours within the short periods of available follow-up [2453, 2695,3140].

In practice, it may be impossible for pathologists to routinely examine an entire sample exhaustively. Therefore, it is quite possible that small foci of invasive carcinoma may be missed, particularly in the setting of extensive in situ carcinoma. For this reason, it may be appropriate to sample the lowest axillary lymph nodes, or sentinel node as a matter of routine, when treating patients by mastectomy for extensive DCIS with or without accompanying microinvasive carcinoma [1472]. The pathology report should provide the size of the largest focus along with the number of foci of invasion, noting any special studies utilized to arrive at the diagnosis, i.e. 1.3 mm, 2 foci, immunocytochemistry.

Until there is a generally accepted definition with reliable follow-up data, microinvasive carcinoma of the breast remains an evolving concept that has not reached the status of a WHO-endorsed disease entity.
Intraductal papillary neoplasms

Definition
Papillary neoplasms are characterized by epithelial proliferations supported by fibrovascular stalks with or without an intervening myoepithelial cell layer. They may occur anywhere within the ductal system from the nipple to the terminal ductal lobular unit (TDLU) and may be benign (intraductal papilloma), atypical, or malignant (intraductal papillary carcinoma).

Intraductal papilloma
A proliferation of epithelial and myoepithelial cells overlying fibrovascular stalks creating an arborescent structure within the lumen of a duct. Intraductal papilloma of the breast is broadly divided into central (large duct) papilloma, usually located in the subareolar region, and peripheral papilloma arising in the TDLU (2092). The confusing term “papillomatosis” should be avoided as it has been used for usual ductal hyperplasia as well as for multiple papillomas.

ICD-O code 8503/0

Central papilloma

Synonyms
Large duct papilloma, major duct papilloma.

Clinical features
Unilateral sanguineous, or serosanguineous, nipple discharge is the most frequent clinical sign, and is observed in 64-88% of patients (3148). A palpable mass is less frequent. Mammographic abnormalities include a circumscribed retro-areolar mass of benign appearance, a solitary retro-areolar dilated duct and, rarely, microcalcifications (401,3148). Small papillomas may be mammographically occult because of their location in the central dense breast and usually lack of calcification. Typical sonographic features include a well defined smooth-walled, solid, hypoechoic nodule or a lobulated, smooth-walled, cystic lesion with solid components. Duct dilatation with visible solid intraluminal echoes is common (3176). Galactography shows an intraluminal smooth or irregular filling defect associated with obstructed or dilated ducts, or a complete duct obstruction with retrograde flow of contrast material. Galactography may be useful to the breast surgeon in identifying and localizing the discharging duct, prior to duct excision (3148).

Macroscopy
Palpable lesions may form well circumscribed round tumours with a cauliflower-like mass attached by one or more pedicles to the wall of a dilated duct containing serous and/or sanguineous fluid. The size of central papillomas varies considerably from a few millimetres to 3-4 cm or larger and they can extend along the duct for several centimetres.
Papillomas are characterized by an arborescent structure composed of fibrovascular stalks covered by a layer of myoepithelial cells with overlying epithelial cells. In some lesions papillary and ductal patterns coexist. When the ductal pattern predominates and is associated with marked sclerosis, the term sclerosing papilloma may be used. Ductal adenoma is considered by some as a variant of generally sclerosing papilloma.

Histopathology

Papilloma may be subject to morphological changes such as inflammation, necrosis, myoepithelial hyperplasia, apocrine, squamous, sebaceous, mucinous, osseous and chondroid metaplasia as well as usual intraductal hyperplasia [148,893,1350,1945,2327,2420,2873]. A pseudo-infiltrative pattern may be observed at the periphery of these lesions particularly in the sclerosing variant. The myoepithelial cell layer may have an uneven distribution both in areas of UDH, ADH, and DCIS [2325]. The entire range of ductal intraepithelial proliferations may arise within, or secondarily involve, a central papilloma. The clinical implications of such lesions have not at this time been fully established and should be considered in the context of the surrounding breast tissue.

Peripheral papilloma

Synonym
Microscopic papilloma.

Epidemiology
The average age at presentation of peripheral papillomas is similar to that of central papillomas or slightly younger [401,1097,1945].

Clinical features
Peripheral papillomas are often clinically occult. They rarely present as a mass and nipple discharge is far less frequent in this group [401]. They are also usually mammographically occult, but they may manifest as peripherally situated microcalcifications, nodular prominent ducts or multiple small peripheral well circumscribed masses [401]. Microcalcifications may be located in the peripheral papillomas or in adjacent non-papillary intraductal proliferative lesions, e.g. ADH.

Macroscopy
Unless they are associated with other changes, peripheral papillomas are usually a microscopic finding.

Histopathology
Peripheral papillomas are usually multiple. They originate within the TDLUs from where they may extend into the larger ducts [2092]. The histological features are basically the same as for central papillomas. Compared to central papillomas, however, peripheral papillomas are more frequently observed in association.
with concomitant usual ductal hyperplasia, atypical intraductal hyperplasia, ductal carcinoma in situ or invasive carcinoma as well as with sclerosing adenosis or radial scar (1097,1945,2091,2092).

The term micropapilloma has been applied to the smallest type of peripheral papillomas corresponding to multiple microscopic papillomas that grow in foci of adenosis. Collagenous spherulosis, consisting of round eosinophilic spherules of basement membrane (type IV collagen), edged by myoepithelial cells may be seen in some peripheral papillomas.

**Atypical papilloma**

Atypical intraductal papillomas are characterized by the presence of a focal atypical epithelial proliferation with low grade nuclei. Such intraepithelial proliferations may occasionally resemble atypical ductal hyperplasia (ADH) or small foci of low grade DCIS.

**Prognosis and predictive features of benign and atypical papillomas**

The risk of subsequent invasive carcinoma associated with papillomas or atypical papillomas should be appreciated in the context of the surrounding breast tissue. A benign papilloma without surrounding changes is associated with a slightly increased relative risk of subsequent invasive breast carcinoma, similar to that of moderate or florid usual ductal hyperplasia in the breast proper (885,2151). The relative risk associated with peripheral papilloma may be higher compared to central papilloma. However, this risk also depends on the concurrent presence of other forms of proliferative disease and as yet no study has been designed to specifically answer this question (2151). There is disagreement as to whether the risk of subsequent invasive breast carcinoma applies only to the same site in the ipsilateral breast or applies to both breasts (2151,2326). The significance of atypia within a papilloma is still not clear and is obscured by the frequent concurrent presence of atypia within the surrounding breast parenchyma. It appears that if epithelial atypia is confined to the papilloma without surrounding proliferation or atypia the risk of subsequent invasive breast carcinoma is similar to that of non-atypical papilloma. As expected, epithelial atypia when present simultaneously both within and outside a papilloma is associated with a moderate to highly increased relative risk (2151); this is not a reflection of the risk associated with pure atypical papilloma, however.

**Intraductal papillary carcinoma**

ICD-O code 8503/2

**Synonym**

Papillary carcinoma, non-invasive.

**Definition**

This lesion is located within a variably distended duct and may extend into its branches. It is characterized by proliferation of fibrovascular stalks and its diagnosis requires that 90% or more of the epithelial cells be synchronous with each other.

---

**Table 1.15**

Differential diagnosis of benign papilloma and intraductal papillary carcinoma.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Papilloma</th>
<th>Papillary intraductal carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell types covering fibrovascular stalks</td>
<td>Epithelial and myoepithelial</td>
<td>Epithelial (myoepithelial cells may be seen at periphery of duct wall)*</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Normochromatic vesicular chromatin; variable in size and shape</td>
<td>May be hyperchromatic, with diffuse chromatin: relatively uniform in size and shape</td>
</tr>
<tr>
<td>Apocrine metaplasia</td>
<td>Frequent</td>
<td>Absent</td>
</tr>
<tr>
<td>Fibrovascular stalks</td>
<td>Usually broad and present throughout lesion; may show sclerosis</td>
<td>Often fine and may be absent in some areas; sclerosis uncommon</td>
</tr>
<tr>
<td>Immunohistochemical markers for myoepithelial cells [e.g. smooth muscle actin, HMW-CK (such as CK 5/6)]</td>
<td>Positive</td>
<td>Negative*</td>
</tr>
</tbody>
</table>

* Myoepithelial cells may be present in some papillary carcinomas—see text for explanation.

---

![Image](https://via.placeholder.com/150)
the papillary processes are totally devoid of a myoepithelial cell layer regardless of presence or absence of notable epithelial proliferation, and/or that any of the recognized patterns of low grade DCIS occupies 90% or more of the lesion. These neoplasms can be either solitary and central in location corresponding to intracystic papillary carcinoma, or multifocal within the TDLU and correspond to the papillary type of DCIS.

**Intracystic papillary carcinoma**

**Definition**

This lesion is a variant of intraductal papillary carcinoma, located within a large cystic duct and characterized by thin fibrovascular stalks devoid of a myoepithelial cell layer and of a neoplastic epithelial cell population with histopathological features characteristic of low grade DCIS.

**ICD-O code**

8504/2

**Synonyms**

Intracystic papillary carcinoma, non-invasive; papillary intraductal carcinoma; papillary ductal carcinoma in situ; encysted papillary carcinoma.

**Epidemiology**

Less than 2% of breast carcinomas correspond to intraductal papillary carcinomas (413, 1945). The average age of occurrence is around 65 (range, 34-92 years) (413, 1618).

**Clinical and macroscopic features**

On the basis of clinical presentation and macroscopy, there are no distinctive features that can separate papilloma from papillary carcinoma, nonetheless, intracystic papillary carcinomas tend to be larger.

**Histopathology**

Intraductal papillary carcinoma is a papillary lesion usually of large size (mean 2 cm, range 0.4-10 cm) located within a large cystic duct characterized by thin fibrovascular stalks devoid of a myoepithelial cell layer and a neoplastic epithelial cell population usually presenting characteristics of low grade DCIS. These cells are arranged in either solid, cribriform, micropapillary or stratified spindle cell patterns (413, 1618, 1945). Some may show a dimorphic cell...
population (featuring epithelial and myoepithelial differentiation) which may be mistaken for two cell types [1618]. Less frequently, the epithelial cell component presents the characteristics of intermediate or high grade DCIS. Concomitant DCIS may be present in the surrounding breast tissue. A complete absence of the myoepithelial cell layer in the papillary processes indicates a carcinoma; the presence of myoepithelial cells does not invariably exclude the diagnosis of intraductal papillary carcinoma, however. A myoepithelial cell layer is usually present in the lining of the duct wall into which the papillary carcinoma proliferates. Solid and transitional cell variants have been described [1752,1905]. The distinctive features of the former are production of extracellular and intracellular mucin, association with mucinous carcinoma and often a spindle cell population. Argyrophilia and neuroendocrine features have been noted in a large number of the solid cases [694,1752,2955]. The transitional cell variant is characterized by proliferation of sheets of transitional type cells overlying the fibrovascular cores. As with benign papillomas entrapment of epithelial structures within the wall can result in a pseudoinvasive pattern. A definitive diagnosis of invasive carcinoma associated with intracystic papillary carcinoma should only be considered when neoplastic epithelial structures infiltrate the breast tissue beyond the fibrous wall and have one of the recognized patterns of invasive carcinoma. Following a needle biopsy (fine needle aspiration or core biopsy), epithelial displacement into the needle tract, scar tissue or lymphatic spaces can mimic invasion [3231].

**Genetic alterations**

Genetic alterations in the form of interstitial deletions [701], LOH [1671], numerical and structural alterations at chromosomes 16q and 1q with fusion of chromosomes 16 and 1 [der(1;16)] [2961] have been described, but the significance of these alterations are as yet, unclear.

**Prognosis and predictive factors**

Intraductal papillary carcinoma in the absence of concomitant DCIS or invasive carcinoma in the surrounding breast tissue has a very favourable prognosis with no reported lymph node metastases or disease-related deaths. The presence of DCIS or invasive carcinoma in the surrounding breast tissue are associated with an increase in frequency of local recurrence (in situ or invasive) in the former, and an increase in local and metastatic rates in the latter [413].

Complete excision of intraductal papillary carcinoma with adequate sampling of the lesion and surrounding breast tissue is mandatory for treatment and appreciation of subsequent breast cancer risk. Prognosis and management of papillary type of DCIS is similar to that of common DCIS and is dealt with in the corresponding chapter.
**Immunoprofile**
There is limited data in hormone receptor expression but all tumours from one series were negative [3158].

**Ultrastructure**
Well developed Golgi apparatus and lipid droplets of different sizes are recognized in the cytoplasm [1546].

**Prognosis and predictive factors**
Despite the positive correlation of lipid content with high histological grade [873] and extensive lymph node metastases in 11 of 12 patients [2330], at the present it is not possible to establish with certainty that lipid rich carcinomas are aggressive tumours. The reported series include very heterogeneous lesions and have very short follow up.

**Secretory carcinoma**

**Definition**
A rare, low grade carcinoma with a solid, microcystic (honeycomb) and tubular architecture, composed of cells that produce abundant intracellular and extracellular secretory (milk-like) material.

**ICD-O code** 8502/3

**Synonym**
Juvenile carcinoma.

**Epidemiology**
This is a rare tumour, with a frequency below 0.15% of all breast cancers [323,1579]. The tumour usually occurs in females, but has also been seen in males including a 3-year-old boy [1401]. It occurs in children [1831] as well as adults [1519,2080]. A recent report [2430] disclosed 67 patients. Twenty-five (37%) were aged less than 20 years, 21 (31%) older than 30 years and the remaining 21 in between. Therefore, the term secretory carcinoma is preferred [2080]. Mucoid carcinoma, invasive lobular carcinoma and signet ring cell carcinoma are "secretory" carcinomas "in sensu strictu", but are all well defined distinct entities and therefore it is preferred to restrict the use of the term secretory carcinoma to this rare tumour type [2080].

**Clinical features**
The tumours manifest as indolent, mobile lumps, located near the areola in about half of the cases, this being especially so in men and children.

**Macroscopy**
SC usually presents as circumscribed nodules, greyish-white or yellow to tan in colour measuring from 0.5 to 12 cm. Larger tumours occur in older patients.

**Histopathology**
Microscopically SC is generally circumscribed, but areas of invasion of the adipose tissue are frequent. Sclerotic tissue in the centre of the lesion may be observed. The lesions are structurally composed of 3 patterns present in varying combinations:
1. A microcystic (honeycombed) pattern composed of small cysts often merge into larger spaces closely simulate thyroid follicles [2722],
2. A compact more solid, and
3. A tubular pattern consisting of numerous tubular spaces containing secretions [1519].

The neoplastic cells have been subdivided into two types [2881] with all possible combinations. One has a large amount of pale staining granular cytoplasm, which on occasions can appear foamy. The nuclei are ovoid and have a small nucleolus. Intracytoplasmic lumina (ICL) are numerous and vary from small to "enormous" [1579]. Fusion of ICL generates the microcystic structures. The secretion located within the ICL or in the extracytoplasmic compartment is intensely eosinophilic and PAS positive after diastase digestion in most of the cases; Alcian blue positive material is also seen. The two types of mucosubstances are usually independently produced and a combination of the two...
as seen in the "tagetoid pattern" of ICL described by Gad and Azzopardi [943] is rarely evident. Mitoses and necrotic areas are rare. Ductal in situ carcinoma of either the secretory or low grade type may be present, either at the margins or within the tumour (2430).

**Immunoprofile**
EMA, alpha lactalbumin and S-100 protein are frequently expressed in SC [323,1579,2430]. Estrogen receptors are mostly undetectable.

**Prognosis and predictive factors**
SC has an extremely favourable prognosis in children and adolescents but seems slightly more aggressive in older patients (2881). Isolated recurrences in children are exceptional [52], but the risk of nodal involvement is similar in young and older patients [2430]. Axillary lymph node metastases are found in approximately 15% of patients [2814] but metastases are confined to 4 lymph nodes at the most [52]. Tumours less than 2 cm in size are unlikely to progress [2881]. Simple mastectomy, as opposed to excision of the tumour, has led to a cure, with the exception of the case reported by Meis (1880). Recurrence of the tumour may appear after 20 years [1519], and prolonged follow up is advocated. Fatal cases are the exception [1519,2881] and have never been reported in children.

**Oncocytic carcinoma**

**Definition**
A breast carcinoma composed of more than 70% oncocytic cells.

**ICD-O code**
8290/3

**Historical annotation**
Oncocyte (a Greek derived word) means "swollen cell", in this case due to an accumulation of mitochondria. The term oncocyte is used when mitochondria occupy 60% of the cytoplasm [990]. Oncocytic tumours can be seen in various organs and tissues [2271,2405]. In oncocyttes, mitochondria are diffusely dispersed throughout the cytoplasm while in mitochondrion-rich cells they are grouped to one cell pole [2948]. The proportion of oncocytes present within a tumour required to call it oncocytic has been arbitrarily proposed by various authors and varies from organ to organ. In a small series of breast oncocytic carcinomas, Damiani et al. [616], using immunohistochemistry with an anti-mitochondrial antibody, found 70-90% of the neoplastic cells packed massively with immunoreactive granules.

**Epidemiology**
Only occasional cases have been described [566,616]. However, the incidence in the breast is probably underestimated as oncocyes are easily overlooked or misdiagnosed as apocrine elements [615]. All described patients have been over 60 years old. There is no predilection for site. One case occurred in a man [566].

**Macroscopy**
The largest tumour measured 2.8 cm [616].

**Histopathology**
The tumours are all similar with defined, circumscribed borders and vary from glandular to solid. The cells have abundant cytoplasm filled with small eosinophilic granules. Nuclei are monotonous and round to ovoid with a conspicuous nucleolus. Mitoses are not frequent. In situ carcinomas with a papillary appearance have been described [616].

**Differential diagnosis**
Oncocytic carcinomas can be distinguished from apocrine, neuroendocrine carcinomas and oncocytic myoepithelial lesions [615,945,2013] by their immunophenotype.

**Fig. 1.53** Secretory carcinoma. The tumour cells have abundant pink eosinophilic cytoplasm.

**Fig. 1.54** Secretory carcinoma. Abundant secretory material is evident.

**Fig. 1.55** Oncocytic carcinoma. Note well circumscribed nodule and cells with abundant eosinophilic cytoplasm.
**Immunoprofile**
The cases studied by Damiani et al. (616) showed diffuse and strong immunoreactivity with an anti mitochondrial antibody. Epithelial membrane antigen outlined the luminal borders of neoplastic glands when these were present. GCDFP-15 was absent in 3 cases and ER was observed in 90% of the cells in one (616).

**Prognosis and predictive factors**
The follow up and number of reported cases is too small to allow meaningful discussion of prognosis.

**Adenoid cystic carcinoma**

**Definition**
A carcinoma of low aggressive potential, histologically similar to the salivary gland counterpart.

**ICD-O code** 8200/3

**Synonyms**
Carcinoma adenoides cysticum, adenocystic basal cell carcinoma, cylindromatous carcinoma.

**Epidemiology**
Adenoid cystic carcinoma (ACC) represent about 0.1% of breast carcinomas (149,1581). It is important that stringent criteria are adopted to avoid misclassified lesions as found in about 50% of the cases recorded by the Connecticut Tumor Registry (2815). The age distribution, is similar to that seen in infiltrating duct carcinomas in general (2419).

**Clinical features**
The lesions are equally distributed between the two breasts and about 50% are found in the sub-areolar region (149). They may be painful or tender and unexpectedly cystic. A discrete nodule is the most common presentation.

**Macroscopy**
The size varies from 0.7 to 12 cm, with an average amongst most reported cases of 3 cm. Tumours are usually circumscribed, and microcysts are evident. They are pink, tan or grey in appearance (2309, 2419).

**Histopathology**
ACC of the breast is very similar to that of the salivary gland, lung and cervix (1538). Three basic patterns are seen: trabecular-tubular, cribriform and solid. The 3 patterns have been used by Ro et al. (2381) to develop their grading system. The cribriform pattern is the most characteristic as the neoplastic areas are perforated by small apertures like a sieve. The “apertures” are of two types: The first, also referred to as pseudolumens (1406), results from intratumoral invaginations of the stroma (stromal space). Accordingly, this type of space is of varying shape, mostly round, and contains myxoid acidic stromal mucosubstances which stain with Alcian blue (152) or strips of collagen with small capillaries. Sometimes the stromal spaces are filled by hyaline collagen and the smallest are constituted by small spherules or cylinders of hyaline material which has been shown ultrastructurally and immunohistochemically to be basal lamina (463). With immunohistochemistry a rim of laminin and collagen IV positive material outlines the stromal spaces. The second type of space is more difficult to see as it is less numerous and usually composed of small lumina. These are genuine secretory glandular structures (glandular space) which contain eosinophilic granular secretion of neutral mucosubstances, and are periodic acid-Schiff positive after diastase digestion (152).

The dual structural pattern reflects a dual cell component. The basaloid cell has scanty cytoplasm, a round to ovoid nucleus and one to two nucleoli (1581). It constitutes the bulk of the lesion and also lines the cribriform stromal spaces. The second type of cell lines the true glandular lumina, and has eosinophilic cytoplasm and round nuclei similar to those of the basaloid cells. A third type of cell seen in 14% of cases by Tavassoli and Norris (2885) consists of sebaceous elements that can occasionally be numerous. ACC contains a central core of neoplastic cells, surrounded by areas of invasion, ductal carcinoma in situ is absent at the periphery. The stroma varies from tissue very similar to that seen in the normal breast to desmoplastic, myxoid or even extensively adipose. ACC has been seen in association with adenomyoepithelioma (2994) and low grade syringomatous (adenosquamous) carcinoma (2419) which suggests a close relationship among these combined epithelial and myoepithelial tumours.

**Differential diagnosis**
ACC must be distinguished from benign collagenous spherulosis (519) and from cribriform carcinoma, which more closely simulates ACC. Cribriform carcinoma is characterized by proliferation of one type of neoplastic cell only, and one type of mucosubstance. In addition, estrogen and progesterone receptors are abundant in cribriform carcinomas and absent from virtually all cases of ACC (2381).

**Immunoprofile and ultrastructure**
The two main cell types are different at both ultrastructural and immunohistochemical levels. Ultrastructurally, the basaloid cells have myoepithelial features particularly when located at the interstitial surface that lines the pseudoglandular spaces (3244). They show thin cytoplasmic filaments with points of focal condensation (3094). These cells have been shown to be positive for actomyosin (105) and similar to myoepithelial cells are posi-
active for smooth muscle actin and calponin (902) as well as keratin 14. Nevertheless, most basaloid cells are nondescript elements showing at electron microscopy level few filaments and organelles without specific features (1507,2885). The cells that line the glandular lumina are cuboidal to spindle-shaped. When cuboidal, they have blunt microvilli along the luminal margins (secretory type). When spindle-shaped, they show abundant tonofilaments along with microvillous cytoplasmic processes such as to merit the design (2885). Accordingly, the secretory type of cell is keratin 7 positive, while the adenosquamous cell is both keratin 7 and 14 positive (902). These cells can undergo squamous metaplasia as seen in two of the cases reported by Lamovec et al. (1581). Squamous metaplasia is more common in breast ACC, but is virtually never seen in salivary gland ACC.

**Prognosis and predictive factors**

ACC is a low grade malignant tumour generally cured by simple mastectomy. Like its analogue in the salivary gland, it rarely spreads via the lymphatic stream. Local recurrence is related to incomplete excision, but patients have been reported to survive 16 years after the excision of the recurrence (2223). Only two cases of axillary node metastases have been reported (2381,3094). Distant metastases occur in about 10% of cases (544) and the lungs are frequently involved.

**Acinic cell carcinoma**

**Definition**

Acinic cell carcinoma (ACCA) is the breast counterpart of similar tumours that occur in the parotid gland and show acinic cell (serous) differentiation.

**ICD-O code**

8550/3

**Epidemiology**

ACCA is a rare tumour. Seven cases have been recorded (619,2561). Other carcinomas showing serous secretion, probably related to ACCA, have also been reported (1287,1483). It affects women between 35 and 80 years (mean 56 years) (619).

**Immunoprofile**

Most of the cells stain intensely with anti-amylase, lysozyme chymotrypsin, EMA and S-100 protein antisera (619). GCDFP-15, the mucoapocrine marker, may also be focally positive.

**Ultrastructure**

Three cases published were composed of cells with cytoplasm filled by zymogen-like granules measuring from 0.08 to 0.9 \( \mu \)m (619,2404,2561).

**Prognosis and predictive factors**

None of the 7 reported cases has died of the tumour, although follow up was limited (maximum 5 years). In two cases axillary lymph nodes contained metastases. Treatments varied from neoadjuvant chemotherapy with radical mastectomy to lumpectomy alone.

**Clinical features**

ACCA presents as a palpable nodule ranging from 2 to 5 cm size. One case was discovered at mammography (619).

**Histopathology**

The tumours show a combination of solid, microcystic and microglandular areas. One case (619) was mostly solid, and another (2404) had comedo-like areas with a peripheral rim of microglandular structures. Cytologically, the cells have abundant, usually granular, amphophilic to eosinophilic cytoplasm. The granules may be coarse and, bright red, reminiscent of those in Paneth cells or amphophilic. However, clear "hypernephroid" cytoplasm is not unusual. The nuclei are irregular, round to ovoid, with a single nucleolus. The mitotic count varies and can be as high as 15 mitoses/10 high power fields (619).

**Fig. 1.58** Adenoid cystic carcinoma. Immunostain for laminin (A) decorates the basement membranes, while cytoplasmic immunoreaction with actin (B) unmasks the neoplastic myoepithelial cell component of the tumour.

**Fig. 1.59** Acinic cell carcinoma showing aggregates of cells with granular cytoplasm.

**Fig. 1.60** Acinic cell carcinoma. Note the absence of nuclear atypia.

**Fig. 1.61** Acinic cell carcinoma, immunostain is positive for lysozyme.
**Glycogen-rich, clear cell carcinoma (GRCC)**

**Definition**  
A carcinoma in which more than 90% of the neoplastic cells have abundant clear cytoplasm containing glycogen.

**ICD-O code** 8315/3

**Synonyms**  
Clear cell carcinoma 8310/3  
Glycogen-rich carcinoma 8315/3

**Epidemiology**  
The frequency is from 1-3% of breast carcinomas [880,1264], with an age range of 41-78 years, median 57 years [2870].

**Clinical features**  
These tumours show similar presentation features to ductal NOS carcinoma.

**Macroscopy**  
The clear cell glycogen-rich carcinoma does not differ grossly from that of usual invasive or intraductal carcinoma [1165]. The neoplasm ranges from 1 to 8 cm in size [2422,2754,2870].

**Histopathology**  
A strict definition for clear cell glycogen-rich is necessary for two reasons. Carcinomas in the breast with a clear cell appearance are uncommon and are due to an artefact produced by extraction of intracytoplasmic substances during tissue processing. However, as the substances that are extracted differ, they may be of different biological significance. In addition, intracytoplasmic glycogen has been observed without significant clear cell in 58% of breast carcinoma [880]. The lesions usually have the structural features of intraductal and infiltrating ductal neoplasms but rarely those of lobular, medullary or tubular types have been noted. GRCCs has either circumscibed or infiltrative borders [880,165,2754,2870]. The in situ component, either in the pure form or in association with most invasive cases has a compact solid, comedo or papillary growth pattern. The invasive tumour is generally composed of solid nests, rarely of tubular or papillary structures. The tumour cells tend to have sharply defined borders and polygonal contours. The clear or finely granular cytoplasm contains PAS positive diastase labile glycogen. The nuclei are hyperchromatic, with clumped chromatin and prominent nucleoli.

**Differential diagnosis**  
To differentiate this tumour from other clear cell tumours, including lipid rich carcinoma, histiocytoid carcinoma, adenomyoepithelioma, clear cell hidradenoma and metastatic clear cell carcinoma (particularly of renal origin), enzyme cytochemistry and immunohistochemistry are useful [702,1165,1549,2754].

**Immunoprofile**  
Hormone receptor status is similar to ductal NOS [880].

**Prognosis and predictive factors**  
Most reports suggest that GRCC is more aggressive than typical ductal carcinoma [2313,2754]. The incidence of axillary lymph node invasion is significantly higher than in the other non-GRCC forms [1264]. The histologic grade is intermediate to high with a paucity of grade I tumours [1165]. Although follow up studies confirm that disease free and overall survival is significantly worse in GRCC, due to the low incidence, there are no multiparametric analyses to compare GRCC stage by stage with the other histological types of breast carcinoma.

**Sebaceous carcinoma**

**Definition**  
A primary breast carcinoma of the skin adnexal type with sebaceous differentiation. There should be no evidence of derivation from cutaneous adnexal sebaceous glands.

**ICD-O code** 8410/3

**Epidemiology**  
Only 4 examples of this rare mammary tumour have been observed [2876]. The women, three of whom were white, were aged 45-62 years [2876,3006].

**Clinical features**  
All the patients presented with a palpable mass.

**Macroscopy**  
The tumours range in size from 7.5-20 cm. The margins are sharply delineated, and the cut surface is solid and bright yellow.

---

**Fig. 1.62** Glycogen-rich carcinoma. **A** Cells with abundant clear cytoplasm and relatively uniform round nuclei grow in a solid pattern supported by branching vessels. **B** Note transition from typical ductal epithelial cells to clear cells in a duct adjacent to the invasive carcinoma.
**Histopathology**

The tumour is characterized by a lobulated or nested proliferation of a varying admixture of sebaceous cells with abundant finely vacuolated cytoplasm surrounded by smaller ovoid to spindle cells with a small amount of eosinophilic cytoplasm and without any vacuolization. The nuclei in both cell types are irregularly shaped to rounded, vesicular with 0 to 2 nucleoli. Mitotic figures are sparse, but may be focally abundant. Focal squamous morules may be present focally. Sebocrine cells with features of both apocrine and sebaceous cells and noted in a variety of apocrine lesions have not been a notable feature of sebaceous carcinoma.

**Immunoprofile**

The tumour cells stain positively with pan-cytokeratin (AE1/AE3/LP34). In the three cases assessed, immunostains for progesterone receptor (PR) were positive in all, two were estrogen receptor (ER) positive, and one was ER negative.

**Differential diagnosis**

Apocrine carcinoma with a large population of sebocrine cells and lipid rich carcinomas enter the differential diagnosis. The former invariably has typical apocrine cells admixed and the latter forms cords and irregular cell clusters with a more subtle vacuolization of the cells.

**Table 1.09**

<table>
<thead>
<tr>
<th>GRCC</th>
<th>Lipid rich carcinoma</th>
<th>Histiocytoid lobular carcinoma</th>
<th>Apocrine carcinoma</th>
<th>Hidradenoma</th>
<th>Secretory carcinoma</th>
<th>Adenomyo-epithelioma</th>
<th>Metastatic clear cell carcinoma from the kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell type</td>
<td>One</td>
<td>One</td>
<td>One</td>
<td>One</td>
<td>Two</td>
<td>One</td>
<td>One</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Empty</td>
<td>Foamy</td>
<td>Foamy</td>
<td>Foamy</td>
<td>Empty</td>
<td>Foamy/empty/granular</td>
<td>Empty</td>
</tr>
<tr>
<td>Nuclei</td>
<td>High grade</td>
<td>High grade</td>
<td>Low grade</td>
<td>Low grade</td>
<td>Low grade</td>
<td>Low grade</td>
<td>Low grade</td>
</tr>
<tr>
<td>PAS</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PAS diastase</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Mucicarmine</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oil red-O</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smooth actin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Vimentin +</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ (apocrine)</td>
</tr>
</tbody>
</table>

Neither has the smaller second cell population or the squamous metaplasia that may be present in sebaceous carcinoma.

**Prognosis and predictive factors**

Not much is known about the behaviour of these tumours. The 7.5 cm tumour was treated by radical mastectomy, but none of the 20 axillary nodes was positive (2876). Another recently reported case was associated with extensive metastases with sebaceous differentiation evident at the distant sites (3006).

**Inflammatory carcinoma**

**Definition**

A particular form of mammary carcinoma with a distinct clinical presentation (1607) believed to be due to lymphatic obstruction from an underlying invasive adenocarcinoma; the vast majority of cases have a prominent dermal lymphatic infiltration by tumour. Inflammatory carcinoma is a form of advanced breast carcinoma classified as T4d (51, 2976). Dermal lymphatic invasion without the character-
istic clinical picture is insufficient to qualify as inflammatory carcinoma.

ICD-O code 8530/3

Epidemiology
The age distribution is similar to ductal NOS carcinoma and breast carcinoma in general [1095,2384]. There is no recognized specific association with younger age and pregnancy but the phenomenon of peritumoral lymphatic vascular invasion is found more frequently in younger women [1095,2795]. The reported frequency of an inflammatory presentation of primary breast carcinoma varies between 1 and 10%, being influenced by the diagnostic criteria (clinical or pathological) and the nature of the reporting centre (local population clinical centre versus tertiary referral centre) [769,1641,2517].

Clinical features
The clinical findings include diffuse erythema, induration, warmth, enlargement and in some cases a palpable ill defined mass. The diagnosis is based on clinical features and should be confirmed by biopsy. Dermal lymphatic tumour emboli are not always found in small diagnostic skin biopsy samples [724,2384].

Histopathology
Despite the name, inflammatory carcinoma is not associated with any significant degree of inflammatory cell infiltration and is not an inflammatory condition. The cutaneous signs are produced as a consequence of lymphatic obstruction and consequent oedema, which produce signs mimicking an inflammatory process. Inflammatory signs can be the primary presenting abnormality (primary inflammatory carcinoma) or develop as a consequence of tumour recurrence (secondary inflammatory carcinoma).

Histologically the underlying invasive carcinoma is not regarded as having specific histological features, the majority of tumours have ductal NOS and are of grade 3 morphology [1708,1851]. These tumours often have an associated lymphoid infiltrate usually of mature lymphocytes and plasma cells, a low frequency of estrogen receptor positivity [445,1490] and ERBB2 overexpression [1074]. The skin often shows co-existing features associated with lymphatic obstruction including separation of collagen fibres with broadening of the reticular dermal layer due to oedema. Involved dermal lymphatics may have an associated lymphoplastacytic infiltrate [2427]. Secondary or recurrent inflammatory carcinoma has been shown to be associated more with ductal NOS and apocrine histological types of breast carcinoma and is rare following presentation with other types, papillary, medullary and mucinous [2384]. The skin may also show stromal metastatic deposits of tumour particularly in secondary or recurrent inflammatory carcinoma.

Differential diagnosis
There may be a discrepancy between clinical presentation with inflammatory features and presence of dermal lymphatic emboli. Dermal vascular emboli may not be present in a biopsy taken from erythematous or oedematous area, or may be present in skin beyond the clinical skin changes. The skin biopsy will usually also show dermal lymphatic dilatation. The clinical features of inflammatory carcinoma are generally regarded as specific but underlying true inflammatory conditions should be excluded if histological confirmation is not achieved.

Prognosis and predictive factors
Prior to the introduction of systemic therapy the prognosis of inflammatory carcinoma even when treated by mastectomy, was very poor with 5 year survival under 5% [1052,2384]. Use of systemic chemotherapy has produced an improvement in survival figures reported as 25 to 50% at 5 years [406,828,1805,1907,2154]. In cases treated with neoadjuvant chemotherapy or radiotherapy, residual tumour, including intravascular emboli, are usually present in the mastectomy specimen even when a clinical response has been observed [2427]. Mastectomy and radiotherapy are considered beneficial for initial local control and palliation of symptoms [406,582,2243]. There are no consistent findings with respect to influence of additional clinical features such as presence of a clinical mass or findings in skin biopsy on survival. However, response to chemotherapy and radiotherapy, and pathological response have been shown to be associated with improved disease free survival [473,828,841,1826].

Bilateral breast carcinoma
Definition
A synchronous breast cancer is one detected within two months of the initial primary tumour. Approximately 5-10% of women treated for breast cancer will have either synchronous bilateral cancers or will develop a subsequent contralateral breast cancer (CBC) [448,872,1219,1491,2383]. The prevalence of synchronous bilateral breast cancer is approximately 1% of all breast cancers [448,648,872,1491,1936]. An increase in the detection
of synchronous cancers has been reported following the introduction of bilateral mammography for the investigation of symptomatic breast disease and for population based breast screening (751,872,1491,1492).

It is well recognized that a previous history of breast cancer increases the risk of subsequent breast cancer in the contralateral breast. The reported annual hazard rates of between 0.5-1% per year (448,872,1491,2383,2798) appear relatively constant up to 15 years (1491) giving a cumulative incidence rate for survivors of around 5% at 10 years and 10% at 15 years.

Family history (253,448,1219) and early age of onset (35,1168,2798) have been reported to increase the risk of CBC development in some studies but others have found no such associations with either early age of onset (252,253,872) or family history (35,872). One study has reported that family history, early age of onset and lobular histology are independent predictors of metachronous contralateral breast cancer development (1492).

These characteristics suggest a possible genetic predisposition. Women with a strong family history who develop breast cancer at an early age are at considerable risk of contralateral breast cancer as a first event of recurrence particularly if the first primary is of lobular histology or is of favourable prognostic type (1491,1492).

Patients with metachronous CBC are younger at the age of onset of the original primary. Many, but not all, series report that a higher percentage of the tumours are of lobular type (35,252,872,1219,1241,1492,2383). This observation does not imply that tumours of lobular type, in isolation from other risk factors such as young age and family history, should be considered to have a higher risk of bilateral breast involvement (1491). A greater frequency of multicaentricty in one or both breast tumours has also been reported (355). There does not appear to be any association with histological grade, other tumour types or the stage of the disease (355,1491,1492).

Prognosis and predictive features

Theoretically women with synchronous CBC have a higher tumour burden than women with unilateral disease which may jeopardize their survival prospects (1035). Indeed, synchronous CBC appears to have a worse prognosis than unilateral cohorts or women with metachronous CBC (164,1092,1233). Others have failed to demonstrate any survival difference between women with unilateral and those with synchronous CBC (911,1053,2555).

**Tumour spread and staging**

**Tumour spread**

Breast cancer may spread via lymphatic and haematogenous routes and by direct extension to adjacent structures. Spread via the lymphatic route is most frequently to the ipsilateral axillary lymph nodes, but spread to internal mammary nodes and to other regional nodal groups may also occur. Although breast cancer may metastasize to any site, the most common are bone, lung, and liver. Unusual sites of metastasis (e.g. peritoneal surfaces, retroperitoneum, gastrointestinal tract, and reproductive organs) and unusual presentations of metastatic disease are more often seen with invasive lobular carcinomas than with other histological types (319,704,1142,1576).

Several models have been proposed to explain the spread of breast cancer. The Halsted model, assumes a spread from the breast to regional lymph nodes and from there to distant sites. This hypothesis provided the rationale for radical en bloc resection of the breast and regional lymph nodes. Others suggest a systemic disease from inception, which implies that survival is unaffected by local treatment. However, clinical behaviour suggests that metastases occur as a function of tumour growth and progression (1181). This concept is supported by the results of axillary sentinel lymph node studies. A sub-classification of isolated tumour cells is provided in TNM publications (51,1195,2976).

**Measurement of tumour size**

The microscopic invasive tumour size (I) is used for TNM Classification (pT). The dominant (largest) invasive tumour focus is measured, except in multifocal tumours where no such large single focus is apparent. In these cases the whole tumour size (w) is used.

**Somatic genetics of invasive breast cancer**

As in other organ sites, it has become evident that breast cancers develop through a sequential accumulation of genetic alterations, including activation of oncogenes (e.g. by gene amplification), and inactivation of tumour suppressor genes, e.g. by gene mutations and deletions.

**Cytogenetics**

As yet no karyotypic hallmarks of breast cancer have been identified, such as the t(8;14) in chronic myelogenous leukaemia (CML), or the (12p) in testicular cancer. There is not even a cytogenetic marker for any of the histological subtypes of breast cancer. One reason for this is certainly the technical difficulty of obtaining sufficient numbers of good
quality metaphase spreads from an individual tumour. However, it may also relate to the genetic complexity of this tumour. Nonetheless, several hundred primary tumours have been karyotyped to date, allowing some general patterns to be discerned (1879). An increased modal chromosome number is the most conspicuous characteristic in many tumours, keeping with the finding that approximately two-thirds of all breast cancers have a hyperploid DNA-content in flow-cytometric analysis. Unbalanced translocations are most often seen as recurrent changes, with the i(1)(q10) and the der(1;16)(q10;p10) the most prominent. For the latter, it is not clear whether loss of 16q or gain of 1q is the selective change, or whether both are. Other conspicuous changes are i(8)(q10), and subchromosomal deletions on chromosomes 1 (bands p13, p22, q12, q42), 3 (p12-p14), and 6 (q21). No specific genes have been associated with any of these changes.

DNA amplification

Classic cytogenetic analysis had already indicated that double minute chromosomes and homogeneously staining regions, are a frequent occurrence in breast cancer. These regions were later shown to contain amplified oncogenes (see below). Comparative genomic hybridization (CGH) has identified over 20 chromosomal subregions with increased DNA-sequence copy-number, including 1q31-q32, 8q24, 11q13, 16p13, 17q12, 17q22-q24 and 20q13. For many of these regions, the critically amplified genes are not precisely known. Chromosomal regions with increased copy-number often span tens of megabases, suggesting the involvement of more than one gene. Loss of chromosomal material is also detected by CGH, and this pattern is largely, though not completely, in agreement with loss of heterozygosity data (see below).

Oncogenes

A number of known oncogenes were initially found to be amplified in subsets of breast cancer by Southern blot analyses and fluorescent in situ hybridization. Subsequently, a number of genes have been identified as critical targets for DNA amplifications by a combination of CGH and gene expression analysis. Oncogenic activation by point-mutation seems to be rare in breast tumours. Listed by chromosome region, the following (onco)gene amplifications seem to be involved in the progression of breast cancer.

1p13-21: DAM1 has been found amplified in two breast cancer cell lines, but it is not certain whether this gene is driving the amplification (1962).

7p13: The epidermal growth factor receptor gene (EGFR), encoding a cell membrane localized growth factor receptor, is amplified in less than 3% of breast carcinomas.

8p12: The fibroblast growth factor receptor 1 gene (FGFR1; formerly called FLG) encoding a cell membrane localized receptor for fibroblast growth factor, is amplified in approximately 10% of breast carcinomas (41).

8q24: MYC encodes a nuclear protein involved in regulation of growth and apoptosis. MYC amplification is found in approximately 20% of breast (250,596). The MYC protein has a very short half-life, precluding the assessment of protein

![Fig. 1.65](image-url)
The fibroblast growth factor receptor-2 (FGFR2, formerly: BEX) gene encodes a cell membrane located receptor for fibroblast growth factor. This gene is amplified in approximately 12% of breast carcinomas [41].

11q13: Amplification of the cyclin D1 gene (CCND1), encoding a nuclear protein involved in cell cycle regulation, has been found in 15-20% of breast tumors, in association with estrogen receptor positivity. Cyclin D1 can also bind to the estrogen receptor, resulting in ligand-independent activation of the receptor (3273). Immunohistochemically, cyclin D1 appears to be overexpressed in 80% of invasive lobular carcinomas, but is not always accompanied by CCND1 gene amplification [2133].

17q12: The human epidermal growth factor receptor-2 (ERBB2) proto-oncogene (also known as HER2, and equivalent to the rodent neu gene) encodes a 185-KD transmembrane glycoprotein with intrinsic tyrosine kinase activity. A ligand for ERBB2 has not been identified but it is hypothesized that ERBB2 amplifies the signal provided by other receptors of this family by heterodimerizing with them. Ligand-dependent activation of ERBB1, ERBB3, and ERBB4 by EGF or heregulin results in heterodimerization and, thereby, ERBB2 activation. ERBB2 amplification results in overexpression of ERBB2 protein, but not all tumours with overexpression have amplified 17q12. Overexpression is found in approximately 20-30% of human breast carcinomas (2962). In breast cancers with normal ERBB2 copy number, expression of ERBB2 may be variable but is very rarely as high as that in tumours with ERBB2 amplification (usually 10-fold to 100-fold higher and equivalent to millions of monomers). Numerous studies have investigated the relationship between ERBB2 status and clinicopathological characteristics in breast cancer (2962).

17q22-q24: At least three genes (RPS6KB1, PAT1, and TXB2) have been found to be co-amplified and overexpressed in ~10% of breast cancers [181]. Further analysis identified RPS6KB1, MUL, APPBP2, TRAP240 and one unknown gene to be consistently overexpressed in two commonly amplified sub-regions [1896]. The ribosomal protein S6 kinase (RPS6KB1) is a serine-threonine kinase whose activation is thought to regulate a wide array of cellular processes involved in the mitogenic response including protein synthesis, translation of specific mRNA species, and cell cycle progression from G1 to S phase. It is presently unknown whether the CSE1L/CAS gene, the NCOA3 gene or any other gene in this region serves as the target for the amplification, which is found in approximately 15% of breast carcinomas. Three independent regions of amplification have been identified and their co-amplification is common. Cellular apoptosis susceptibility (CAS) encodes a protein, which may have a function in the control of apoptosis and cell proliferation [346]. NCOA3 gene encodes a co-activator of the estrogen receptor (109), and its amplification has been found to be associated with estrogen receptor positivity. High resolution mapping of the amplified domains has suggested that a putative oncogene, ZNF217, and CYP24 (encoding vitamin D 24 hydroxylase), whose overexpression is likely to lead to abrogation of growth control mediated by vitamin D, may be targets for the amplification [60]. The STK15 gene (also known as BTAK and Aurora-A) is amplified in approximately 12% of primary breast tumours, as well as in breast, ovarian, colon, prostate, neuroblastoma, and cervical cancer cell lines [3259]. STK15 encodes a centrosome-associated serine-threonine kinase, and may also be overexpressed in tumours without amplification of 20q13 (1885). Centrosomes appear to maintain genomic stability through the establishment of bipolar spindles during cell division, ensuring equal segregation of replicated chromosomes to daughter cells. Deregulated duplication and distribution of centrosomes are implicated in chromosomal segregation abnormalities, leading to aneuploidy seen in many cancer cell types. Elevated STK15 expression induces centrosome amplification and overrides the checkpoint mechanism that monitors mitotic spindle assembly, leading to chromosomal instability [63,1885,3259].

Loss of heterozygosity (LOH)

Loss of heterozygosity (LOH) has been found to affect all chromosome arms...
in breast cancer to varying degrees (265,680). Unfortunately, collation of LOH data into a coherent map has been complicated enormously by the use of different terminology and technology in this area [679]. A tumour specific loss of an allele, but also an imbalance in allele intensities (allelic imbalance) are both called LOH. LOH is often equated with 'deletion' although it may also be caused by somatic recombination. Complete loss of an allele can only be reliably and unequivocally measured in tumour DNA samples with very low levels of contamination from non-malignant cells (i.e. <25%). Without microdissection or flow sorting of tumour cells, this cannot be obtained from many primary breast cancer tissues. In addition, allelic imbalance can also be caused by chromosomal aneuploidy (trisomies etc), or low-copy amplification of certain chromosome regions, which is fundamentally different from 'classical' LOH. These factors impede meta-analysis of published allelic imbalance/LOH data in breast cancer, although it is clear that there are chromosome arms where LOH occurs at very high rates.

LOH is interpreted in the light of Knudson’s two-hit model for the inactivation of a tumour suppressor gene [679]. Numerous studies have attempted to map common regions of LOH on chromosome arms with frequent LOH. Such a region could flag the position of a tumour suppressor gene more accurately, aiding its identification.

Tumour suppressor genes

Several chromosome regions showing frequent LOH have been extensively investigated because of the presence of appealing candidate tumour suppressor genes. Many of these regions are supported by CGH and cytogenetic analyses. They include 1p32-36, 3p14-21, 6q25, 7q31, 8p12-21, 9p21, 13q12-q14, 16q22, 16q24, 17p13, 18q21. Several interesting candidate tumour suppressor genes lie in these regions (for example, FANCA in 16q24, HIC1 in 17p13, PDGFRα in 8p21, FHT in 3p14, CDKN2A in 9p21, TP73 in 1p36), but their role in breast cancer remains to be established. By definition, a tumour suppressor gene is a gene whose normal function inhibits the initiation or progression of tumour growth. This can be demonstrated by cell biological, biochemical or genetic evidence, which are not always in full agreement. For example, transfection of the retinoblastoma gene RB1 into some breast cancer cell lines reverts their tumorigenic phenotype in vitro, yet no inactivating RB1 mutations have been reported in primary breast tumours. RASSF1A is located in the region 3p21, which is frequently deleted in breast cancer. It might serve as a Ras effector, mediating the apoptotic effects of oncogenic RAS [621]. In breast tumour cell lines, the promoter of RASSF1A is highly methylated and its expression is down-regulated [622]. In primary tumours, the proportion with promoter-hypermethylation is lower, and so is the effect on expression down-regulation [42]. No inactivating mutations in the coding regions have been detected, and the relationship between LOH and promotor-methylation status is presently unclear [1368]. To avoid these difficulties in interpreting the available data, we shall restrict ourselves here to those genes for which acquired inactivating mutations in the coding region have been demonstrated in a proportion of primary breast cancers or breast cancer cell lines. Using these criteria, very few tumour suppressor genes have been identified in breast cancer. Listed by chromosomal site, they are:

6q26: IGF2R. The M6P/IGF2R gene, encoding the insulin-like growth factor II (IGF-II)/mannose-6-phosphate receptor, is frequently inactivated during carcinogenesis. IGF2R is postulated to be a tumour suppressor due to its ability to bind and degrade the mitogen IGF-II, promote activation of the growth inhibitor TGFβ, and regulate the targeting of lysosomal enzymes. Several missense mutations in M6P/IGF2R disrupt the ligand binding functions of the intact IGF2R. Missense mutations have been found in about 6% of primary breast tumours [1125].

7q31: ST7 (for suppression of tumourigenicity 7) is a gene with unknown cellular function. Transfection of ST7 into the prostate-cancer-derived cell line PC3, abrogated its tumourigenicity in vivo. Three breast tumour cell lines harboured frame shifting mutations in ST7, which was accompanied by LOH in at least one of them. A role of ST7 in primary breast cancer has been questioned [358,2912].

8q11: RB1CC1. The RB1CC1 protein is a key regulator of the tumour suppressor gene RB1. It is localized in the nucleus and has been proposed to be a transcription factor because of its leucine zipper motif and coiled-coil structure. Seven of 35 (20%) primary breast cancers examined contained mutations in RB1CC1, including 9 large interstitial deletions predicted to yield markedly truncated RB1CC1 proteins [440]. In all 7 cases, both RB1CC1 alleles were inactivated, and in each case both mutations were acquired somatically.

**Fig. 1.67** Lobular carcinoma of breast. Immunohistochemical staining of a lobular breast carcinoma with a mutated CDH1 gene. Normal duct epithelium shows positive staining for membrane associated E-cadherin, which is lacking in tumour cells.
16q22: CDH1. The cell-cell adhesion molecule E-cadherin acts as a strong invasion suppressor in experimental tumour cell systems. Frequent inactivating mutations have been identified in CDH1 in over 60% of infiltrating lobular breast cancers, but not in ductal carcinomas [251]. Most mutations cause translational frameshifting, and are predicted to yield secreted truncated E-cadherin fragments. Most mutations occur in combination with LOH, so that no E-cadherin expression is detectable immunohistochemically. This offers a molecular explanation for the typical scattered tumour cell growth in infiltrative lobular breast cancer. Lobular carcinoma in situ (LCIS) has also been found to contain CDH1 mutations [3034].

17p13: TP53 encodes a nuclear protein of 53 kD, which binds to DNA as a tetramer and is involved in the regulation of transcription and DNA replication. Normal p53 may induce cell cycle arrest or apoptosis, depending on the cellular environment [3147]. Mutations, which inactivate or alter either one of these functions, are found in approximately 20% of breast carcinomas [2237]. Most of these are missense changes in the DNA-binding domain of the protein; a small proportion (~20%) are frame shifting. The large majority of these mutations are accompanied by loss of the wildtype allele (LOH). Missense mutations in TP53 can be detected immunohistochemically because mutated p53 fails to activate expression of MDM2. The MDM2 protein normally targets p53 for ubiquitin-mediated degradation, constituting a feedback loop to maintain low levels of p53 protein in the cell.

Microsatellite instability
Microsatellite instability (MSI) is a genetic defect caused by mutations in mismatch repair genes (MLH1, MSH2, MSH6, PMS1, and PMS2), reflected by the presence of multiple alleles at loci consisting of small tandem repeats or mononucleotide runs. MSI in breast cancer is negligible, with the possible exception of breast cancer arising in the context of the HNPCC inherited colon cancer syndrome. The most convincing study is probably that of Anbazhagan et al., who have analysed 267 breast carcinomas at 104 microsatellite loci (85); not one single case of MSI was detected. Somatic mutations in the mismatch repair genes have not yet been detected in breast cancer.

Gene expression patterns
Expression profiling is expression-analysis of thousands of genes simultaneously using microarrays [69,1072,1171,2218,2756,3104]. Tumours show great multidimensional variation in gene expression, with many different sets of genes showing independent patterns of variation. These sets of genes relate to biological processes such as proliferation or cell signalling. Despite this variation, there are also striking similarities between tumours, providing new opportunities for tumour classification. ER-positive and ER-negative cancers show distinct expression profiles [1072,2986,3104]. Breast cancers arising in women carrying a BRCA1 mutation could be distinguished from sporadic cases, and from those that developed in BRCA2 carriers [1171,2986]. Although this field is still in its infancy, 5 distinct gene expression patterns were discerned among 115 tumours [2218,2756,2757], one basal-like, one ERBB2-overexpressing, two luminal-like, and one normal breast tissue-like subgroup. Approximately 25% of the tumours did not fit any of these classifications. The luminal-like tumours express keratins 8 and 18, and show strong expression of the estrogen receptor cluster of genes. The tumours of the other groups were mainly ER-negative. The basal-like group is characterized by high expression of keratins 5/6 and 17 and laminin. The ERBB2 group also expresses several other genes in the ERBB2 amplicon, such as GRB7. The normal breast-like group shows a high expression of genes characteristic of adipose tissue and other non-epithelial cell types. Cluster analyses of 2 published, independent data sets representing different patient cohorts from different laboratories, uncovered the same breast cancer subtypes [2757].

Somatic genetics of breast cancer metastases
According to the present view, metastasis marks the end in a sequence of genomic changes underlying the progression of an epithelial cell to a lethal cancer. Not surprisingly, therefore, lymph node metastases and distant metastases in general contain more genomic aberrations than their cognate primary tumours [1117,2028]. Flow cytometric DNA content measurement has demonstrated extensive DNA ploidy heterogeneity in primary breast carcinomas, with the current presence of diploid and multiple aneuploid DNA stemlines. Identical het-
erogeneity is often present in their cognate lymph node metastases, suggesting that the generation of DNA ploidy diversity has taken place prior to metastasis \(^{197}\). LOH analysis of these DNA ploidy stemlines showed that all allelic imbalances observed in the diploid clones recurred in the cognate aneuploid clones, but were, in the latter, accompanied by additional allelic imbalances at other loci and/or chromosome arms \(^{313}\). This indicates that the majority of allelic imbalances in breast carcinomas are established during generation of DNA ploidy diversity. Identical allelic imbalances in both the diploid and aneuploid clones of a tumour suggests linear tumour progression. But the simultaneous presence of early diploid and advanced aneuploid clones in both primary and metastatic tumour sites suggests that the precursors of metastasis are derived from the most advanced clone within the primary tumour, these data suggest that breast tumour cells may disseminate in a far less progressed genomic state than previously thought, and that they acquire genomic aberrations typical of metastatic cells thereafter. These findings have two major clinical implications. First, all adjuvant therapies that do not target genetic or epigenetic events occurring early during tumourigenesis are unlikely to eradicate minimal residual disease, because disseminated cancer cells may not uniformly share mutations that are acquired later on. Second, because disseminated cells progress independently from the primary tumour, a simple extrapolation from primary tumour data to disseminated cancer cells is impossible.

### Genetic susceptibility: familial risk of breast cancer

**Introduction**

Breast cancer has been recognized for over 100 years as having a familial component \(^{349}\). Epidemiological investigations have attempted to quantify the risks associated with a positive family history and to examine whether the pattern of related individuals is consistent with the effects of a single gene of large effect, shared environmental effects, many genes acting in an additive manner, or most likely, a combination of two or more of these. In addition a number of specific genes have been identified as playing a role. The most important ones are **BRCA1** and **BRCA2** which are discussed in Chapter 8. However, these two genes account for only about a fifth of overall familial breast cancer \(^{107,592,2230}\) and explain less than half of all high risk, site-specific breast cancer families \(^{898,2631}\).

**Familial risk of breast cancer**

**Fig. 1.69** Hierarchical clustering of 115 tumour tissues and 7 nonmalignant tissues using gene expression profiling. Experimental dendrogram showing the clustering of the tumours into five subgroups (top panel). Gene clusters associated with the ERBB2 oncogene, luminal subtype B, basal subtype, normal breast-like group, luminal subtype A with high estrogen receptor expression. Scale bar represents fold change for any given gene relative to the median level of expression across all samples. From T. Sorlie et al. \(^{2757}\).

**Introduction**

Breast cancer has been recognized for over 100 years as having a familial component \(^{349}\). Epidemiological investigations have attempted to quantify the risks associated with a positive family history and to examine whether the pattern of related individuals is consistent with the effects of a single gene of large effect, shared environmental effects, many genes acting in an additive manner, or most likely, a combination of two or more of these. In addition a number of specific genes have been identified as playing a role. The most important ones are **BRCA1** and **BRCA2** which are discussed in Chapter 8. However, these two genes account for only about a fifth of overall familial breast cancer \(^{107,592,2230}\) and explain less than half of all high risk, site-specific breast cancer families \(^{898,2631}\).

**Family risk of breast cancer**

**Fig. 1.70** Auxillary lymph node. The nodal architecture is destroyed by massive metastatic ductal carcinoma.
first-degree relatives of breast cancer probands diagnosed before age 80 estimated a relative risk of 1.8 in the relatives (1029). When the breast cancer was of early onset (diagnosed before age 50), the relative risk among first-degree relatives increased to 2.6 and the risk for early-onset breast cancer among these relatives was 3.7 (95% CI: 2.6—4.6). The risk to subsequent relatives in families with two affected sisters was increased to 2.7 with a particularly high risk of 4.9 of early onset breast cancer. A second registry-based study in Sweden found essentially identical results to the Utah study (715).

Perhaps the largest population-based study (the Cancer and Steroid Hormone (CASH) case-control study) of probands with breast cancer diagnosed between the ages of 20 and 54 estimated the risk of breast cancer in first-degree relatives compared with controls was 2.1 (501). A study of cancer at a number of sites in a large set of twins in Scandinavia (1658), estimated the proportion of variance due to genetic (heritability), shared environment, and random (individual-specific) environmental effects for each cancer site. Based on this data, the authors calculated a co-twin relative risk of 2.8 in DZ and 5.2 in MZ twins, and estimated that 27% of breast cancer is due to inherited cause while only 6% could be attributed to shared environment.

The role of other factors with respect to family history has been examined. Larger familial effects among relatives of young bilateral probands compared with young probands with unilateral breast cancer have been found (93,1246,2129). The relationship of histology to familial risks to all other sites among such probands was examined statistically and random (individual-specific) environmental effects for each cancer site. Based on this data, the authors calculated a co-twin relative risk of 2.8 in DZ and 5.2 in MZ twins, and estimated that 27% of breast cancer is due to inherited cause while only 6% could be attributed to shared environment.

The role of other factors with respect to family history has been examined. Larger familial effects among relatives of young bilateral probands compared with young probands with unilateral breast cancer have been found (93,1246,2129). The relationship of histology to familial risks to all other sites among such probands was examined statistically and random (individual-specific) environmental effects for each cancer site. Based on this data, the authors calculated a co-twin relative risk of 2.8 in DZ and 5.2 in MZ twins, and estimated that 27% of breast cancer is due to inherited cause while only 6% could be attributed to shared environment.

The role of other factors with respect to family history has been examined. Larger familial effects among relatives of young bilateral probands compared with young probands with unilateral breast cancer have been found (93,1246,2129). The relationship of histology to familial risks to all other sites among such probands was examined statistically and random (individual-specific) environmental effects for each cancer site. Based on this data, the authors calculated a co-twin relative risk of 2.8 in DZ and 5.2 in MZ twins, and estimated that 27% of breast cancer is due to inherited cause while only 6% could be attributed to shared environment.

The role of other factors with respect to family history has been examined. Larger familial effects among relatives of young bilateral probands compared with young probands with unilateral breast cancer have been found (93,1246,2129). The relationship of histology to familial risks to all other sites among such probands was examined statistically and random (individual-specific) environmental effects for each cancer site. Based on this data, the authors calculated a co-twin relative risk of 2.8 in DZ and 5.2 in MZ twins, and estimated that 27% of breast cancer is due to inherited cause while only 6% could be attributed to shared environment.

Possible models to explain the familial risk of breast cancer

BRCA1 and BRCA2 explain only a minority (about 20%) of the overall familial risk of breast cancer although they may contribute much more substantially to the four-fold increased risk at younger ages. Assuming an overall two-fold increased risk among first-degree female relatives

### Table 1.10

<table>
<thead>
<tr>
<th>Relative affected, status of proband</th>
<th>Estimate of relative risk</th>
<th>(Reference) (Study Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>3.0</td>
<td>(1221a) (a)</td>
</tr>
<tr>
<td>Sister</td>
<td>3.0</td>
<td>(1221a) (a)</td>
</tr>
<tr>
<td>Mother</td>
<td>2.0</td>
<td>(2214) (a)</td>
</tr>
<tr>
<td>Sister</td>
<td>3.0</td>
<td>(2214) (a)</td>
</tr>
<tr>
<td>Sister, premenopausal proband</td>
<td>5.0</td>
<td>(92a) (b)</td>
</tr>
<tr>
<td>Sister, postmenopausal proband</td>
<td>2.0</td>
<td>(92a) (b)</td>
</tr>
<tr>
<td>First-degree relative (FDR)</td>
<td>2.0</td>
<td>(346a) (c)</td>
</tr>
<tr>
<td>Sister, bilateral proband</td>
<td>6.0</td>
<td>(2129) (c)</td>
</tr>
<tr>
<td>Sister</td>
<td>2.0</td>
<td>(412a) (d)</td>
</tr>
<tr>
<td>Mother</td>
<td>2.0</td>
<td>(412a) (d)</td>
</tr>
<tr>
<td>First-degree relative (FDR)</td>
<td>2.0</td>
<td>(2596a) (a)</td>
</tr>
<tr>
<td>FDR&lt;45, proband&lt;45</td>
<td>3.0</td>
<td>(2596a) (a)</td>
</tr>
<tr>
<td>FDR&gt;45, proband&gt;45</td>
<td>1.5</td>
<td>(2596a) (a)</td>
</tr>
<tr>
<td>First degree relative</td>
<td>2.1</td>
<td>(501) (c)</td>
</tr>
<tr>
<td>First degree relative, proband &lt;55</td>
<td>2.3</td>
<td>(1248) (a)</td>
</tr>
<tr>
<td>First degree relative, proband &gt;55</td>
<td>1.6</td>
<td>(1246) (a)</td>
</tr>
<tr>
<td>FDR, bilateral proband</td>
<td>6.4</td>
<td>(1246) (a)</td>
</tr>
<tr>
<td>First degree relative</td>
<td>2.3</td>
<td>(3720a) (c)</td>
</tr>
<tr>
<td>Second degree relative</td>
<td>1.8</td>
<td>(3720a) (c)</td>
</tr>
<tr>
<td>First degree relative</td>
<td>1.8</td>
<td>(896) (a)</td>
</tr>
<tr>
<td>FDR&lt;50, proband&lt;50</td>
<td>3.7</td>
<td>(896) (a)</td>
</tr>
<tr>
<td>FDR, 2 affected probands</td>
<td>2.7</td>
<td>(896) (a)</td>
</tr>
<tr>
<td>Mother</td>
<td>1.9</td>
<td>(715) (a)</td>
</tr>
<tr>
<td>Sister</td>
<td>2.0</td>
<td>(715) (a)</td>
</tr>
</tbody>
</table>

(a) Ratio of observed frequencies in cancer families to expected frequencies in the general population; (b) Odds ratio from case-control study with non-cancer controls; (c) Odds ratio from case-control study with non-cancer controls; (d) Relative risk from prospective study.
of breast cancer cases and that, as is likely, these genes act in an additive manner with the other loci involved in familial aggregation, then we are left with a residual familial risk of 1.8 to be explained by other genes and/or correlated family environment. There could be several genes similar in action to BRCA1 and BRCA2, with lower breast cancer risks, or a set of more common polymorphisms in biologically relevant genes, each associated with only a small increase in risk, or something in between. Genes are not the only factor which could cause the observed familial correlation. Shared lifestyle or environmental risk factors would also cause some degree of familial clustering, however it can be demonstrated that the known environmental risk factors for breast cancer are unlikely to contribute significantly to the overall familial risk [1238].

Based on a model of the contribution of genetic variation to the overall familial risk, it can be estimated that variation in as few as 70 of the 30,000 genes in the human genome may contribute to breast cancer susceptibility. Of course, this model is based on a number of unverifiable assumptions and does not include potential gene-gene and gene-environment interactions, so should be interpreted cautiously. However, it seems clear that there are not going to be hundreds of loci involved (or if there are, they will be impossible to find given the weakness of the effects). Only until more of these loci are identified, and their interaction with known epidemiological risk factors assessed, will we be able to untangle the underlying causes of the observed familial risk.

**Prognosis and predictive factors**

**Clinical features**

**Age**

The prognostic significance of age and menopausal status in patients with breast carcinoma is controversial. Younger patients have been found to have a poor prognosis [59,2029], a favourable outcome (2500) or no correlation has been found with age at all [1207]. These discrepancies may be due to differences in patient selection, age grouping, and other factors, including high grade, vascular invasion, extensive in situ component, steroid receptor negativity, high proliferation, TP53 abnormalities. An increased incidence of node positivity was found in two large studies of patients under 35 years.

**Pregnancy**

Breast cancer developing during pregnancy is generally considered to have an unfavourable prognosis. There is, however, conflicting data as to whether this is an independent factor. It may be partly, or entirely, due to the poor prognosis associated with young age and also the fact that the cancer is often detected at a late stage as small tumours are not felt in the pregnant or lactating breast [91,311,1079]. Pregnancy in women who have been treated for breast cancer does not appear to affect prognosis [119].

**Morphological factors**

The traditional pathological factors of lymph node status, tumour size, histological type, and histological grade are the most useful prognostic factors in breast cancer patients [886,1763], although this is now challenged by gene expression profiling.

**Lymph node status**

The status of the axillary lymph nodes is the most important single prognostic factor for patients with breast cancer. Numerous studies have shown that disease-free and overall survival rates decrease as the number of positive nodes increases [886]. The clinical significance of micrometastases and isolated tumour cells in the nodes, particularly those identified exclusively by immunohistochemistry, remains a matter of debate [71,1655] although virtually all studies with more than 100 patients have shown that micrometastases are associated with a small but significant decrease in disease-free and/or overall survival [1655]. Approximately 10-20% of patients considered to be node-negative by routine pathological examination have identifiable tumour cells as determined by serial sectioning, immunohistochemical staining for epithelial markers, or both. However, at present, it appears premature to recommend the routine use of step sections and/or immunohistochemistry to evaluate sentinel or non-sentinel lymph nodes [71].

**Tumour size**

Tumour size is an important prognostic factor. Even among patients with breast cancers 1 cm and smaller (T1a and T1b), size is an important prognostic factor for axillary lymph node involvement and outcome [461]. However, the manner in which the pathological tumour size is reported varies. Some pathologists report the macroscopic size, some a microscopic size that includes both the invasive and in situ components, and others report the microscopic size of the invasive compo-
sent only. There is often poor correlation between the tumour size determined by gross pathological examination and the size of the invasive component as determined by histological measurement [27]. The size of the invasive component is clinically significant, and so the pathological tumour size for classification (pT) is a measurement of only the invasive component [51]. Therefore, when there is a discrepancy between the gross and the microscopic size of the invasive component, the microscopic size takes precedence, and should be indicated in the pathology report and used for pathological staging.

**Histological type**

Some special histological types of breast cancer are associated with a particularly favourable clinical outcome [771,2433]. These include tubular, invasive cribriform, mucinous, and adenoid cystic carcinomas. Some authors also include tubulolobular and papillary carcinomas. The 20-year recurrence-free survival of special type tumours 1.1 to 3.0 cm in size is similar to that of invasive ductal carcinomas of no special type 1 cm and smaller (87% and 86%, respectively) [2433]. The prognostic significance of medullary carcinoma remains controversial and is discussed elsewhere (see medullary carcinoma).

**Histological grade**

Grading is recommended for all invasive carcinomas of the breast, regardless of morphological type [1984, 2216,2905]. This practice has been criticized by some pathologists who feel that grading is not appropriate for the special histological types such as pure tubular, invasive cribriform, mucinous, medullary and infiltrating lobular carcinomas. For example, most infiltrating lobular carcinomas, especially those of classical subtype, are assessed as grade 2 and the overall survival curve of lobular carcinoma overlies that of all other types of grade 2 carcinoma. In mucin carcinoma and in carcinoma of mixed morphological type, grading provides a more appropriate estimate of prognosis than type alone [2216]. In medullary carcinoma no additional prognostic value has been found. Higher rates of distant metastasis and poorer survival are seen in patients with higher grade (poorly differentiated) tumours, independent of lymph node status and tumour size [550,777,836, 868,886,1031,1763,2030,2434]. Tumour grading has prognostic value even in breast cancers 1 cm and smaller [461]. The optimal grading method [777] has been detailed earlier in this chapter. The combination of histological type and grade provides a more accurate assessment of prognosis than does histological type alone [2216]. Histological grade may also provide useful information with regard to response to chemotherapy and, therefore, be a predictive factor as well as a prognostic indicator. Several studies have suggested that high histological grade is associated with a better response to certain chemotherapy regimens than low histological grade [2254]. However, additional studies are required to define this relationship more clearly [612].

**Lymphatic and blood vessel invasion**

Lymphatic vessel invasion has been shown to be an important and independent prognostic factor, particularly in patients with T1, node-negative breast cancers [461,1606,1623, 2433,2445,2452]. Its major value is in identifying patients at increased risk of axillary lymph node involvement [627,839,1592,2253,2415] and adverse outcome [186a,627,1623, 2415,2434]. As with histological grade, the ability of pathologists to reproducibly identify lymphatic vessel invasion has been challenged [998] but can be improved if stringent criteria are employed [627,2109,2253,2415, 2452]. Lymphatic vessel invasion must be distinguished from tumour cell nests within artefactual tissue spaces created by shrinkage or retraction of the stroma during tissue processing.

Blood vessel invasion has been reported to have an adverse effect on clinical outcome. However, there is a broad range in the reported incidence, from under 5% to almost 50% [1470,1592, 2444,2445,2452, 3083]. This is due to a variety of factors including the patient population, the criteria and methodology used, and difficulty in identifying blood vessels.

**Perineural invasion**

Perineural invasion is sometimes observed in invasive breast cancers, but it has not been shown to be an independent prognostic factor [2426].

**Tumour cell proliferation**

Markers of proliferation have been extensively investigated to evaluate prognosis [886,1304]. Mitotic count is part of histological grading. Other methods include DNA flow cytometry measurement of S-phase fraction (SPF). Many studies indicate that high SPF is associated with inferior outcome. Ki-67/MIB-1 is a labile, non-histone nuclear protein detected in the G1 through M phases of the cell cycle, but not in resting cells and is therefore a direct indicator of the growth fraction. The percentage of Ki-67 positive cells can be used to stratify patients into good and poor survivors. Quantitative RT-PCR in detecting the mRNA level has also been introduced as well as array based quantification of proliferation (see below).

**Tumour necrosis**

In most studies [2452], the presence of necrosis has been associated with an adverse effect on clinical outcome [414, 877,999,2175], although in one, necrosis was associated with a worse prognosis only within the first two years after diagnosis [999].

**Inflammatory cell infiltrates**

The presence of a prominent mononuclear cell infiltrate has been correlated in some studies with high histological grade [2030]. However, the prognostic significance of this finding is controversial, with some studies noting an adverse effect on clinical outcome [67,286,2785] and others observing either no significant effect or a beneficial effect [635,1601,2445,2785].
Index takes into consideration tumour size, lymph node status and histological grade, and stratifies patients into good, moderate and poor prognostic groups. The presence of a fibrotic focus in the centre of an invasive carcinoma has also been reported to be an independent adverse prognostic indicator [545,1153].

**Combined morphologic prognostic factors**

The best way to integrate histological prognostic factors is an unresolved issue [1833]. The Nottingham Prognostic Index takes into consideration tumour size, lymph node status and histological grade, and stratifies patients into good, moderate and poor prognostic groups with annual mortality rates of 3%, 7%, and 30%, respectively [954]. Another proposal for a prognostic index includes tumour size, lymph node status and mitotic index (morphometric prognostic index) [2993].

**Molecular markers and gene expression**

A large number of genetic alterations have been identified in invasive breast carcinomas, many of which are of potential prognostic or predictive value. Some provide treatment-independent information on patient survival, others predict the likelihood that a patient will benefit from a certain therapy. Some alterations may have both prognostic and predictive value.

**Steroid hormone receptors**

(Estrogen receptor (ER) and Progesterone receptor PR)

Estrogen is an important mitogen exerting its activity by binding to its receptor (ER). Approximately 60% of breast carcinomas express the ER protein. Initially, ER-positive tumours were associated with an improved prognosis, but studies with long-term follow-up have suggested that ER-positive tumours, despite having a slower growth rate, do not have a lower metastatic potential. Nonetheless, ER status remains very useful in predicting the response to adjuvant tamoxifen [4, 366,1304,1832,2120]. Measurement of both ER and PR has been clinical practice for more than 20 years. PR is a surrogate marker of a functional ER. In estrogen target tissues, estrogen treatment induces PR. Both can be detected by ligand binding assay, or more commonly nowadays, by immunohistochemical (IHC) analysis using monoclonal antibodies. ER/PR-positive tumours have a 60-70% response rate compared to less than 10% for ER/PR-negative tumours. ER-positive/PR-negative tumours have an intermediate response of approximately 40%. Hormone receptor status is the only recommended molecular marker to be used in treatment decision [9,886,1030]. The impact of hormone receptor status on prognosis and treatment outcome prediction is complex. The finding, in cell lines, that tamoxifen can interact with the recently identified ERβ receptor (ERB) may provide new clues towards improvement of predicting tamoxifen responsiveness [1526,1925,3269].

Epidermal growth factor receptor (EGFR), and transforming growth factor alpha (TGFα), antiapoptotic protein bcl-2, cyclin dependent kinase inhibitor p27 are other potential prognostic markers that look promising. Elevated expression of EGFR in the absence of gene amplification, has been associated with estrogen receptor negativity [2509].

The **ERBB2 / HER2 oncogene**

The prognostic value of ERBB2 over-expression, first reported in 1987 [2719], has been extensively studied [2962,3173]. ERBB2 over-expression is a weak to moderately independent predictor of survival, at least for node-positive patients. Gene amplification or over-expression of the ERBB2 protein can be measured by Southern blot analysis, FISH, differential PCR, IHC and ELISA [2958]. Studies of the predictive value of ERBB2-status have not been consistent. A recent review [3173] concluded that ERBB2 seems to be a weak to moderately strong negative predictor for response to alkylating agents and a moderately positive predictive factor for response to anthracyclines. There was insufficient data to draw conclusions on the response to taxanes or radiotherapy. In an adjuvant setting, ERBB2 status should not be used to select adjuvant systemic chemotherapy or endocrine therapy. Conversely, when adjuvant chemotherapy is recommended, anthracycline-based therapy should be preferred for ERBB2 positive patients. A humanized anti-ERBB2 monoclonal antibody, trastuzumab (Herceptin), has been developed as a novel anti-cancer drug targeting overexpressed ERBB2 [529]. This has been shown to be effective in 20% of patients with ERBB2 amplified tumours.

**TP53 mutations**

Approximately 25% of breast cancers have mutations in the tumour suppressor gene TP53, most of which are missense mutations leading to the accumulation of a stable, but inactive protein in the tumour cells [1196,2759,2761]. Both DNA sequencing and IHC have been used to assess TP53-status in the tumour. However, some 20% of the mutations do not yield a stable protein and are thus not detected by IHC, while normal (wildtype) protein may accumulate in response to DNA damage or cellular stress signals. Studies using DNA sequencing all showed a strong association with survival whereas those using only IHC did not, or did so only weakly [5,886,1304,2237,2760]. Given the diverse cellular functions of the p53 protein and the location and type of alteration within the gene, specific mutations might conceivably be associated with a particularly poor prognosis. Patients with mutations in their tumours affecting the L2/L3 domain of the p53 protein, which is important for DNA binding, have a particularly poor survival [251,317,976,1523]. The role of p53 in the control of the cell cycle, DNA damage repair, and apoptosis, provides a strong biological rationale for investigating whether mutations are predictors of response to DNA damaging agents. Several studies using DNA sequencing of the entire gene have addressed this in relation to different chemotherapy and radiotherapy regimes [16,241,249,976]. A strong
association between specific mutations and short survival and poor response to treatment was seen, emphasizing the importance of DNA sequence analysis of the entire coding region of TP53 when evaluating its prognostic and predictive value.

Loss of heterozygosity (LOH)
LOH at the TP53 gene has been shown to be a marker for prognosis and predictor of response to certain therapies (see above). Other regions with LOH that appear to correlate to short survival include 11q23 and several regions on 3p (1216,1552). Deletion of 9q13 is also associated with shorter survival. The target gene(s) in these areas have still to be identified (1326).

DNA amplification
Conventional as well as array-based CGH have identified a number of amplified regions containing putative oncogenes with prognostic potential. Amplification of the FGFR1 gene on 8q12 has been correlated with reduced disease-free survival, especially if the gene is amplified together with the cyclin D1 gene (596). The MYC gene on 8q24 is amplified in approximately 20% of breast carcinomas, which is associated with estrogen receptor negativity (596), locally advanced disease and poor prognosis (250). On 11q13, cyclin D1 (CCND1) is amplified in 15-20% of breast tumours. In ER-positive tumours, CCND1 amplification is associated with a relatively poor prognosis (596,2982), and is more frequent in lobular carcinomas compared to ductal carcinomas.

Expression profiling
Much recent work has been focused on the potential of gene expression profiles to predict the clinical outcome of breast cancer (257,1257,2328,2757,2986,2990). These studies, although heterogeneous in patient selection and numbers of tumours analysed, have indicated that gene expression patterns can be identified that associate with lymph node or distant metastasis, and that are capable of predicting disease course in individual patients with high accuracies (circa 90%). In the largest study to date (2990), analysing 295 tumours, the expression profile was a strong independent factor and outcompeted lymph node status as a predictor of outcome. These findings suggest that some primary tumours express a “metastasis signature”, which is difficult to reconcile with the classic tumour progression model in which a rare subpopulation of tumour cells have accumulated the numerous alterations required for metastasis to occur. Interestingly, some of the genes in the signature seem to be derived from non-epithelial components of the tumour (2328), suggesting that stromal elements represent an important contributing factor to the metastatic phenotype. Survival differences were also noted between the different subtypes of breast tumours as defined by expression patterns (2756,2757). The patients with basal-like and ERBB2+ subtypes were associated with the shortest survival, while a difference in the outcome for tumours classified as luminal A versus luminal B was also evident. The luminal subtype B may represent a class of ER-positive tumours with poor outcome, possibly not responding to tamoxifen. This strongly supports the idea that many of these breast tumour subtypes represent biologically distinct disease entities with different clinical outcome.

A remarkable feature of the expression signatures identified in these studies is that they usually involve fewer than 100 genes (257,2986), in one instance even only 17 genes (2328). However, what confusing is that the overlap between the different sets of genes thus defined is incomplete (1257,2757). Further comparative studies are required to elucidate the critical components of the poor prognosis signature, while the clinical utility of this new diagnostic tool must now be demonstrated in a prospective trial setting. At a more fundamental level, it will be interesting to establish whether the observed association between expression signatures and survival reflects an intrinsic biological behaviour of breast tumour cells or a differential response to therapy.
Benign epithelial proliferations

Localization
There is little data on location or laterality of most benign breast lesions. As with carcinoma, the majority arise within the terminal duct lobular unit (TDLU). A major exception is the benign solitary intraductal papilloma, approximately 90% of which occurs in the large ducts in the central region of the breast [1098]. Other benign lesions specific to the nipple areolar complex include nipple adenoma and syringoma and are discussed in the chapter on nipple.

Clinical features
The predominant presenting symptoms in women attending a breast clinic are described in the section on Invasive Carcinoma, where signs and symptoms most likely to be associated with a low risk of malignancy are described. The frequency of benign conditions varies considerably with the age of the patient. Fibroadenoma is most frequent in younger patients, other localized benign lesions and cysts occur most frequently in women between the ages of 30 and 50. This contrasts with carcinoma, which is rare below the age of 40.

The mammographic appearances of benign epithelial lesions are varied but common lesions such as cysts are typically seen as well defined or lobulated mass lesions. Calcification is also a common feature of fibrocystic change and sclerosing adenosis. Other benign lesions such as radial scar, complex sclerosing lesion and fat necrosis can produce ill defined or spiculate mass lesions, which are indistinguishable from some forms of breast carcinoma.

Adenosis

Definition
A frequent, benign, proliferative process that affects mainly the lobular (acinar) component of the breast parenchyma. It can be accompanied by fibrosis causing considerable distortion of the glands simulating an invasive process. Frequently it is a small and microscopic change, but it may be widespread. In some instances, it may form a palpable mass and has been called nodular adenosis or adenosis tumour. Several histological types have been described, but there is not complete agreement on their designation. Only the most frequent variants are discussed.

Radial scar/complex sclerosing lesion which incorporates a combination of benign changes including adenosis is also included in this section.

Epidemiology
This lesion occurs most frequently in women in their third and fourth decade.

Macroscopy
Adenosis may be non-distinctive, showing unremarkable fibrous or cystic breast tissue. A few cases assume the appearance of a firm rubbery grey mass.

Histopathology
Adenosis in its simplest form is characterized by a usually loosely structured proliferation of acinar or tubular structures, composed of an epithelial and myoepithelial cell layer and surrounded by a basement membrane.

Sclerosing adenosis
Sclerosing adenosis (SA) is characterized by a compact proliferation of acini with preservation of the luminal epithelial and the peripheral myoepithelial (ME) cell layers along with a surrounding basement membrane. These elements can easily be demonstrated by immunohistochemical staining for keratin, smooth-muscle actin and laminin, respectively. Although compression or attenuation of the acini by surrounding fibrosis may be marked, sclerosing adenosis nearly always retains an organic or lobulated configuration often best observed at low power view. Microcalcifications are common within the glands. Areas of apocrine metaplasia are also common. Rarely neural invasion is encountered and vascular invasion has been reported [149]. Lesions which form a mass show adenosis with a mixture of growth patterns [2015], the most frequent of which is sclerosing adenosis.

In rare cases sclerosing adenosis may be involved by DCIS or LIN [1046, 1275a, 1846a, 2015, 2336a, 3104a].

Differential diagnosis
Sclerosing adenosis can mimic invasive carcinoma. The overall lobulated architecture, persistence of ME cells, and lack of epithelial atypia help to exclude carcinoma [221, 1046]. In cases involved by in situ carcinoma, the immunohistochemical demonstration of persistent myoepithelial cells is crucial in excluding invasion.

Fig. 1.107 Sclerosing adenosis. Typical organic configuration of the lesion.

Fig. 1.108 Sclerosing adenosis. The myoepithelial cells are prominent with immunostain for smooth muscle actin.

G. Bussolati
F.A. Tavassoli
B.B. Nielsen
I.O. Ellis
G. MacGrogan
Apocrine adenosis

**Synonym**
Adenosis with apocrine metaplasia.

Apocrine adenosis (AA) is an ambiguous term, as it has been used for several different lesions [805,2698,2699]. In this context, it is used for adenosis, particularly sclerosing adenosis, with widespread apocrine metaplasia constituting at least 50% of the adenotic area [3093]. The apocrine epithelium may exhibit cytological atypia, so that the histological appearance mimics invasive carcinoma [2621,2698,2699].

**Blunt duct adenosis**

The term blunt duct adenosis (BDA) has been used for an organoid microscopic form of adenosis with variable distension of lumens showing columnar cell metaplasia [2015].

**Microglandular adenosis**

Microglandular adenosis (MGA) is a rare lesion, characterized by a diffuse haphazard proliferation of small round glands [507,692,2413,2884]. These may be clustered, but without sclerosis or compression [507,3081]. The surrounding collagenous stroma may be hypocellular or hyalinized. There is no elastosis. The glands have a round lumen, which frequently contains periodic acid-Schiff (PAS) positive, eosinophilic secretory material. The epithelium is cuboid and without snouts. The cytoplasm may be clear or eosinophilic and granular. There is no nuclear atypia. There are no myoepithelial cells [184,321,797,2884], but a surrounding basement membrane, not always recognizable without immunohistochemical staining for laminin or collagen IV [692,2884,3081], is present. Electron microscopy shows a multilayered basement membrane surrounding the tubules of MGA [2884]. The epithelium of MGA is positive for S-100 in addition to cytokeratin [1372]. When carcinoma arises in association with MGA it may retain an alveolar pattern [1331] or be of ductal or one of the special types [2016]; the vast majority of these invasive carcinomas retain S-100 immunoreactivity regardless of their subtype [1484].

Adenomyoepithelial adenosis

Adenomyoepithelial adenosis (AMEA) is an extremely rare type of adenosis, which seems to be associated with adenomyoepithelioma [803,805,1454] (see section on adenomyoepithelial lesions).

**Prognosis and predictive factors of adenosis**

Most types of adenosis are not associated with increased risk of subsequent carcinoma. However, there are exceptions, as nearly one third of cases of MGA harbour an invasive carcinoma [803,1454], and apocrine adenosis has been found to be monoclonal and perhaps a putative precancerous lesion [3093].

Radial scar / Complex sclerosing lesion

**Definition**

A benign lesion that on imaging, grossly and at low power microscopy resembles invasive carcinoma because the lobular architecture is distorted by the sclerosing process. The term radial scar (RS) has been applied to small lesions and com-
plex sclerosing lesion (CSL) to larger ones that contain a variety of ductal epithelial hyperplasia along with sclerosis.

Synonyms
Radial scar, sclerosing papillary lesion, radial sclerosing lesion, scleroelastotic scar, stellate scar, benign sclerosing ductal proliferation, non-encapsulated sclerosing lesion, infiltrating epitheliosis.

Epidemiology
The reported incidence varies depending on the mode of detection and how detected by mammography when the appearance mimics that of an infiltrating carcinoma producing an irregular stellate density. Very occasionally they are of sufficient size to produce a palpable mass (2725). They are often multiple and frequently bilateral.

Macroscopy
These lesions may be undetected on gross examination or may be of sufficient size to produce an irregular area of firmness which can exhibit yellow streaks reflecting the elastotic stroma. The appearance may be indistinguishable from that of a carcinoma.

Histopathology
RSs are composed of a mixture of benign changes of which adenosis forms a major part. They have a stellate outline with central dense hyalinized collagen and sometimes marked elastosis. Entrapped in the scar are small irregular tubules. The two cell layer is usually retained although this may not always be visible on haematoxylin and eosin staining and the myoepithelial layer is occasionally inapparent. The tubules sometimes contain eosinophilic secretions. Around the periphery of the lesion there are various degrees of ductal dilatation, ductal epithelial hyperplasia, apocrine metaplasia and hyperplasia. In the more complex larger CSLs, several of these lesions appear to combine and then converge with prominent areas of sclerosing adenosis, and small, frequently sclerosing, peripheral papillomas and various patterns of intraepithelial proliferation.

Differential diagnosis
Distinction from carcinoma depends on the characteristic architecture of a CSL, the lack of cytological atypia, the presence of a myoepithelial layer (in most cases) and basement membrane around the tubular structures (demonstration by immunohistochemistry may be necessary), the presence of a dense hyalinized stroma and lack of a reactive fibroblastic stroma.
Prognosis and predictive factors
It has been suggested that these lesions are pre-neoplastic or even represent early invasive carcinomas (1668) and also that they may represent a marker of risk for the subsequent development of carcinoma. Follow up studies, however, have been few and contradictory (843,1320) suggesting that an apparent risk is related to the various patterns of associated intraductal hyperplasia. It is doubtful that, without epithelial proliferation, there is a risk of the subsequent development of invasive carcinoma. In larger lesions the risk may be slightly higher as the increase in size is usually due to various forms of epithelial hyperplasia. A high incidence of atypical hyperplasia and carcinoma (both in situ and invasive) has been reported in CSLs detected by mammography, particularly in lesions measuring over 0.6 cm, and in women over 50 years old (719,2725).

Tubular adenoma
Definition
Benign, usually round, nodules formed by a compact proliferation of tubular structures composed of the typical epithelial and myoepithelial cell layers. The epithelial cells are similar to those of the normal resting breast, but adenoma variants have been described where these show apocrine or lactating features.

ICD-O code 8211/0

Epidemiology
Tubular adenomas occur mainly in young females (1202,1211,1919,2074). They rarely occur before menarche or after menopause (1600,2025). They reportedly account for 0.13 to 1.7% of benign breast lesions (1202,1211,2874). Patients with lactating adenomas are nursing mothers who have noted an area of increased firmness, either during lactation or, earlier, during pregnancy.

Lactating adenoma
ICD-O code 8204/0

During pregnancy and lactation, the epithelial cells of a tubular type adenoma may show extensive secretory changes warranting a designation of lactating adenoma (1332,2074). It has been suggested that such lesions represent focal accumulation of hyperplastic lobules.
Apocrine adenoma

ICD-O code  8401/0

Synonym
Nodular adenosis with apocrine metaplasia.

Sometimes the epithelial cells of nodular adenosis show extensive apocrine metaplasia; these lesions may be termed apocrine adenoma [561,1713,2442].

Immunoprofile
The immunophenotype of adenomas is similar to normal breast and reflects the various metaplastic and secretory changes affecting them.

Differential diagnosis
Differentiation of adenomas from fibroadenomas is based on the prominent proliferating stromal component and the often elongated and compressed epithelial elements in the intracanalicular variant of the latter.

Pleomorphic adenoma

Definition
A rare lesion morphologically similar to pleomorphic adenoma (benign mixed tumour) of the salivary glands. Some authors [2442, 2730,2753] consider pleomorphic adenoma to be a form of intraductal papilloma with extensive cartilaginous metaplasia. Because of the presence of a chondroid stromal component, pleomorphic adenomas pose a difficult differential diagnosis from metaplastic carcinomas with a mesenchymal component and primary sarcomas of the breast. The presence of foci of intraductal or invasive carcinoma points to the diagnosis of metaplastic carcinoma, while extensive cellular anaplasia characterizes sarcomas.

Ductal adenoma

Definition
A well circumscribed benign glandular proliferation located, at least in part, within a duct lumen [151].

ICD-O code  8503/0

Synonym
Sclerosing papilloma.

Epidemiology
These lesions have been reported in patients (mainly females) over a wide range of age [172,454]. Multiple tumours have been described [454,2874]. Calcification is common and gives a diagnostically important sign on mammography.

Histopathology
The histological picture is the same as that seen in pleomorphic adenomas of salivary glands. Some authors [2442, 2730,2753] consider pleomorphic adenoma to be a form of intraductal papilloma with extensive cartilaginous metaplasia. Because of the presence of a chondroid stromal component, pleomorphic adenomas pose a difficult differential diagnosis from metaplastic carcinomas with a mesenchymal component and primary sarcomas of the breast. The presence of foci of intraductal or invasive carcinoma points to the diagnosis of metaplastic carcinoma, while extensive cellular anaplasia characterizes sarcomas.

Clinical features
They may present as a mass or rarely as a nipple discharge. Imaging shows a density which can mimic a carcinoma.

Histopathology
Arranged mainly at the periphery are glandular structures with typical dual cell layer while in the centre there is dense scar-like fibrosis. The compact proliferating tubules, compressed or slightly dilated, and surrounded by fibrosis may impart a pseudoinfiltrative appearance. Epithelial and stromal changes similar to those observed in intraductal papillomas can occur; apocrine metaplasia is frequent. Papillary fronds are not always detectable in a given plane of section.

Prognosis and predictive factors of mammary adenomas
All adenomas of the breast are benign lesions that do not recur if adequately excised and do not predispose to carcinoma.
Myoepithelial lesions

Definition
Lesions either derived from, or composed of, a dominant to pure population of myoepithelial (ME) cells. They include adenoid cystic carcinoma, pleomorphic adenoma, myoepithelioma, adenomyoepithelioma (benign or malignant) and malignant myoepithelioma (myoepithelial carcinoma). The first two lesions are discussed elsewhere. In this section, the focus will be on the others.

Immunohistochemical profile of myoepithelial cells
Myoepithelial cells show positive immunoreaction with alpha smooth muscle actin, calponin, caldesmon, smooth muscle myosin heavy chain (SMM-HC) maspin S-100 protein and high MW cytokeratins 34betaE12, CK5 and CK14. Nuclear immunoreactivity with p63 is also a feature of ME cells. Rarely there is staining with glial fibrillary acidic protein (GFAP). Myoepithelial cells are negative for low MW cytokeratins (CK 8/18), estrogen receptor (ER), progesterone receptor (PR), and desmin (191,1516,1573,1741,2418,2702,2738,2953,3099).

Epidemiology
Patients range in age from 22 to 87 years (2418,2868,2875,3192).

Clinical features
Apart from myoepitheliosis, which is rarely palpable, these lesions usually present as a palpable tumour and/or mammographic density without distinctive features.

Myoepitheliosis

Definition
A multifocal, often microscopic, proliferation of spindle to cuboidal myoepithelial cells growing into and/or around small ducts and ductules.

Macroscopy
Myoepitheliosis generally appears as a firm irregular area.

Histopathology
The intraductal proliferating spindle cells may develop a prominent palisading pattern. The cuboidal cells may have longitudinal nuclear grooves resembling transitional cells. Rarely atypia and mitotic activity appear, warranting a designation of atypical myoepitheliosis.

Fig. 1.125 Myoepitheliosis, periductal type. A The myoepithelial cells with abundant eosinophilic cytoplasm proliferate around the epithelial cells compressing the ductular lumens. This change is often multifocal. B Immunostain for actin is positive in the myoepithelial cells, but negative in the epithelial-lined compressed ductular spaces.

Fig. 1.126 Adenomyoepithelial adenosis. A Prominent clear myoepithelial (ME) cells are evident around several ductules. B Both the clear and normal ME cells are intensely immunoreactive for S-100 protein.

Fig. 1.127 Adenomyoepitheloma, lobulated type. A The lobulated nature of the tumour is apparent with massive central infarction in the two adjacent nodules. The lighter cells reflect the proliferating ME cells, while the darker cells represent the epithelial cells. B Adenomyoepitheloma. In this case, the proliferating ME cells have a clear cell phenotype and surround a few spaces lined by darker epithelial cells.
Adenomyoepithelial adenosis

Definition
An extremely rare type of adenosis associated with adenomyoepithelioma (803, 805,1454).

Histopathology
Adenomyoepithelial adenosis (AMEA) consists of a diffuse proliferation of round or irregular tubular structures lined by a cuboidal to columnar epithelium, which may show apocrine metaplasia. There is a prominent, focally hyperplastic myoepithelial cell layer with strikingly clear cytoplasm. There is no significant nuclear atypia or mitotic activity, but most described cases blend with or surround an adenomyoepithelioma (803,805,1454).

Adenomyoepithelioma

Definition
Composed of a predominantly and usually solid proliferation of phenotypically variable myoepithelial cells around small epithelial lined spaces, in rare instances, the epithelial, the myoepithelial or both components of an adenomyoepithelioma (AME) may become malignant (malignant AME).

ICD-O codes
Benign 8983/0
Malignant 8983/3

Macroscopy
Well delineated, benign adenomyoepitheliomas are rounded nodules with a median size of 2.5 cm.

Histopathology
Histologically, AMEs they are characterized by a proliferation of layers or sheaths of ME cells around epithelial lined spaces. The tumour may display a spindle cell, a tubular, or, most often, a lobulated growth pattern. Fibrous septae with central hyalinization or infarction are common in the lobulated lesions. The ME cell phenotype is most variable in the lobulated pattern ranging from clear to eosinophilic and hyaline (plasmacytoid) types. Satellite nodules, seen adjacent to the lobulated variant in some cases reflect an intraductal extension of the lesion. The tubular variant has an ill defined margin. Mitotic activity of the proliferating myoepithelial cells in benign lesions is generally in the range of 1-2/10, always ≤2/10 high power field (hpf).

Either the epithelial, the myoepithelial or both components of an adenomyoepithelioma may become malignant and give rise to a carcinoma while the background lesion retains its adenomyoepitheliomatous appearance (793,900,903, 1695,2868,2953). The aggressive myoepithelial component may assume a spindle configuration and develop into nodules resembling myofibroblastic lesions. A variety of epithelial derived carcinomas, sarcomas and carcinosarcomas occur in this setting (Table1.16) (2868). Rarely, both components develop into either separate malignancies or a single malignant infiltrative process composed of angulated tubules lined by both epithelial and myoepithelial cells.

Differential diagnosis
The tubular variant of AME should be distinguished from a tubular adenoma; the latter may have prominent ME cells, but lacks the myoepithelial proliferation typical of an AME. Furthermore, tubular adenoma is sharply circumscribed unlike the ill defined tubular AME. The lobulated and spindle cell variants of AME should be distinguished from

Table 1.16
Classification of myoepithelial lesions.

<table>
<thead>
<tr>
<th>1. Myoepitheliosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Intraductual</td>
</tr>
<tr>
<td>b. Periductal</td>
</tr>
<tr>
<td>2. Adenomyoepithelial adenosis</td>
</tr>
<tr>
<td>3. Adenomyoepithelioma</td>
</tr>
<tr>
<td>a. Benign</td>
</tr>
<tr>
<td>b. With malignant change (specify the subtype)</td>
</tr>
<tr>
<td>– Myoepithelial carcinoma arising in an adenomyoepithelioma</td>
</tr>
<tr>
<td>– Epithelial carcinoma arising in an adenomyoepithelioma</td>
</tr>
<tr>
<td>– Malignant epithelial and myoepithelial components</td>
</tr>
<tr>
<td>– Sarcoma arising in adenomyoepithelioma</td>
</tr>
<tr>
<td>– Carcinosarcoma arising in adenomyoepithelioma</td>
</tr>
<tr>
<td>4. Malignant myoepithelioma (ME carcinoma)</td>
</tr>
</tbody>
</table>

Fig. 1.128 Adenomyoepithelioma, spindle cell type. A There is a solid proliferation of spindled myoepithelial cells surrounding irregular epithelial lined spaces. B The epithelial spaces may show apocrine metaplasia. C Immunostain for S-100 protein shows positivity in the proliferating myoepithelial cells, while the epithelial cells fail to react.

Fig. 1.129 Adenomyoepithelioma, adenosis type. A At least focally well delineated, these tumours superficially resemble a tubular adenoma. B Higher magnification shows proliferation of ME cells in the tubules beyond the normal single layer.
pleomorphic adenoma; the latter generally has prominent areas of chondroid and/or osseous differentiation.

**Prognosis and predictive factors**
The majority of AME are benign (1573, 1695, 2418, 2581, 2868). Lesions that contain malignant areas, those with high mitotic rate, or infiltrating margins have a potential for recurrence and metastases. Local recurrence (1440, 2868, 3192) as well as distant metastasis (2875) have been described, mainly among those with aggressive features.

### Malignant myoepithelioma

**Definition**
An infiltrating tumour composed purely of myoepithelial cells (predominantly spindled) with identifiable mitotic activity.

**Synonyms**
Infiltrating myoepithelioma, myoepithelial carcinoma.

**ICD-O code**
8982/3

**Macroscopy**
Ranging from 1.0 to 21 cm in size, these tumours are generally well defined with focal marginal irregularity, although some are stellate. There may be foci of necrosis and haemorrhage on the firm rubbery cut surface in larger tumours and sometimes nodular areas of hyalinization even in smaller tumours.

**Histopathology**
Histologically, there is an infiltrating proliferation of spindle cells often lacking significant atypia. Mitotic activity may not exceed 3-4 mf/10hpf. The spindled tumour cells appear to emanate from the myoepithelial cells of ductules entrapped in the periphery of the lesion. Aggregates of collagen and prominent central hyalinization may be evident.

**Differential diagnosis**
The differential diagnosis includes spindle cell carcinomas, fibromatosis and a variety of myofibroblastic lesions. The presence of a dominant nodule with irregular and shallow infiltration at the margins is helpful in distinguishing this lesion from fibromatosis and myofibroblastic tumours. Immunohistochemistry is, and, rarely, electron microscopy may be, required to confirm the myoepithelial nature of the neoplastic cells.

**Prognosis and predictive factors**
Local recurrence or distant metastases have rarely been documented (1573, 2581, 2875). Complete excision with uninvolved margins is recommended.

---

**Table 1.17**

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Smooth muscle actin</th>
<th>Calponin</th>
<th>S-100</th>
<th>Kermix*</th>
<th>CAM5.2**</th>
<th>ER</th>
<th>Desmin</th>
<th>CD34</th>
<th>HMB45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoepithelioma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+/–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Smooth muscle cell tumours</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>–/–</td>
<td>+/–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Myofibroblastic lesions</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>–</td>
<td>–/–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–/–</td>
</tr>
<tr>
<td>Melanoma</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–/–</td>
</tr>
</tbody>
</table>

* Kermix a cocktail of AE1/AE3 (cytokeratin 1-19), and LP34 (CK5,6 & 18)
**Cam 5.2 (CK8 & 18)
Mesenchymal tumours

Definition
Benign and malignant mesenchymal tumours morphologically similar to those occurring in the soft tissues as well as those occurring predominantly in the breast.

Benign vascular tumours

Haemangioma

Definition
A benign tumour or malformation of mature vessels.

ICD-O code 9120/0

Epidemiology
Haemangiomas of the breast have been described in both male and female patients from 18 months to 82 years old (1373,2874). They rarely present as palpable lesions but an increasing number of non-palpable mammary haemangiomas are nowadays detected by breast imaging (3077). Incidental "perilobular" haemangiomas are found in 1.2% of mastectomies and 4.5% of benign breast biopsies (2443) and 11% in a series of post mortem cases (age range 29–82 years) (1633).

Macroscopy
Rarely palpable, the lesions are well circumscribed and vary from 0.5-2 cm with a reddish-brown spongy appearance.

Histopathology
Symptomatic haemangiomas may be of cavernous, capillary or venous subtypes (2435,2611). Cavernous haemangioma is the most common type; it consists of dilated thin walled vessels lined by flattened endothelium and congested with blood. Thrombosis may be present with papillary endothelial hyperplasia (Masson’s phenomenon) (1946). Dystrophic calcification may be found in organizing thrombi as well as in the stroma between the vascular channels. Capillary haemangiomas are composed of nodules of small vessels with a lobular arrangement around a larger feeding vessel. The intervening stroma is fibrous. The endothelial lining cells may have prominent hyperchromatic nuclei but without tufting or a solid spindle cell growth pattern. Venous haemangiomas consist of thick walled vascular channels with smooth muscle walls of varying thickness (2435).

In perilobular haemangiomas, the lobulated collections of thin-walled, wide vascular channels are seen within the intralobular stroma. Expansion into the extralobular stroma and adjacent adipose tissue is often present. The vascular channels are lined by flattened endothelium without a surrounding muscle layer (1373). Occasional cases with prominent hyperchromatic endothelial nuclei have been described and designated atypical haemangiomas (1225). An anastomosing growth pattern, papillary endothelial proliferations and mitoses are absent and their presence should arouse suspicion and careful exclusion of an angiosarcoma.

Prognosis and predictive factors
Recurrence, even after incomplete excision, has not been reported. Careful evaluation of the whole lesion to exclude a well differentiated angiosarcoma is indicated in all symptomatic vascular breast lesions.

Angiomatosis

Definition
A diffuse excessive proliferation of well formed vascular channels affecting a large area in a contiguous fashion.

Synonym
Diffuse angioma.

Epidemiology
This very rare benign vascular lesion may be congenital. Most cases have been described in women between 19 and 61 years old (1921,2416). One case was in a male.

Clinical features
Angiomatosis presents as a breast mass. Rapid increase in size has been described in a woman during pregnancy (76).
**Pathology**
Macroscopic and histopathological appearances are similar to angiomatosis at other sites. The haemorrhagic spongy lesions are composed of usually thin walled large blood or lymphatic vessels diffusely extending throughout the parenchyma of the breast.

**Prognosis and predictive factors**
Recurrence after incomplete excision has been reported, and may occur after a long disease-free interval [2416]. In many cases, complete excision requires a mastectomy.

---

**Haemangiopericytoma**

**Definition**
A circumscribed area of bland ovoid to spindled cells proliferating around branching and “stag-horn” vessels.

**ICD-O codes**
- Benign: 9150/0
- NOS: 9150/1
- Malignant: 9150/3

**Epidemiology**
This is a rare mesenchymal tumour. Around 20 primary haemangiopericytomas have been reported in the breast. The patients are mostly women aged 22–67, but a few cases have been reported in children (5 and 7 years old) and in men [118,2889].

**Clinical features**
Patients usually present with a mass that appears as a well circumscribed area of density on mammography.

**Macroscopy**
The tumours are round to oval, well circumscribed and range in size from 1 to 19 cm [118,1415,2855,2889]. They are firm with a solid, yellow-tan to grey-white cut surface. Myxoid areas alternate with small cysts filled with watery fluid. Haemorrhage and necrosis are evident in some larger tumours.

**Histopathology**
The histological and immunophenotype appearances are similar to haemangiopericytomas described elsewhere [2889]. They are composed of a compact proliferation of plump ovoid to spindle cells with indistinct cell margins arranged around an abundance of usually thin-walled, irregularly branching vascular channels. Some of the branching vessels assume a “stag-horn” configuration. Mammary ducts and ductules are often trapped focally in the periphery of the lesion.

**Prognosis and predictive factors**
Most cases of mammary haemangiopericytoma have been benign. There is no well documented example of metastatic disease or even recurrence [118, 1415,2855,2889]. Wide local excision rather than mastectomy is often sufficient for complete tumour excision.

---

**Pseudoangiomatous stromal hyperplasia**

**Definition**
A benign lesion consisting of complex anastomosing slit-like pseudovascular spaces, that are either acellular or lined by slender spindle-shaped stromal cells.

**Epidemiology**
The clinicopathological spectrum of mammary pseudoangiomatous stromal hyperplasia (PASH) extends from insignificant microscopic changes, often associated with either benign or malignant breast disease, to diffuse involvement of the breast or cases where a localized palpable or non-palpable breast mass is produced (nodular PASH) (1275,2270,3037). The latter is uncommon and reported to occur in 0.4% of breast biopsies [2270]. Focal or multifocal PASH without mass formation has been reported in 23% of breast biopsies, usually as an incidental finding. PASH has been reported in at least 25% of cases of gynaecomastia [157,1865].

**Aetiology**
The immunophenotype of the proliferating cells confirms that PASH is of myofibroblastic origin [1113,2279,2510,3249]. The pseudoangiomatous spaces are also discernible in frozen sections, indicating that they are not a fixation artefact [157,3037].

**Clinical features**
Nodular PASH usually present as a painless, well circumscribed, mobile palpable mass, clinically indistinguishable from fibroadenoma [532,1275,2270,2279,3037,3249]. Smaller lesions may be detected by mammography [532,2270]. On imaging, nodular PASH is indistinguishable from fibroadenoma [2270]. Diffuse lesions are an incidental finding [1275]. Bilateral lesions may occur [157]. Rapid growth has been reported [532,2270,2765,3026].

**Macroscopy**
Macroscopically, nodular PASH usually present as a painless, well circumscribed, mobile palpable mass, clinically indistinguishable from fibroadenoma ranging in size from 1 to 17 cm. The cut surface is pale tan-pink to yellow [92, 1275,2279,2622,3037].

**Histopathology**
PASH may be present in normal breast tissue or in various benign lesions [867, 887],...
There is a complex pattern of interanastomosing empty slit-like spaces, present within and between breast lobules with a perilobular concentric arrangement (1275,2279). In gynaecomastia, a periductal pattern is found (157). The spaces are formed by separation of collagen fibres and are either acellular or lined by spindle cells, simulating endothelial cells. Mitoses, tufting, atypia and pleomorphism are absent (92,1275,2279,3037,3249). There is no destruction of normal breast tissue, no necrosis, nor invasion of fat (1275) and collagen IV cannot identify a basement membrane around the spaces (867). The intervening stroma often consists of dense, hyalinated collagen and spindle cells with nuclei displaying pointed ends (1275,2510). In rare more proliferative lesions, a fascicular pattern is found: the stroma is composed of bundles of plump spindle cells that may obscure the underlying pseudoangiomatous architecture (2279).

At low power, PASH may resemble low-grade angiosarcoma but can be distinguished by its growth pattern and cytological features. The immunohistochemical characteristics are also different.

Immunoprofile

The spindle cells adjacent to the clefts are positive for CD34, vimentin, actin, calponin, but negative for the endothelial cell markers Factor VIII protein, Ulex europaeus agglutinin-1 and CD31. They are also negative for S100, low and high MW cytokeratins, EMA and CD68. Desmin is usually negative, but may be positive in fascicular lesions (157,928,1865,2279,3037).

Prognosis and predictive factors

PASH is not malignant but local recurrence has been rarely reported possibly attributable to growth after incomplete excision, or the presence of multiple lesions that were not all excised (2270,2279,3037).

Myofibroblastoma

Definition

A benign spindle cell tumour of the mammary stroma composed of myofibroblasts.

ICD-O code 8825/0

Epidemiology

Myofibroblastoma (MFB) occurs in the breast of both women and men aged between 40 and 87 years (1023,1735). In a few cases, an association with gynaecomastia has been documented.

Clinicopathology

Myofibroblastoma is composed of spindle to oval cells arranged in intersecting fascicles interrupted by thick bands of collagen. Some adipose tissue is present in the right upper corner.

Fig. 1.134 Myofibroblastoma. An expansile tumour composed of spindle to oval cells arranged in intersecting fascicles interrupted by thick bands of collagen. Some adipose tissue is present in the right upper corner.

Fig. 1.135 Myofibroblastoma. A more epithelioid cell population may develop focally.

Histopathology

An expansile tumour with pushing borders, myofibroblastoma is composed of spindle to oval cells arranged in short, haphazardly intersecting fascicles interrupted by thick bands of brightly eosinophilic collagen. The cells have relatively abundant, ill defined, pale to deeply eosinophilic cytoplasm with a round to oval nucleus containing 1 or 2 small nucleoli. Necrosis is usually absent and mitoses are only rarely observed (up to 2 mitoses x 10 high power fields). There is no entrapment of mammary ducts or lobules within the tumour. Variable numbers of scattered mast cells may be seen in the stroma but otherwise inflammatory...
Tumours of the breast

Fibromatosis

**Definition**

This uncommon, locally aggressive, lesion without metastatic potential originates from fibroblasts and myofibroblasts within the breast parenchyma, excluding mammary involvement by extension of a fibromatosis arising from the pectoral fascia.

**ICD-O code** 8821/1

**Synonym** Desmoid tumour.

**Epidemiology**

Fibromatosis accounts for less than 0.2% of all breast lesions (390,681,1083,2432,3063). It is seen in women from 13 to 80 years (average 46 and median 40) and is more common in the childbearing age than in perimenopausal or post-menopausal patients (681). A few cases have been reported in men (378,2482).

**Clinical features**

The lesion presents as a solitary, painless, firm or hard palpable mass. Bilateral tumours are rare (681,2432,3063). Skin or nipple retraction may be observed (294) and rarely nipple discharge (3063). Mammographically, fibromatosis is indistinguishable from a carcinoma (681).

**Macrosopic**

The poorly demarcated tumour measures from 0.5 to 10 cm (average 2.5 cm) (681,2432,3063) with a firm, white-grey cut surface.

**Histopathology**

Mammary fibromatoses are histologically similar to those arising from the fascia or aponeuroses of muscles elsewhere in the body with the same immunophenotype. Proliferating spindled fibroblasts and myofibroblasts form sweeping and interlacing fascicles; the periphery of the lesion reveals characteristic infiltrating finger-like projections entrapping mammary ducts and lobules (3063). Fibromatosis must be distinguished from several entities in the breast.

**Immunoprofile**

The neoplastic cells react positively for vimentin, desmin, α-smooth muscle actin and variably for CD34, bcl-2 protein, CD99 and sex steroid hormone receptors (estrogen, progesterone and androgen receptors) (1022,1023,1733,1913).

**Synonym**

Desmoid tumour.

**Epidemiology**

Fibromatosis accounts for less than 0.2% of all breast lesions (390,681,1083,2432,3063). It is seen in women from 13 to 80 years (average 46 and median 40) and is more common in the childbearing age than in perimenopausal or post-menopausal patients (681). A few cases have been reported in men (378,2482).

**Clinical features**

The lesion presents as a solitary, painless, firm or hard palpable mass. Bilateral tumours are rare (681,2432,3063). Skin or nipple retraction may be observed (294) and rarely nipple discharge (3063). Mammographically, fibromatosis is indistinguishable from a carcinoma (681).

**Macrosopically**

The poorly demarcated tumour measures from 0.5 to 10 cm (average 2.5 cm) (681,2432,3063) with a firm, white-grey cut surface.

**Histopathology**

Mammary fibromatoses are histologically similar to those arising from the fascia or aponeuroses of muscles elsewhere in the body with the same immunophenotype. Proliferating spindled fibroblasts and myofibroblasts form sweeping and interlacing fascicles; the periphery of the lesion reveals characteristic infiltrating finger-like projections entrapping mammary ducts and lobules (3063). Fibromatosis must be distinguished from several entities in the breast.

**Immunoprofile**

The neoplastic cells react positively for vimentin, desmin, α-smooth muscle actin and variably for CD34, bcl-2 protein, CD99 and sex steroid hormone receptors (estrogen, progesterone and androgen receptors) (1022,1023,1733,1913).

**Synonym**

Desmoid tumour.

**Epidemiology**

Fibromatosis accounts for less than 0.2% of all breast lesions (390,681,1083,2432,3063). It is seen in women from 13 to 80 years (average 46 and median 40) and is more common in the childbearing age than in perimenopausal or post-menopausal patients (681). A few cases have been reported in men (378,2482).

**Clinical features**

The lesion presents as a solitary, painless, firm or hard palpable mass. Bilateral tumours are rare (681,2432,3063). Skin or nipple retraction may be observed (294) and rarely nipple discharge (3063). Mammographically, fibromatosis is indistinguishable from a carcinoma (681).

**Macrosopy**

The poorly demarcated tumour measures from 0.5 to 10 cm (average 2.5 cm) (681,2432,3063) with a firm, white-grey cut surface.

**Histopathology**

Mammary fibromatoses are histologically similar to those arising from the fascia or aponeuroses of muscles elsewhere in the body with the same immunophenotype. Proliferating spindled fibroblasts and myofibroblasts form sweeping and interlacing fascicles; the periphery of the lesion reveals characteristic infiltrating finger-like projections entrapping mammary ducts and lobules (3063). Fibromatosis must be distinguished from several entities in the breast.

**Immunoprofile**

The neoplastic cells react positively for vimentin, desmin, α-smooth muscle actin and variably for CD34, bcl-2 protein, CD99 and sex steroid hormone receptors (estrogen, progesterone and androgen receptors) (1022,1023,1733,1913).

**Synonym**

Desmoid tumour.

**Epidemiology**

Fibromatosis accounts for less than 0.2% of all breast lesions (390,681,1083,2432,3063). It is seen in women from 13 to 80 years (average 46 and median 40) and is more common in the childbearing age than in perimenopausal or post-menopausal patients (681). A few cases have been reported in men (378,2482).

**Clinical features**

The lesion presents as a solitary, painless, firm or hard palpable mass. Bilateral tumours are rare (681,2432,3063). Skin or nipple retraction may be observed (294) and rarely nipple discharge (3063). Mammographically, fibromatosis is indistinguishable from a carcinoma (681).

**Macrosopy**

The poorly demarcated tumour measures from 0.5 to 10 cm (average 2.5 cm) (681,2432,3063) with a firm, white-grey cut surface.

**Histopathology**

Mammary fibromatoses are histologically similar to those arising from the fascia or aponeuroses of muscles elsewhere in the body with the same immunophenotype. Proliferating spindled fibroblasts and myofibroblasts form sweeping and interlacing fascicles; the periphery of the lesion reveals characteristic infiltrating finger-like projections entrapping mammary ducts and lobules (3063). Fibromatosis must be distinguished from several entities in the breast.

**Immunoprofile**

The neoplastic cells react positively for vimentin, desmin, α-smooth muscle actin and variably for CD34, bcl-2 protein, CD99 and sex steroid hormone receptors (estrogen, progesterone and androgen receptors) (1022,1023,1733,1913).

**Synonym**

Desmoid tumour.

**Epidemiology**

Fibromatosis accounts for less than 0.2% of all breast lesions (390,681,1083,2432,3063). It is seen in women from 13 to 80 years (average 46 and median 40) and is more common in the childbearing age than in perimenopausal or post-menopausal patients (681). A few cases have been reported in men (378,2482).

**Clinical features**

The lesion presents as a solitary, painless, firm or hard palpable mass. Bilateral tumours are rare (681,2432,3063). Skin or nipple retraction may be observed (294) and rarely nipple discharge (3063). Mammographically, fibromatosis is indistinguishable from a carcinoma (681).

**Macrosopy**

The poorly demarcated tumour measures from 0.5 to 10 cm (average 2.5 cm) (681,2432,3063) with a firm, white-grey cut surface.

**Histopathology**

Mammary fibromatoses are histologically similar to those arising from the fascia or aponeuroses of muscles elsewhere in the body with the same immunophenotype. Proliferating spindled fibroblasts and myofibroblasts form sweeping and interlacing fascicles; the periphery of the lesion reveals characteristic infiltrating finger-like projections entrapping mammary ducts and lobules (3063). Fibromatosis must be distinguished from several entities in the breast.

**Immunoprofile**

The neoplastic cells react positively for vimentin, desmin, α-smooth muscle actin and variably for CD34, bcl-2 protein, CD99 and sex steroid hormone receptors (estrogen, progesterone and androgen receptors) (1022,1023,1733,1913).

**Synonym**

Desmoid tumour.
Inflammatory myofibroblastic tumour

Definition
A tumour composed of differentiated myofibroblastic spindle cells accompanied by numerous inflammatory cells.

ICD-O code 8825/1

Synonyms
Inflammatory pseudotumour, plasma cell granuloma.

Epidemiology
Inflammatory myofibroblastic tumour (IMT) is a heterogeneous clinicopathological entity (1845) that may occur at any anatomical location. There is uncertainty as to whether IMT is reactive or neoplastic in nature. Some authors regard IMT as a low grade sarcoma (1845). Only rare cases of IMT have been reported in the breast (276,467,2235,3183).

Clinical features
IMT usually presents as a palpable circumscribed firm mass.

Macroscopy
Gross examination usually shows a well circumscribed firm white to grey mass.

Histopathology
The lesion consists of a proliferation of spindle cells with the morphological and immunohistochemical features of myofibroblasts, arranged in interlacing fascicles or in a haphazard fashion, and variably admixed with an inflammatory component of lymphocytes, plasma cells and histiocytes. IMT should be distinguished from other benign and malignant spindle cell lesions occurring in the breast. The hallmark of IMT is the significant inflammatory cell component.

Prognosis and predictive factors
Although the clinical behaviour of IMT cannot be predicted on the basis of histological features, in the breast most reported cases have followed a benign clinical course after complete surgical excision (276,467,2235), with the exception of a bilateral case with local recurrence in both breasts after 5 months (3183). Additional cases with longer follow-up are needed to define the exact clinical behaviour.

Lipoma

Definition
A tumour composed of mature fat cells without atypia.

ICD-O code 8850/0

Epidemiology
Although adipose tissue is quantitatively an important component of the normal breast tissue, pathologists rarely encounter intramammary lipomas. Subcutaneous lipomas are more often resected. Most common lipomas become apparent in patients 40-60 years of age.

Clinical features
Lipomas usually present as a slow growing solitary mass with a soft doughy consistency.

Macroscopy
Lipomas differ little from the surrounding fat. They may be altered by fibrous tissue, often hyalinized or show myxoid changes. Secondary alterations like lipogranulomas, lipid cysts, calcifications, may occur as a result of impaired blood supply or trauma.

Histopathology
Lipomas differ little from the surrounding fat. They may be altered by fibrous tissue, often hyalinized or show myxoid changes. Secondary alterations like lipogranulomas, lipid cysts, calcifications, may occur as a result of impaired blood supply or trauma.

Variants of lipoma
These include angiolipoma (1268,2876,3232) which, unlike angiolipomas at other sites, in the breast are notoriously painless. Microscopy reveals mature fat cells separated by a branching network of small vessels that is more pronounced in the subcapsular areas. Characteristically, thrombi are found in some vascular channels. Some lesions rich in vessels are called cellular angiolipomas. Other variants which have been described in the breast include spindle cell lipomas.
lipoma [1645], hibernoma [2425] and chondrolipoma [1774a]. Adenomas containing glandular breast tissue such as adenolipoma are considered as hamartomas by some and variants of lipoma by others.

**Granular cell tumour**

**Definition**
A tumour of putative schwannian origin consisting of cells with eosinophilic granular cytoplasm.

**ICD-O code** 9580/0

**Epidemiology**
Granular cell tumour (GCT) can occur in any site of the body. It is relatively uncommon in the breast [2114]. It occurs more often in females than in males [430] with a wide age range from 17-75 years [325, 617,668,3090]. GCT is a potential mimick of breast cancer, clinically, radiologically and grossly [608,617,995,2549].

**Clinical features**
GCT generally presents as a single, firm, painless mass in the breast parenchyma but may be superficial causing skin retraction and even nipple inversion, whereas location deep in the breast parenchyma may lead to secondary involvement of the pectoralis fascia. Rarely, patients have simultaneous GCTs occurring at multiple sites in the body, including the breast [1920,1922]. Imaging typically shows a dense mass with stellate margin.

**Macroscopy**
GCT appears as a well circumscribed or infiltrative firm mass of 2-3 cm or less with a white to yellow or tan cut surface.

**Histopathology**
The histology is identical to that seen in GCT at other sites of the body. There is an infiltrating growth pattern, even in lesions, which appear circumscribed on gross examination. The cellular component is composed of solid nests, clusters or cords of round to polygonal cells with coarsely granular, eosinophilic periodic acid-Schiff (PAS) positive (diastase resistant) cytoplasm. Due to the presence of abundant intracytoplasmic lysosomes. Awareness that GCT can occur in the breast is essential.

**Prognosis and predictive factors**
The clinical behaviour of GCT is usually benign following complete surgical excision. Rarely, lymph node metastases have been reported [668]. In contrast, a malignant course should be expected in the extremely rare malignant mammary GCTs which show nuclear pleomorphism, mitoses and necrosis [468].

**Benign peripheral nerve sheath tumours**

**Definition**
Benign peripheral nerve sheath tumours (BPNST) include three distinct lesions usually occurring in the peripheral nerves or soft tissues: schwannomas composed of differentiated Schwann cells; neurofibromas consisting of a mixture of Schwann cells, perineurial like cells and fibroblasts and perineuromas composed of perineurial cells.

**ICD-O codes**
- Schwannoma 9560/0
- Neurofibroma 9540/0

**Epidemiology**
The breast is only rarely the primary site of BPNST. There are only a few case reports of schwannomas [881,953,1081] and neurofibromas [1223,1675,2645], but to our knowledge primary perineuromas of the breast has not been recorded. Since neurofibromas may be part of neurofibromatosis type I (NF1), follow-up is needed because of the potential for malignant degeneration. The occurrence of breast cancer in the context of breast neurofibromas has been reported [1948].

**Clinical features**
The lesions present as a painless nodule and the pathology and immunophenotype is identical to their counterparts at other sites of the body.

**Angiosarcoma**

**Definition**
A malignant tumour composed of neoplastic elements with the morphological properties of endothelial cells.

**ICD-O code** 9120/3

**Synonyms**
These tumours include lesions which were formerly termed haemangiosarcoma, haemangioblastoma, lymphangiosarcoma and metastasizing haemangioma. Lymphangiosarcomas probably exist as a specific sarcoma of lymphatic endothelium but, at present, there is no...
reliable criterion upon which to make a histological distinction between tumours derived from endothelia of blood and lymphatic vessels.

**Epidemiology**

Mammary angiosarcoma can be subdivided into 1) Primary (de novo) forms in the breast parenchyma; 2) Secondary in the skin and soft tissues of the arm following ipsilateral radical mastectomy and subsequent lymphoedema - the Stewart Treves (S-T) syndrome; 3) Secondary in the skin and chest wall following radical mastectomy and local radiotherapy; 4) Secondary in the skin or breast parenchyma or both following conservation treatment and radiotherapy. Angiosarcomas, as with other sarcomas of the breast, are rare and their incidence is about 0.05% of all primary malignancies of the organ (2876). While the incidence of primary breast angiosarcomas has remained constant, the incidence of secondary forms has changed. S-T syndrome has dramatically declined in recent years in institutions in which more conservation surgical treatments have been adopted, while angiosarcomas of the breast developing after conserving surgery with supplementary radiation therapy have been diagnosed since the late 1980s (570).

**Primary (de novo) angiosarcoma of breast parenchyma**

In patients with primary angiosarcoma, the age ranges from 17 to 70 years (median 38 years) with no prevalence of laterality (2436). The tumours are deeply located in the breast tissue (2784). Approximately 12% of patients present with diffuse breast enlargement (2876). When the tumour involves the overlying skin a bluish-red discoloration may ensue. Imaging is of little help (1656, 2564, 3118).

**Macroscopy**

Angiosarcomas vary in size from 1 to 20 cm, averaging 5 cm (2425), have a spongy appearance and a rim of vascular engorgement which corresponds to a zone of well differentiated tumour. Poorly differentiated tumours appear as an ill defined indurated fibrous lesion similar to that of any other poorly differentiated sarcoma. Angiosarcomas must be sampled extensively to look for poorly differentiated areas that on occasion constitute the minority of a tumour.

**Histopathology**

Two systems have been used to grade angiosarcomas of the breast (717,1847). Although very similar, the one proposed by Donnell et al. (717) has gained wide impact as it was tested in a large number of patients with adequate follow up (2436).

- **Grade I (well differentiated)** angiosarcomas consist of interanastomosing vascular channels that dissect the interlobular stroma. The neoplastic vessels have very wide lumina filled with red blood cells. The nuclei of the endothelium lining the neoplastic vessels are prominent and hyperchromatic. Care must be taken to differentiate grade I angiosarcoma from benign vascular tumours.

- **Grade III (poorly differentiated)** angiosarcomas are easy to diagnose as interanastomosing vascular channels are intermingled with solid endothelial or spindle cell areas that show necrotic foci and numerous mitoses. In a grade III angiosarcoma, more than 50% of the total neoplastic area is composed of solid and spindle cell components without evident vascular channels (2425). A tumour qualifies as grade II (intermediately differentiated) angiosarcoma when at least 75% of the bulk of the tumour is formed by the well differentiated pattern seen in grade I, but in addition there are solid cellular foci scattered throughout the tumour.

**Clinical feature**

The average age of patients with grade I angiosarcomas is 43 years while 34 and 29 years are the respective figures for grade II and III angiosarcomas (717).

**Immunoprofile**

Factor VIII, CD34 and CD31 are the most widely used antibodies that characterize endothelial differentiation. While present
in all grade I and most grade II angiosarcomas these markers may be lost in more poorly differentiated tumours or areas of tumour.

Prognosis and predictive factors
If well differentiated angiosarcomas (Grade I) were excluded, this breast tumour is usually lethal (457). Grading systems highlight the relative benignity of well differentiated angiosarcomas. The survival probability for grade I tumours was estimated as 91% at 5 years and 81% at 10 years. For grade III tumours the survival probability was 31% at 2 years and 14% at 5 and 10 years. Grade II lesions had a survival of 68% at 5 and 10 years. Recurrence free survival at 5 years was 76% for grade I, 70% for grade II and 15% for grade III angiosarcomas (2436). Metastases are mainly to lungs, skin bone and liver. Very rarely axillary lymph nodes show metastases at presentation (457). The grade can vary between the primary tumour and its metastases (2876). Radio and chemotherapy are ineffective.

Angiosarcoma of the skin of the arm after radical mastectomy followed by lymphoedema
Stewart and Treves in 1949 gave a lucid description of a condition subsequently named S-T syndrome (2793). They reported six patients who had: 1) undergone mastectomy for breast cancer including axillary dissection; 2) developed an “immediate postmastectomy oedema” in the ipsilateral arm; 3) received irradiation to the breast area together with the axilla; 4) developed oedema which started in the arm and extended to the forearm and finally the dorsum of the hands and digits. The patients ranged in age from 37-60 years, with a mean age of 64 years (3149). The angiosarcomatous nature of S-T syndrome has been conclusively proved by ultrastructure and immunohistochemistry in most of the cases studied (1049, 1462,1862,2690).

The oedema is preceded by radical mastectomy for breast carcinoma including axillary dissection (275) and develops within 12 months. Nearly 65% of patients also had irradiation of the chest wall and axilla (2425). The interval to tumour appearance varies from 1-49 years (2425), but most become evident about 10 years following mastectomy (2752,3149). S-T syndrome is a lethal disease with a median survival of 19 months (3149). Lungs are the most frequent site of metastasis.

Post-radiotherapy angiosarcoma
Angiosarcoma can manifest itself after radiotherapy in two separate settings.
1) In the chest wall when radiotherapy has been administered after mastectomy for invasive breast carcinoma with a latency time ranging from 30 to 156 months (mean 70 months). The age is more advanced than that of de novo angiosarcoma ranging from 61 to 78 years (2223). In these cases the neoplastic endothelial proliferation is necessarily confined to the skin (392).
2) In the breast after conservation treatment for breast carcinoma. Fifty two cases had been reported as of December 1997. The first case was described in 1987 (1764). This type of angiosarcoma involves only the skin in more than half the cases, while exclusive involvement of breast parenchyma is very rare. Most tumours (81%) are multifocal and a large majority of patients harbour grade II to III angiosarcomas. Radiotherapy and chemotherapy are ineffective (2876).

Liposarcoma
Definition
A variably cellular or myxoid tumour containing at least a few lipoblasts.

ICD-O code 8850/3
Epidemiology
Primary liposarcoma should be distinguished from liposarcomatous differentiation in a phylloides tumour. It occurs predominantly in women ranging in age from 19-76 years (median, 47 years) (116, 138). The tumour only rarely occurs in the male breast (3027). Liposarcoma following radiation therapy for breast carcinoma has been reported.

Clinical features
Patients present most often with a slowly enlarging, painful mass. In general, skin changes and axillary node enlargement are absent. Rarely the tumour is bilateral (3027).

Macroscopy
Liposarcomas are often well circumscribed or encapsulated, about one-third have infiltrative margin. With a median size of 8 cm, liposarcomas may become enormous exceeding 15 cm (116,138). Necrosis and haemorrhage may be present on the cut surface of larger tumours.

Histopathology
The histopathology and immunophenotype is identical to that of liposarcoma at other sites. The presence of lipoblasts establishes the diagnosis. Practically every variant of soft tissue liposarcoma has been reported in the breast, including the pleomorphic, dedifferentiated and myxoid variants. Despite the well delineated gross appearance, many mamma-ry liposarcomas have at least partial infiltrative margins on histological examination. Atypia is often present at least focal-ly. The well differentiated and myxoid variants have a delicate arborizing vascu-
lar network and few lipoblasts. These may assume a signet-ring appearance in the myxoid variant. The pleomorphic vari-
ant is composed of highly pleomorphic cells and bears significant resemblance to malignant fibrous histiocytoma; the presence of lipoblasts identifies the lesion as a liposarcoma. Mitotic figures are readily identifiable in this variant.

Differential diagnosis
Vacuolated cells in a variety of lesions may be confused with lipoblasts. Typical lipoblasts have scalloped irregular nuclei with sharply defined vacuoles that contain lipid rather than glycogen or mucin. Clear nuclear pseudo-inclusions are a characteristic of the bizarre large cells in atypical lipomatous tumours and help distinguish these atypical cells from true lipoblasts that are diagnostic of a liposarcoma.
Prognosis and predictive factors
Both the myxoid and pleomorphic variants of liposarcoma can recur and metastasize. Axillary node metastases are exceptionally rare. Recurrences generally develop within the first year and patients who die from their disease usually do so within a year of the diagnosis. Because of the high frequency of marginal irregularity, complete excision with tumour free margins is necessary. Liposarcomas behave particularly aggressively when associated with pregnancy.

Rhabdomyosarcoma

Definition
A tumour composed of cells showing varying degrees of skeletal muscle differentiation.

ICD-O codes
Rhabdomyosarcoma 8900/3
Alveolar type 8920/3
Pleomorphic type 8901/3

Epidemiology
Pure primary rhabdomyosarcoma of the breast is very uncommon, and, although primary mammary rhabdomyosarcoma has been described, it usually represents a metastasis from a soft tissue rhabdomyosarcoma occurring in children, young females or males (2402). More frequently, rhabdomyosarcomatous differentiation may be observed in older women as an heterologous component of a malignant phylloides tumour or a metaplastic carcinoma.

Pathology
Primary rhabdomyosarcoma has been reported in adolescents (773,1166,1198, 2402), when it is predominantly of the alveolar subtype; the pleomorphic subtype has been reported in older women over forty (2871). Metastatic rhabdomyosarcoma to the breast is again predominantly of the alveolar subtype (1166,1248). The primary lesion is usually located on the extremities, in the nasopharynx/paranasal sinuses or on the trunk (1166). A metastasis from an embryonal rhabdomyosarcoma to the breast is less frequent (1166, 2531). Metastatic breast tumours may occur as part of disseminated disease or as an isolated lesion.

Mammary osteosarcoma

Definition
A malignant tumour composed of spindle cells that produce osteoid and/or bone together with cartilage in some cases.

ICD-O code
9180/3

Synonym
Mammary osteogenic sarcoma.

Epidemiology
Mammary osteosarcomas occur mainly in older women with a median age of 64.5 years; the age range is 27–89 years (2681). The vast majority of patients are women who are predominantly Caucasian. A prior history of radiation therapy or trauma has been noted in some women (331).

Clinical features
The tumour presents as an enlarging mass which is associated with pain in one-fifth of cases. Bloody nipple discharge or nipple retraction occurs in 12% of the women. Mammographically, osteosarcomas present as a well circumscribed mass with focal to extensive coarse calcification. Because of their predominantly circumscribed nature, they may be misinterpreted as a benign lesion (3072).

Macroscopy
Osteosarcomas vary in size from 1.4 to 13 cm; most are about 5 cm in size and are sharply delineated. The consistency varies from firm to stony hard depending on the proportion of osseous differentiation. Cavitation and necrosis are seen in larger tumours.

Histopathology
The histopathological appearance and immunophenotype are similar to that of
Leiomyoma and leiomyosarcoma

Definition
Benign and malignant tumours composed of intersecting bundles of smooth muscle which is mature in benign lesions. Malignant lesions are larger in size and show more mitotic activity in the neoplastic cells.

ICD-O codes
Leiomyoma 8890/0
Leiomyosarcoma 8890/3

Epidemiology
Benign and malignant smooth muscle tumours of the breast are uncommon and represent less than 1% of breast neoplasms. The majority of leiomyomas originate from the areolar-nipple complex and a minority occur within the breast proper (1981). Leiomyosarcomas arise mainly within the breast (821).

Clinical features
Both leiomyomas and leiomyosarcomas usually present as a slowly growing palpable mobile mass that may be painful. Incidental asymptomatic leiomyomas discovered in mastectomy specimens have been reported (1981).

Macroscopy
These lesions appear as well circumscribed firm nodules with a whorled or lobulated cut surface. Their size ranges from 0.5 to 15 cm (770,2000).

Histopathology
The histopathology and immunophenotype are identical to that seen in smooth muscle tumours elsewhere in the body. These neoplasms may be well circumscribed (1981) or show irregular infiltrative borders (2000). Both are composed of spindle cells arranged in interlacing fascicles. In leiomyomas, these cells have elongated cigar-shaped nuclei and eosinophilic cytoplasm without evidence of atypia. Mitoses are sparse and typically fewer than 3 per 10 high power fields (458). In leiomyosarcomas, nuclear atypia and mitotic activity are more prominent (821). Tumour necrosis may also be observed. Infiltrating margins may not be evident in some leiomyosarcomas.

Differential diagnosis
A diagnosis of a smooth muscle tumour of the breast should be considered only after excluding other breast lesions that may show benign or malignant smooth muscle differentiation i.e. fibroadenoma, muscular hamartoma and sclerosing adenosis should be distinguished from leiomyoma; spindle cell myoepithelioma and sarcomatoid carcinoma from leiomyosarcoma.

Prognosis and predictive factors
Leiomyomas are best treated by complete excision whereas, wide excision with tumour-free margins is recommended for leiomyosarcomas. Late local recurrence and metastasis have been reported in cases of mammary leiomyosarcoma (458,2014).

extraosseous osteosarcoma at other sites of the body. Despite the predominantly circumscribed margins, characteristically, at least focal infiltration is present. The tumour is composed of a spindle to oval cell population with variable amounts of osteoid or osseous tissue; cartilage is present in over a third of the cases (2681) but no other differentiated tissues.

The appearance of the tumours varies depending on the cellular composition (fibroblastic, osteoblastic, osteoclastic) as well as the type and amount of matrix (osteoid, osseous, chondroid).

The osteoclastic giant cells are immunoreactive with the macrophage marker CD68 (clone KP1) while the spindle cells fail to immunoreact with either estrogen receptor (ER) or progesterone receptor (PR) or epithelial markers.

Prognosis and predictive factors
Mammary osteosarcomas are highly aggressive lesions with an overall five-year survival of 38% (2681). Recurrences develop in over two-thirds of the patients treated by local excision and 11% of those treated by mastectomy. Metastases to the lungs and absence of axillary node involvement are typical of osteosarcomas. Many of the patients who develop metastases die of the disease within 2 years of initial diagnosis (2681).

Fibroblastic osteosarcomas are associated with a better survival compared to the osteoblastic or osteoclastic variants. Large tumour size at presentation, prominent infiltrating margins and necrosis are associated with more aggressive behaviour.

Fig. 1.145 Leiomyoma. A The well circumscribed margin (left) is apparent. B The bland smooth muscle cells proliferate in whorls and fascicles.
**Fibroepithelial tumours**

**Definition**
A heterogeneous group of genuine biphasic lesions combining an epithelial component and a quantitatively predominant mesenchymal component (also called stromal component) which is responsible for the gross appearance. Depending on the benign or malignant nature of each component, various combinations may occur. They are classified into two major categories: fibroadenomas and phyllodes tumours. Hamartomas are not fibroepithelial tumours, but represent pseudotumoral changes. As they contain glandular and stromal tissue, and sometimes may resemble fibroadenomas, they have been included in this chapter.

**Fibroadenoma**

**Definition**
A benign biphasic tumour, fibroadenoma (FA) occurs most frequently in women of childbearing age, especially those under 30.

**ICD-O code** 9010/0

**Aetiology**
Usually considered a neoplasm, some believe FA results from hyperplasia of normal lobular components rather than being a true neoplasm.

**Clinical features**
FA presents as a painless, solitary, firm, slowly growing (up to 3 cm), mobile, well defined nodule. Less frequently it may occur as multiple nodules arising synchronously or asynchronously in the same or in both breasts and may grow very large (up to 20 cm) mainly when it occurs in adolescents. Such lesions, may be called “giant” fibroadenomas. With the increasing use of screening mammography, small, non-palpable FAs are being discovered.

**Macroscopy**
The cut surface is solid, firm, bulging, greyish in colour, with a slightly lobulated pattern and slit like spaces. Variations depend on the amount of hyalinization and myxoid change in the stromal component. Calcification of sclerotic lesions is common.

**Histopathology**
The admixture of stromal and epithelial proliferation gives rise to two distinct growth patterns of no clinical significance. The pericanalicular pattern is the result of proliferation of stromal cells around ducts in a circumferential fashion; this pattern is observed most frequently during the second and third decades of life. The intracanalicular pattern is due to compression of the ducts into clefts by the proliferating stromal cells. The stromal component may sometimes exhibit focal or diffuse hypercellularity (especially in women less than 20 years of age), atypical bizarre multinucleated giant cells (233,2278), extensive myxoid changes or hyalinization with dystrophic calcification and, rarely, ossification (especially in postmenopausal women). Foci of lipomatous, smooth muscle (1040), and osteochondroid (1852,2762) metaplasia may rarely occur. Mitotic figures are uncommon. Total infarction has been reported, but rarely.

The epithelial component can show a wide spectrum of typical hyperplasia, mainly in adolescents (411,1525,1861,2250), and metaplastic changes such as apocrine or squamous metaplasia may be seen. Foci of fibrocystic change, sclerosing adenosis and even extensive myoepithelial proliferation can also occur in FA. In situ lobular, and ductal carcinoma occasionally develop within FAs (693,1525).

Juvenile (or cellular) fibroadenomas are characterized by increased stromal cellularity and epithelial hyperplasia (1861,2250). The term giant FA has been used as a synonym for juvenile fibroadenoma by some, but is restricted to massive fibroadenomas with usual histology by others.

**Fig. 1.146** A Fibroadenoma showing lobulated, bulging cut surface. B Fibroadenoma with intracanalicular growth pattern.

**Fig. 1.147** Juvenile fibroadenoma. A Lobulated sectioned surface in a 8 cm tumour. Patient was 16 years old. B Periductal growth pattern with moderate stromal hypercellularity.
Tumours of the breast

Differential diagnosis
Most FAs, especially those of large size, cellular stroma and epithelial clefts need to be distinguished from phyllodes tumours (see below). Another breast lesion, which can simulate FA, is haematoma.

Prognosis and predictive features
Most FAs do not recur after complete surgical excision. In adolescents, there is a tendency for one or more new lesions to develop at another site or even close to the site of the previous surgical treatment. The risk of developing cancer within a FA or in breasts of patients previously treated for FA is low, although a slightly increased risk has been reported (734, 1640).

Phyllodes tumours

Definition
A group of circumscribed biphasic tumours, basically analogous to fibroadenomas, characterized by a double layered epithelial component arranged in clefts surrounded by an overgrowing hypercellular mesenchymal component typically organized in leaf-like structures. Phyllodes tumours (PTs) are usually benign, but recurrences are not uncommon and a relatively small number of patients will develop haematogenous metastases. Depending on the bland or overtly sarcomatous characteristics of their mesenchymal component (also called stromal component), PTs display a morphological spectrum lying between fibroadenomas (FAs) and pure stromal sarcomas. Still widespread in the literature, the generic term “cystosarcoma phyllodes”, is currently considered inappropriate and potentially dangerous since the majority of these tumours follow a benign course. It is highly preferable to use the neutral term “phyllodes tumour”, according to the view already expressed in the WHO classification of 1981 (3154), with the adjunction of an adjective determining the putative behaviour based on histological characteristics.

ICD-O codes
Phyllodes tumour, NOS 9020/1
Phyllodes tumour, benign 9020/0
Phyllodes tumour, borderline 9020/1
Phyllodes tumour, malignant 9020/3
Periductal stromal sarcoma, low grade 9020/3

Epidemiology
In western countries, PTs account for 0.3-1% of all primary tumours and for 2.5% of all fibroepithelial tumours of the breast. They occur predominantly in middle-

Fig. 1.148 Phyllodes tumour. A well circumscribed 6.5 cm mass with a few clefts was histologically benign.

Fig. 1.149 Phyllodes tumour. A circumscribed 9 cm tumour contained a large yellow nodule of liposarcoma (yellow) adjacent to a nodule of malignant phyllodes tumour (pink).

Fig. 1.150 Benign phyllodes tumour. A Leaf-like pattern and well defined interface with the surrounding normal tissue. B Higher magnification shows stromal cellularity.

Fig. 1.151 Malignant phyllodes tumour. A Periductal stromal growth with malignant features. B Note severe stromal atypia and multiple mitoses.
aged women (average age of presentation is 40-50 years) around 15-20 years older than for FAs. In Asian countries, PTs occur at a younger age (average 25-30 years) {487}. Malignant PTs develop on average 2-5 years later than benign PTs. Among Latino whites, especially those born in Central and South America, malignant phyllodes is more frequent {254}. Isolated examples of PTs in men have been recorded {1424a,2023}.

Aetiology

PTs are thought to be derived from intralobular or periductal stroma. They may develop de novo or from FAs. It is possible, in rare cases, to demonstrate the presence of a pre-existing FA adjacent to a PT.

Clinical features

Usually, patients present with a unilateral, firm, painless breast mass, not attached to the skin. Very large tumours (>10 cm) may stretch the skin with striking distension of superficial veins, but ulceration is very rare. Due to mammographic screening, 2-3 cm tumours are becoming more common, but the average size remains around 4-5 cm {775,2425}. Bloody nipple discharge caused by spontaneous infarction of the tumour has been described in adolescent girls {1781,2833}. Multifocal or bilateral lesions are rare {1932}. Imaging reveals a rounded, usually sharply defined, mass containing clefts or cysts and sometimes coarse calcifications.

Macroscopy

PTs form a well circumscribed firm, bulging mass. Because of their often clearly defined margins, they are often shelled out surgically. The cut surface is tan or pink to grey and may be mucoid. The characteristic whorled pattern with curved clefts resembling leaf buds is best seen in large lesions, but smaller lesions may have an homogeneous appearance. Haemorrhage or necrosis may be present in large lesions.

Histopathology

PTs typically exhibit an enhanced intracanalicular growth pattern with leaf-like projections into dilated lumens. The epithelial component consists of luminal epithelial and myoepithelial cells. Apocrine or squamous metaplasia is occasionally present and hyperplasia is not unusual. In benign phyllodes tumours, the stroma is more cellular than in FAs, the spindle cell nuclei are monomorphic and mitoses are rare. The stromal cellularity may be higher in zones in close contact with the epithelial component. Areas of sparse stromal cellularity, hyalinisation or myxoid changes are not uncommon. Necrotic areas may be seen in very large tumours. The presence of occasional bizarre giant cells should not be taken as a mark of malignancy. Lipomatous, cartilagenous and osseous metaplasia have been reported {2057,2730}. The margins are usually well delimited, although very small tumour buds may protrude into the surrounding tissue. Such expansions may be left behind after surgical removal and are a source of local recurrence. Malignant PTs have infiltrative rather than pushing margins. The stroma shows frankly sarcomatous, usually fibrosarcomatous changes. Heterologous differentiation such as liposarcoma, osteosarcoma, chondrosarcoma or rhabdomyosarcoma may occur {536,1161,2057,2249,2308}. Such changes should be indicated in the diagnostic report. Due to overgrowth of the sarcomatous components, the epithelial component may only be identified after examining multiple sections. Borderline PTs (or low grade malignant PTs) display intermediate features and the stroma often resembles low-grade fibrosarcoma. Malignant epithelial transformation (DCIS or LIN and their invasive counterparts) is uncommon {2136}.

Differential diagnosis

Benign PTs may be difficult to distinguish from fibroadenomas. The main features are the more cellular stroma and the formation of leaf-like processes. However, the degree of hypercellularity that is required to qualify a PT at its lower limit is difficult to define. Leaf-like
processes may be found in intracanalicular FAs with hypocellular and oedematous stroma, but the leaf-like processes are few in number and often poorly formed.

The term giant FA as well as juvenile (or cellular) FA have often been used inappropriately as a synonym for benign PT. Although the term periductal stromal sarcoma has been used as a synonym for PTs [2079], it is better restricted to a very rare non circumscribed biphasic lesion characterized by a spindle cell proliferation localized around tubules that retain an open lumen and absence of leaf-like processes [2876]. These often low grade lesions may recur and rarely progress to a classic PT.

Malignant PTs may be confused with pure sarcomas of the breast. In such case, diagnosis depends on finding residual epithelial structures. However, the clinical impact of these two entities appears to be similar [1887].

Grading
Several grading systems have been proposed with either two subgroups [1596,2876], or three subgroups [1473, 1887]. None is universally applied since prediction of the behaviour remains difficult in an individual case.

Grading is based on semi-quantitative assessment of stromal cellularity, cellular pleomorphism, mitotic activity, margin appearance and stromal distribution. Because of the structural variability of PTs, the selection of one block for every 1 cm of maximal tumour dimension is appropriate [2876]. PTs should be subclassified according to the areas of highest cellular activity and most florid architectural pattern. The different thresholds of mitotic indices vary substantially from author to author. Since the size of high power fields is variable among different microscope brands, it has been suggested that the mitotic count be related to the size of the field diameter [1887]. Stromal overgrowth has been defined as stromal proliferation to the point where the epithelial elements are absent in at least one low power field (40x) [3058]. So defined, stromal overgrowth is not uncommon.

Table 1.18
Main histologic features of the 3 tiered grading subgroups for phyllodes tumours.

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Borderline</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromal hypercellularity</td>
<td>modest</td>
<td>modest</td>
<td>marked</td>
</tr>
<tr>
<td>Cellular pleomorphism</td>
<td>little</td>
<td>moderate</td>
<td>marked</td>
</tr>
<tr>
<td>Mitosis</td>
<td>few if any</td>
<td>intermediate</td>
<td>numerous (more than 10 per 10 HPF)</td>
</tr>
<tr>
<td>Margins</td>
<td>well circumscribed, pushing</td>
<td>intermediate</td>
<td>invasive</td>
</tr>
<tr>
<td>Stromal pattern</td>
<td>uniform stromal distribution</td>
<td>heterogeneous stromal expansion</td>
<td>marked stromal overgrowth</td>
</tr>
<tr>
<td>Heterologous stromal differentiation</td>
<td>rare</td>
<td>rare</td>
<td>not uncommon</td>
</tr>
<tr>
<td>Overall average distribution</td>
<td>60%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Prognosis and predictive factors
Local recurrence occurs in both benign and malignant tumours. Recurrence may mirror the microscopic pattern of the original tumour or show dedifferentiation (in 75% of cases) [1067]. Metastases to nearly all internal organs have been reported, but the lung and skeleton are the most common sites of spread. Axillary lymph node metastases are rare, but have been recorded in 10-15% in cases of systemic disease [1887,2876]. Recurrences generally develop within 2 years, while most deaths from tumour occur within 5 years of diagnosis, sometimes after mediastinal compression through direct chest wall invasion.

The frequency of local recurrence and metastases correlate with the grade of PTs but vary considerably from one series to another. The average in pub-
lished data suggests a 21% rate of local recurrence overall, with a 17%, 25% and 27% rate in benign, borderline and malignant PTs, respectively, and a 10% rate of metastases overall, with a 0%, 4% and 22% rate in benign, borderline and malignant PTs, respectively (1887). Local recurrence after surgery is strongly dependent on the width of the excision margins (186).

**Mammary hamartomas**

**Definition**
A well-demarcated, generally encapsulated mass, composed of all components of breast tissue.

**Epidemiology**
Hamartomas occur predominantly in the peri-menopausal age group, but may be found at any age, including teenagers and post-menopausal women.

**Clinical features**
Hamartomas are frequently asymptomatic and only revealed by mammography (3042). They are detected in 0.16% of mammograms (1204). Very large lesions can deform the breast. Due to their well-defined borders they are easily enucleated.

**Macroscopy**
Hamartomas are round, oval, or discoid, ranging in size from 1 cm to more than 20 cm. Depending on the composition of the lesion the cut surface may resemble normal breast tissue, a lipoma or may be rubbery and reminiscent of a FA.

**Histopathology**
Generally encapsulated, this circumscribed mass of breast tissue may show fibrocystic or atrophic changes; pseudoangiomatous hyperplasia (PASH) is frequent (446). The lesion gives the impression of "breast within breast". In adolescents, differentiation between the appearance of the normal adolescent breast and FAs or asymmetric virginal hypertrophy can be difficult. Rare examples resembling phyllodes tumours, have been observed (2876).

**Variants of hamartoma**
Adenolipoma (867), adenohibernoma (618), and myoid hamartoma (624) could all be considered variants of mammary hamartoma.

**Prognosis**
The lesion is benign with no tendency to recur.
Nipple adenoma

Definition
A compact proliferation of small tubules lined by epithelial and myoepithelial cells, with or without proliferation of the epithelial component, around the collecting ducts of the nipple.

ICD-O code 8506/0

Synonyms
Nipple duct adenoma; papillary adenoma; erosive adenomatosis; florid papillomatosis; papillomatosis of the nipple, subareolar duct papillomatosis.

Historical annotation
Under the designation of nipple adenoma (NA), several morphological lesions (some of which overlap) have been included {1356,2222,2429,2894}.
1. The largest group consists of cases showing an adenosis pattern in its classical form, with sclerosis and/or pseudoinvasive features, sclerosing papillomatosis {2429}, and infiltrative epitheliosis {149}).
2. Epithelial hyperplasia (papillomatosis (2429); epitheliosis {149}) of the collecting ducts.
3. Lesions composed of a combination of epithelial hyperplasia and sclerosing adenosis.

Epidemiology
NA is rare with a wide age range from 20 to 87 years) {2894} and may occur in males {2429}.

Clinical features
Presenting symptoms are most frequently a sanguineous or serous discharge and occasionally erosion of the nipple or underlying nodule {2222}.

Histopathology
In the adenosis type, proliferating two cell layered glands sprout from and compress the collecting ducts {2222} resulting in cystic dilatation of the latter and formation of a discrete nodule. The epidermis may undergo hyperkeratosis. Rarely the adenosis expands to cause erosion of the epidermis {2429}).

When the sclerosis and pseudoinfiltrative patterns are prominent, an invasive carcinoma is closely simulated. The background stroma shows loose myxoid features, large collagenous bands or elastosis {149}.

Epithelial hyperplasia may be florid within the tubules of adenosis or mainly within the collecting ducts. Enlargement of the galactophore ostia and exposure of the epithelial proliferation to the exterior in a fashion reminiscent of "ectropion" of the uterine cervix may occur.

Prognosis and predictive factors
Occasional recurrences have been described after incomplete excision {2425}. Association with carcinoma has been reported but is rare {1367, 2429}.

Syringomatous adenoma

Definition
A non metastasizing, locally recurrent, and locally invasive tumour of the nipple/areolar region showing sweat duct differentiation.

ICD-O code 8407/0
Synonym
Infiltrating syringomatous adenoma.

Epidemiology
Syringomatous adenoma (SyT) is a rare lesion {1365,2414,2816}. While only 24 cases have been reported under this designation (98), other cases have been reported as examples of low grade adenosquamous carcinoma {2431,2816, 2995}. The age range is from 11 to 67 years with an average age of 40 years.

Clinical features
SyA presents as a firm discrete mass (1–3 cm) situated in the nipple and subareolar region {269,1365}.

Macroscopy
The lesion appears as a firm, ill defined nodule.

Histopathology
SyA consists of nests and branching cords of cells, glandular structures and small keratinous cysts permeating the nipple stroma in between bundles of muscle as well as in perineural spaces {1365,3056}. Extensions of the tumour may be present at a great distance from the main mass with intervening normal tissue. Cytologically, most of the proliferating elements appear bland with scant eosinophilic cytoplasm and regular round nuclei. The cells lining the gland lumina are cuboidal or flat. Frequently the glandular structures display two layers of cells: i.e. inner luminal and outer cuboidal basal cells occasionally containing smooth muscle actin. Mitoses are rare and necrotic areas are absent. The stroma is usually sclerotic, but myxoid areas containing spindle cells are frequent.

Differential diagnosis
This includes tubular carcinoma (TC) which rarely involves the nipple and low grade adenosquamous carcinoma which occurs in the breast parenchyma {2431}.

Prognosis and predictive factors
Recurrence has been reported {269}. Optimal treatment is excision with generous margins.

Paget disease of the nipple
Definition
The presence of malignant glandular epithelial cells within the squamous epithelium of the nipple, is almost always associated with underlying intraductal carcinoma, usually involving more than one lactiferous duct and more distant ducts, with or without infiltration, deep in the underlying breast. Paget disease (PD) of the nipple without an underlying carcinoma is rare.

ICD-O code 8540/3
Epidemiology
PD may be bilateral and may occur in either gender but at a relatively higher rate in men. The incidence is estimated at 1-4.3% of all breast carcinomas.

Aetiology
The glandular nature of the neoplastic cells in PD is confirmed by electron microscopic studies that show intraepithelial lumen with microvilli {2505}. Immunohistochemical studies confirm that Paget cells have the same phenotype as the underlying intraductal carcinoma cells {530,1423}. Suggested mechanisms of development are: a) intraepithelial epidermotropic migration of malignant cells of intraductal carcinoma to the epidermis; b) direct extension of underlying intraductal carcinoma to the nipple and overlying skin; and c) in situ neoplastic transformation of multi-potential cells located in the basal layer of the lactiferous duct and epidermis.

Clinical features
Depending on the extent of epidermal involvement, the skin may appear unremarkable or show changes ranging from focal reddening to a classical eczematous appearance, which may extend to the areola and adjacent epidermis. There is sometimes retraction of the nipple.

Histopathology
In the epidermis, there is proliferation of atypical cells with large nuclei and abundant clear or focally dense cytoplasm. They are disposed in small clus-
Tumours which are often closely packed in the centre of the lesion and lower portion of the epidermis but tend to be dispersed in single cells at the periphery and upper portion of the epidermis. The underlying lactiferous ducts contain a usually high grade DCIS that merges with the PD. Rarely, lobular intraepithelial neoplasia is encountered. Even when the in situ carcinoma is in the deep breast tissue, an involved lactiferous duct with or without skip areas can almost always be identified by serial sectioning.

An associated infiltrating carcinoma occurs in one-third of patients who present without a palpable mass and in more than 90% of those with a palpable mass. Special stains reveal the presence of mucin in the Paget cells in a large number of cases. Paget cells occasionally contain melanin pigment granules as a result of phagocytosis.

**Immunoprofile**

Immunohistochemically, Paget cells demonstrate similar properties to the underlying intraductal carcinoma cells with positive immunoreactivity for carcinoembryonic antigen, low molecular weight cytokeratin and ERBB2. On occasion, one of these antisera may be negative. Squamous carcinoma is commonly non-reactive for these antisera, but rarely may be immunoreactive for cytokeratin 7 (3128). Contrary to malignant melanoma, PD is usually S-100 protein and HMB45 negative. In PD, TP53 and estrogen receptor may be negative or positive, depending on the immunoprofile of the corresponding underlying carcinoma.

**Differential diagnosis**

PD occasionally poses differential diagnostic problems with malignant melanoma due to the pagetoid pattern of spread and the presence of pigment granules and also with squamous cell carcinoma in situ, due to the proliferation of atypical dark cells. The application of histochemical techniques and the use of immunostains will solve the question in most cases.

**Prognosis and predictive factors**

The prognosis is dependent on the presence or absence of underlying intraductal carcinoma and associated invasive carcinoma in the deep breast tissue.

---

Fig. 1.158 Paget disease of the nipple. A Atypical cells with clear cytoplasm admixed with those with dense cytoplasm. B, C Immunostaining for cytokeratin 7 (B) and ERBB2 (C) decorate the neoplastic cells predominantly located in the lower portion of the epidermis.
**Malignant lymphoma and metastatic tumours**

**Malignant lymphoma**

**Definition**
Malignant lymphoma of the breast may present as a primary or secondary tumour; both are rare. There is no morphological criterion to differentiate between the two (117,1792).

The criteria for defining and documentation of primary breast lymphoma, first proposed by Wiseman and Liao (3136) and, with minor modifications, accepted by others, are as follows:

1. Availability of adequate histological material.
2. Presence of breast tissue in, or adjacent to, the lymphoma infiltrate.
3. No concurrent nodal disease except for the involvement of ipsilateral axillary lymph nodes.
4. No previous history of lymphoma involving other organs or tissues.

As such criteria seem too restrictive and leave no room for primary breast lymphomas of higher stages, some authors include cases in which the breast is the first or major site of presentation, even if, on subsequent staging procedures, involvement of distant nodal sites or bone marrow is discovered (359,1261,1753).

**Epidemiology**
Primary breast lymphoma may appear at any age, but the majority of patients are postmenopausal women. A subset of patients is represented by pregnant or lactating women with massive bilateral breast swelling; most of these cases were reported from Africa (2643) although non-African cases are also on record (1753). The disease is exceedingly rare in men (2540).

**Clinical features**
Clinical presentation of primary breast lymphoma usually does not differ from that of breast carcinoma. It usually presents with a painless lump sometimes multinodular, which is bilateral in approximately 10% of cases. Imaging usually reveals no feature which helps to distinguish primary from secondary lymphoma (1657,2199). The value of MR imaging in breast lymphomas has not been clearly determined (1952,1961).

**Macroscopy**
Primary and secondary breast lymphomas most commonly appear as a well circumscribed tumour of varying size, up to 20 cm in largest diameter. On cut surface, the neoplastic tissue is white to white-grey, soft or firm, with occasional haemorrhagic or necrotic foci (994, 1580,1753,3136).

**Histopathology**
Microscopically, the majority of primary breast lymphomas are diffuse large B cell lymphomas, according to the most recent WHO classification (352,1144). In older literature, cases designated as reticulum cell sarcoma, histiocytic lymphoma and at least some lymphosarcoma cases would nowadays most probably be included in the above category. More recently, such lymphomas were diagnosed as centroblastic or immunoblastic by the Kiel classification or diffuse large cell cleaved or noncleaved and immunoblastic lymphomas by the Lukes-Collins classification and Working Formulation (18,296,534,706,994,1261,1346,1580,1665).

A minor proportion of primary lymphomas of the breast reflect Burkitt lymphoma, extranodal marginal-zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT) type, follicular lymphoma, lymphoblastic lymphoma of either B or T type, and, extremely rarely, T-cell lymphomas of variable subtypes by the current WHO classification.

---

Fig. 1.159 Diffuse large B-cell lymphoma. **A** Medullary carcinoma-like appearance. **B** Circumscribed mass, composed of large pleomorphic neoplastic lymphoid cells.
The relationship of the surrounding mammary tissue to the lymphomatous infiltration differs from case to case. In some, the bulk of the lesion is located in the subcutaneous tissue, and breast parenchyma is found only peripherally. In others, numerous ducts and lobules are embedded in the infiltrate but clearly separated from it. Sometimes lymphoma cells infiltrate the ducts to different degrees and, in rare cases, the latter are overgrown by lymphoma cells and barely visible, sometimes revealed only by using keratin immunostaining. The stroma may be scant or abundant and the infiltrates may have a “medullary” appearance. In some cases, lymphoma cells form cords and ribbons simulating an infiltrating lobular carcinoma.

**Diffuse large B-cell lymphoma**

**ICD-O code** 9680/3

Lymphoma of this type is characterized by a diffuse pattern of infiltration of breast tissue by large lymphoma cells varying in appearance from quite uniform to pleomorphic. Generally, the lymphoma cells resemble centroblasts or immunoblasts. The nuclei are oval, indented or even lobated, usually with distinct, single or multiple nucleoli, and the amount of cytoplasm is variable. Mitoses are usually numerous. Numerous tingible-body macrophages are evenly dispersed among the neoplastic cells producing the characteristic, “starry sky” appearance of the lymphoma. The breast tissue is usually hyperplastic and secretory.

Patients are usually pregnant or lactating women, particularly from tropical Africa where Burkitt lymphoma is endemic [2643]. Less frequently, non-endemic, sporadic cases, primarily presenting in the breasts, have been observed [1378]. Tumours typically present with massive bilateral breast swelling [2643].

**Burkitt lymphoma**

**ICD-O code** 9687/3

The morphological features of Burkitt lymphoma of the breast are identical with those seen in such a lymphoma in other organs and tissues: the infiltrate is composed of sheets of uniform, primitive looking, cells of medium size, with round nuclei, multiple nucleoli, coarse chromatin and a rather thick nuclear membrane. The cells are cohesive and the cytoplasm is moderate in amount with fine vacuoles containing lipids; it squares off with the cytoplasm of adjacent cells. Mitoses are very numerous. Numerous tingible-body macrophages are evenly dispersed among the neoplastic cells producing the characteristic, but by no means pathognomonic, “starry sky” appearance of the lymphoma. The breast tissue is usually hyperplastic and secretory.

Patients are usually pregnant or lactating women, particularly from tropical Africa where Burkitt lymphoma is endemic [2643]. Less frequently, non-endemic, sporadic cases, primarily presenting in the breasts, have been observed [1378]. Tumours typically present with massive bilateral breast swelling [2643].

**Extranodal marginal-zone B-cell lymphoma of MALT type**

**ICD-O code** 9699/3

At least some breast lymphomas appear to belong to the category of MALT lymphomas although the data on their frequency vary substantially. The breast was suggested to be one component of a common mucosal immune system [268] and may acquire lymphoid tissue as a part of an autoimmune process [2585] within which the lymphoma may develop. A number of recent series on breast lymphoma include examples of MALT lymphoma [534,994,1261,1580,1792]; they were not encountered in other series [117, 296,1346,1665].

Classically, MALT lymphomas are composed of small lymphocytes, marginal zone (centrocyte-like) and/or monocytophoid B-cells, often interspersed with larger blasts. Monotypic plasma cells may be numerous and sometimes predominant. The infiltrate is diffuse and neoplastic colonization of pre-existent reactive follicles may be seen. A lymphoepithelial lesion, defined originally as an infiltration of glandular epithelium by clusters of neoplastic centrocyte-like cells [1305], is rarely seen. Neoplastic infiltration and destruction of mammary ducts by lymphoma cells, most commonly encountered in large B-cell lymphomas or infiltration of ductal epithelium by non-neoplastic T cells should not be confused with a true lymphoepithelial lesion. However, the presence of such a lesion is not a prerequisite for a diagnosis of MALT lymphoma. Inflammatory reactive conditions may mimic MALT lymphomas; perhaps many cases previously described as pseudolymphoma were in reality MALT lymphomas given enough time to follow their evolution.

Immunohistochemically, pan-B markers are positive, surface Ig, usually of IgM type, is also positive. In addition, CD10 and bcl-6 are commonly positive, while CD5, bcl-2 and TdT are negative. EBV is frequently demonstrated in endemic but not in sporadic cases. IgH and IgL genes are rearranged.

**Fig. 1.160** CD20 immunorexpression in diffuse large B-cell lymphoma.

**Fig. 1.161** Burkitt lymphoma. Bilateral breast involvement may be the presenting manifestation during pregnancy and puberty. BL cells have prolactin receptors.
such as CD20 and CD79a; it is usually bcl-2 positive but negative for CD10, CD5 and CD23. The translocation t(11;18)(q21;q21) has been identified in many MALT lymphomas although not in the few analysed breast cases [2125]. Furthermore, trisomy 3 has been identified in a number of MALT lymphomas at different sites but breast cases were not included in the study [3157].

Follicular lymphoma

ICD-O code 9690/3

Follicular lymphoma is another type of lymphoma, which is included in recent primary breast lymphoma series [113, 296, 534, 994, 1261, 1346, 1580, 1665, 1792]. It features neoplastic follicles composed of centrocytes and centroblasts in different proportions and may be either grade 2 or 3, depending on the number of centroblasts inside the neoplastic follicles. Immunohistochemically, the lymphoma cells show positivity for pan B antigens, CD10 and bcl-2 but are negative for CD5 and CD23. Follicular dendritic cells in tight clusters positive for CD21 delineate neoplastic follicles.

Differential diagnosis

Malignant lymphoma of the breast may, on routine haematoxilin and eosin stained slides without using immunohistochemical methods, be misdiagnosed as carcinoma, particularly infiltrating lobular or medullary carcinoma [18]. In addition, some cases of granulocytic sarcoma (myeloid cell tumour) may be confused with T cell lymphomas if only a limited number of immunoreactions are used. Inflammatory conditions in the breast may mimic MALT lymphoma.

Prognosis and predictive factors

Primary breast lymphomas behave in a way similar to lymphomas of corresponding type and stage in other sites.

Metastasis to the breast from extramammary malignancies

Epidemiology

Metastatic involvement of the breast is uncommon as an initial symptom of a non-mammary malignant neoplasm [2424] accounting for 0.5-6% of all breast malignancies [982,3029]. Women are affected five to six times more frequently than men are [982, 3029]. The clinically reported incidence is lower than that found at autopsy. It is also higher when lymphoma and leukaemia are included [2940,3029]. Metastases within the breast are more frequent in patients with known disseminated malignancy (25-40%) [2424]. After lymphoma and leukaemia, malignant melanoma [2135,2424,2872,3020,3163] is the most common source from an extramammary site followed by rhabdomyosarcoma in children or adolescents [393,1129], and tumours of lung, ovary, kidney, thyroid, cervix, stomach and prostate [344,393,982,1111,1129,1530,1758,2134,2481,3020,3029,3038].

Clinical features

The patient usually presents with a palpable lesion, generally well circumscribed and rapidly growing to a size of 1-3 cm. Tumours are solitary in 85% of cases [2424], usually situated in the upper outer quadrant [778] and located superficially. The lesions may be bilateral (5-25%) [982] or multinodular. They can rarely simulate an inflammatory breast carcinoma [3020]. Axillary lymph node involvement is frequent [3029]. Mammographically, metastatic lesions are well circumscribed and without calcification excluding those from ovarian lesions, making mammographic differentiation from medullary or intracystic carcinoma difficult [1758, 2134,3038].

Macroscopy

Typically the tumour is nodular, solitary and well circumscribed. Multinodularity, when is present, would be an important feature favouring a metastatic carcinoma.

Histopathology

It is important to recognize that the morphology is not that of a primary mammary carcinoma and to consider the possibility of a metastasis from an extramammary primary. This is particularly crucial with the increasing use of fine needle and tissue core biopsies [982]. However, some metastatic tumours may have some similarities to primary breast neoplasms such as squamous, mucinous, mucoepidermoid, clear cell or spindle cell neoplasms, but they lack an intraductal component and are generally well circumscribed [2424].

Differential diagnosis

Immunohistochemistry is useful in separating metastatic from primary carcinoma. The expression of hormonal receptor and GCDFP-15 is in favour of a breast primary carcinoma. A panel of antibodies such as those to cytokeratin 7, 20, CA19-9, CA125, S100, vimentin and HMB45 can be helpful depending on the morphological appearance of the lesion [778,2424].

Prognosis and predictive factors

Metastatic involvement of the breast is a manifestation of generalized metastases in virtually all cases [2424,3020]. The prognosis of patients with metastatic disease in the breast is dependent on the site of the primary and the histological type [3029].
Tumours of the male breast

Definition
Breast tumours occur much less frequently in men than in women. The most common male breast lesions are gynaecomastia, carcinoma, and metastatic cancers. Other benign or malignant lesions also occur, but much more rarely.

Gynaecomastia

Definition
Gynaecomastia is a non-neoplastic, often reversible, enlargement of the rudimentary duct system in male breast tissue with proliferation of epithelial and mesenchymal components resembling fibroadenomatous hyperplasia of the female breast.

Synonym
Fibrosis mammae virilis (no longer used).

Epidemiology
There are three typical, steroid dependent, age peaks; neonatal, adolescent (2nd/3rd decade) and the so-called male climacteric phase (6th/7th decade). There is always relative or absolute endogeneous or exogeneous estrogenism. Gynaecomastia is frequent in Klinefelter syndrome and also occurs in association with liver cirrhosis, endocrine tumours and certain medications {1263, 2572}.

Clinical features
Gynaecomastia generally involves both breasts but is often clinically more distinct in one. Nipple secretion is rare. There is a palpable retroareolar nodule or plaque like induration. Occasionally there is aching pain.

Macroscopy
There is generally circumscribed enlargement of breast tissue which is firm and grey white on the cut surface.

Histopathology
There is an increased number of ducts lined by epithelial and myoepithelial cells. The surrounding cellular, myxoid stroma contains fibroblasts and myofibroblasts, intermingled with lymphocytes and plasma cells. Lobular structures, with or without secretory changes, are rare and mostly occur in response to exogenous hormonal stimulation such as transsexual estrogen therapy. This florid phase is followed by an inactive fibrous phase with flat epithelial cells and hyalinized periductal stroma. An intermediate phase with a combination of features also occurs. Occasionally, duct ectasia, apocrine or squamous metaplasia develop. An increase in the amount of adipose breast tissue alone may be called lipomatous pseudogynaecomastia.

Immunoprofile
Patients with Klinefelter syndrome exhibit elevated amounts of estrogen (ER) and progesterone (PR) receptors but other examples of gynaecomastia do not demonstrate significant elevation [2215, 2666].

In gynaecomastia induced by antiandrogen therapy, but not in carcinoma of the breast, there may be strong focal prostate specific antigen (PSA) immunoreactivity in normal or hyperplastic duct epithelium, while PSAP activity is negative. These findings should not be misinterpreted as indicating a metastasis from a prostatic carcinoma [968].

Prognosis and predictive factors
Recurrence of gynaecomastia is possible. Atypical ductal epithelial hyperplasia and carcinoma in situ are rarely seen in cases of gynaecomastia but there is no convincing evidence that gynaecomastia, per se, is precancerous.

Carcinoma

Definition
Carcinoma of the male breast is a rare malignant epithelial tumour histologically identical to that seen in the female breast. Both in situ and invasive carcinoma occur, at a ratio of about 1:25 [713].
male population both in the USA and the European Union (EU). A higher incidence with a lower average age and more cases in an advanced stage is reported in native Africans and Indians [39,1281,1329,1330,2539,2985]. This is reinforced by the consistently higher incidence rates for the black compared to the white male population in the US cancer registries [2169].

Aetiology

Some aspects of the aetiology of male breast cancer are similar to those of the much more common female counterpart. Thus, a direct association has been suggested with socio-economic class (i.e. increased risk in higher socio-economic classes) [607,1551,2539], although this remains controversial [1627,2906]. Likewise, it has been reported that both never married men and Jewish men are at higher risk [1726,2539,2906]. Family history of breast cancer in female and male first degree relatives has repeatedly been associated with male breast cancer risk, although quantification of relative and attributable risks on a population level remains undefined [418, 607,1185,1551,2449,2539,2799]. It has been estimated that there is a family history in about 5% of male breast cancer patients, but these patients do not present at a younger age [1210,2297]. Hereditary factors are discussed elsewhere (see genetic chapter).

Again, as for female breast cancer, anthropometric characteristics have been investigated, and body mass index (BMI) was directly associated with male breast cancer risk [418,607,1551,2539]. In a large case-control study [1253], the relative risk was 2.3 for the highest quartile of BMI. This study also suggested an association with height but the relative risk was only 1.5 and of borderline significance [1253].

Previous breast or testicular disease and gynaecomastia have been related to male breast cancer, and associations have been reported with an undescended testis [2231,2577,2906], orchectomy, orchitis, testicular injury, late puberty and infertility [2939].

Male breast cancer is more common among those with Klinefelter syndrome [418,2539] and infertility or low fertility, possibly as a consequence of Klinefelter syndrome or other hormonal abnormalities [607,1551,2539,2906]. Similar to the role of estrogen in female breast cancer [36,225,540,1128], high estrogen and prolactin levels have been reported as risk factors for male breast cancer [2539], and several small studies have found higher serum or urinary estrogen levels in cases than in controls [386,2024,2107,2363]. This is supported by retrospective cohort studies in Denmark, indicating an excess occurrence of breast cancer among men with cirrhosis and relative hyperoestrogenism [2755]. However, not all the results were consistent with this pattern of hormonal influence [173,3110].

Other endocrine factors may play an important role in the aetiology [815,1253,2539]. It has been suggested that diabetes mellitus may increase risk, possibly through hormonal mechanisms [815,1253,2539].

Reports on lifestyle factors have shown in general no material association with smoking, alcohol or coffee consumption [1253,2231,2449], although one study found a significant protective effect of smoking [2231]. A higher risk was associated with limited physical exercise and frequent consumption of red meat, while consumption of fruit and vegetables was related to a decreased risk, although the trends were not significant [1253]. In another large study from ten population-based cancer registries [2449], no trends in risk were observed with increased dietary intakes of several foods and nutrients, and no association was found with the use of any dietary supplement. Dietary factors are unlikely to be strong determinants of breast cancer in men [2449], though moderate associations, as described for female breast cancer [1636,1639], remain possible.

Although an association with electromagnetic field exposure has been suggested in the past [669,1784,2791], the Report of an Advisory Group on Non-Ionising Radiation to the National Radiological Protection Board (2001) concluded that there is no evidence that electromagnetic fields are related to adult male breast cancer [2355].

Invasive carcinoma

Clinical features

The most frequent sign is a palpable subareolar mass. Nipple ulceration or sanguineous secretion is seen in 15–30%. In 25–50% of patients, there is fixation to or ulceration of the overlying skin. A quarter of patients complain of pain. Male breast cancer is usually unilateral and occurs more frequently in the left breast. Synchronous bilateral tumours are found in less than 5% of cases.
Macroscopy
The majority of male breast cancers measure between 2 and 2.5 cm. Multiple separate nodules are rare as is involvement of the entire breast.

Histopathology
The histological classification and grading of male and female invasive breast carcinoma are identical, but lobular carcinoma does not usually occur in men even in those exposed to endogenous or exogenous hormonal stimulation (1855,2521,2552) and should only be diagnosed if E-cadherin expression is absent (34).

Immunoprofile
Compared to breast carcinoma in women, male breast carcinomas have a somewhat higher frequency of ER positivity in the 60-95% range, while PR positivity occurs in 45-85% of cases (315, 578,1836,1917). The concentrations are independent of patient age and similar to those found in postmenopausal women (2297). Androgen receptors are expressed in up to 95% of cases.

Prognosis and predictive factors
The prognosis and predictive factors are the same as for female breast cancer at comparative stages.

Metastasis to the breast
The ratio of primary breast cancer and a metastasis from another primary site to the breast is about 25:1. The most frequent primaries are prostatic carcinoma, adenocarcinoma of the colon, carcinoma of the urinary bladder, malignant melanoma and malignant lymphoma.

Carcinoma and sarcoma secondary to previous treatment
As in women, carcinoma following previous chemotherapy and/or irradiation has been reported (326,601), as has post irradiation sarcoma (2644).

Carcinoma in situ
ICD-O code 8500/2
Clinical features
In the absence of mammographic screening in men, the two most frequent symptoms are sero-sanguineous nipple discharge and/or subareolar tumour.

Histopathology
The histological features are in general similar to those in the female breast but two major studies have found that the most frequent architectural pattern is papillary, while comedo DCIS occurs rarely (602,1221). Lobular intraepithelial neoplasia is also extremely rare. Paget disease may be relatively more common among men compared to women due to the shorter length of the duct system in male breast.

Other tumours
Almost all breast tumours which occur in women have also, been reported in men, albeit rarely.

Genetics in male breast cancer
Very little is currently known about the molecular events leading to the development and progression of sporadic breast cancer in males. Loss of heterozygosity (LOH) and comparative genomic hybridisation (CGH) studies and cytogenetic analysis have shown that somatic genetic changes in sporadic male breast carcinomas are quantitatively and qualitatively similar to those associated with sporadic female breast cancer (2532,2927,3134,3265). Tumour phenotypic markers, such as ERBB2 and TP53 expression, are also quite similar between the sexes (3129). Ki-ras mutations are not significantly increased in male breast cancer (636). LOH on chromosome 8p22 and 11q13 are frequently identified in male breast cancer (490,1073) suggesting that the presence of one or more tumour suppressor genes in these regions may play a role in the development or progression of the disease. LOH at 11q13 is found more often in carcinomas with positive nodal status than in carcinomas without lymph node metastasis (1073). Frequent allelic losses on chromosome 13q are reported in familial, as well as in sporadic, male breast cancer (2296, 3134). Chromosome 13q is the region containing the BRCA2, BRUSH-1, and retinoblastoma gene. Depending on the population, studies demonstrated that 4-38% of all male breast cancers are associated with BRCA2 alterations (918,1550, 2921). Other putative target genes are also situated here, including protocadherin 9 and EMK (serine/threonine protein kinase). Possibly, multiple tumour suppressor genes may influence the observed pattern of loss of heterozygosity (1083).

The role of aberrant hormone secretion or hormone receptor function in the development or progression of the disease remains controversial. Hormonal imbalances, such as those in Klinefelter syndrome or Reifenstein syndrome (mutation of the androgen receptor gene: Xq11-12) are known risk factors for breast cancer in males (427, 1213,2484). In three men, germline mutations in the androgen receptor gene was reported including two brothers with Reifenstein syndrome (1686,3152). However it has been shown that mutations of the androgen receptor are not obligatory for the development of male breast cancer (1213).

Cytogenetic studies reveal clonal chromosomal anomalies: Loss of the Y chromosome and gain of an X chromosome, as well as the gain of chromosome 5, are all frequently observed (1213,2484). Taken together with previous data, the present findings suggest close similarities between the molecular pathogenesis of male and female breast cancers.
CHAPTER 2

Tumours of the Ovary and Peritoneum

Tumours of the ovary represent about 30% of all cancers of the female genital system. Age-adjusted incidence rates are highest in the economically advanced countries where they are almost as common as cancers of the corpus uteri and invasive cancer of the cervix. Carcinomas of surface epithelial-stromal origin account for 90% of these cancers in North America and Western Europe. In some Asian countries, including Japan, germ cell tumours account for a significant proportion (20%) of ovarian malignancies. High parity and the use of oral contraceptives are consistently associated with a reduced risk of developing surface epithelial-stromal tumours while long-term estrogen replacement therapy appears to increase the risk in postmenopausal women.
### Tumours of the ovary and peritoneum

#### WHO histological classification of tumours of the ovary

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Subtype</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface epithelial-stromal tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serous tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Adenocarcinoma</td>
<td>8441/3</td>
</tr>
<tr>
<td></td>
<td>Surface papillary adenocarcinoma</td>
<td>8461/3</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinofibroma (malignant adenofibroma)</td>
<td>9014/3</td>
</tr>
<tr>
<td>Borderline tumour</td>
<td>8442/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Papillary cystic tumour</td>
<td>8462/1</td>
</tr>
<tr>
<td></td>
<td>Surface papillary tumour</td>
<td>8463/1</td>
</tr>
<tr>
<td></td>
<td>Adenofibroma, cystadenofibroma</td>
<td>9014/1</td>
</tr>
<tr>
<td>Benign</td>
<td>Cystadenoma</td>
<td>8441/0</td>
</tr>
<tr>
<td></td>
<td>Papillary cystadenoma</td>
<td>8460/0</td>
</tr>
<tr>
<td></td>
<td>Surface papillaoma</td>
<td>8461/0</td>
</tr>
<tr>
<td></td>
<td>Adenofibroma and cystadenofibroma</td>
<td>9014/0</td>
</tr>
<tr>
<td><strong>Mucinous tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Adenocarcinoma</td>
<td>8400/3</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinofibroma (malignant adenofibroma)</td>
<td>9015/3</td>
</tr>
<tr>
<td>Borderline tumour</td>
<td>8472/1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intestinal type</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endocervical-like</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>Cystadenoma</td>
<td>8470/0</td>
</tr>
<tr>
<td></td>
<td>Adenofibroma and cystadenofibroma</td>
<td>9015/0</td>
</tr>
<tr>
<td><strong>Mucinous cystic tumour with mural nodules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mucinous cystic tumour with pseudomyxoma peritonei</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endometrioid tumours including variants with squamous differentiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Adenocarcinoma, not otherwise specified</td>
<td>8380/3</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinofibroma (malignant adenofibroma)</td>
<td>8381/3</td>
</tr>
<tr>
<td>Malignant müllerian mixed tumour</td>
<td>8950/3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adenosarcoma</td>
<td>8933/3</td>
</tr>
<tr>
<td></td>
<td>Endometrioid stromal sarcoma (low grade)</td>
<td>8805/3</td>
</tr>
<tr>
<td>Benign</td>
<td>Cystadenoma</td>
<td>8380/1</td>
</tr>
<tr>
<td></td>
<td>Adenofibroma and cystadenofibroma</td>
<td>8381/1</td>
</tr>
<tr>
<td><strong>Clear cell tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transitional cell tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Transitional cell carcinoma (non-Brenner type)</td>
<td>8120/3</td>
</tr>
<tr>
<td></td>
<td>Malignant Brenner tumour</td>
<td>9000/3</td>
</tr>
<tr>
<td>Borderline</td>
<td>Brenner tumour</td>
<td>9000/1</td>
</tr>
<tr>
<td></td>
<td>Proliferating variant</td>
<td>9000/1</td>
</tr>
<tr>
<td>Benign</td>
<td>Brenner tumour</td>
<td>9000/0</td>
</tr>
</tbody>
</table>

### Metaplastic variant

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertoli-Leydig cell tumour group (androblastomas)</td>
<td>8631/0</td>
</tr>
<tr>
<td>Of intermediate differentiation</td>
<td>8631/1</td>
</tr>
<tr>
<td>Variant with heterologous elements (specify type)</td>
<td>8634/1</td>
</tr>
<tr>
<td>Poorly differentiated (sarcomatoid)</td>
<td>8631/3</td>
</tr>
<tr>
<td>Variant with heterologous elements (specify type)</td>
<td>8634/3</td>
</tr>
<tr>
<td>Retiform</td>
<td>8633/3</td>
</tr>
<tr>
<td>Variant with heterologous elements (specify type)</td>
<td>8634/3</td>
</tr>
<tr>
<td>Sertoli cell tumour</td>
<td>8640/1</td>
</tr>
<tr>
<td>Stromal-Leydig cell tumour</td>
<td>8650/1</td>
</tr>
<tr>
<td>Sex cord-stromal tumour, unclassified</td>
<td>8670/3</td>
</tr>
<tr>
<td><strong>Steroid cell tumours</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Germ cell tumours</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Additional Notes:**

- Squamous cell tumours
- Epidermoid cyst
- Mixed epithelial tumours (specify components)
- Malignant
- Borderline
- Benign
- Undifferentiated and unclassified tumours
- Undifferentiated carcinoma
- Adenocarcinoma, not otherwise specified
- Sex cord-stromal tumours
- Granulosa-stromal cell tumours
- Adult granulosa cell tumour
- Juvenile granulosa cell tumour
- Thecoma-fibroma group
- Thecoma, not otherwise specified
- Typical
- Luteinized
- Fibroma
- Cellular fibroma
- Fibrosarcoma
- Stromal tumour with minor sex cord elements
- Sclerosing stromal tumour
- Unclassified (fibrothecoma)
- Sertoli-Leydig cell tumour group (androblastomas)
- Leydig cell tumour group
- Hilus cell tumour
- Leydig cell tumour, non-hilar type
- Leydig cell tumour, not otherwise specified
- Steroid cell tumour, not otherwise specified
- Well differentiated
- Malignant
- Primitive germ cell tumours
- Dysergeminoma
- Yolk sac tumour
- Polyvesicular vitelline tumour
- Glandular variant
- Hepatoid variant
- Embryonal carcinoma
### Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (http://snomed.org).

Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9072/3</td>
<td>Germ cell sex cord-stromal tumours</td>
</tr>
<tr>
<td>9100/3</td>
<td>Gonadoblastoma</td>
</tr>
<tr>
<td>9080/3</td>
<td>Variant with malignant germ cell tumour</td>
</tr>
<tr>
<td>9110/3</td>
<td>Mixed germ cell-sex cord-stromal tumour</td>
</tr>
<tr>
<td>9080/0</td>
<td>Variant with malignant germ cell tumour</td>
</tr>
</tbody>
</table>

**Tumours of the rete ovarii**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9110/3</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>9110/0</td>
<td>Adenoma</td>
</tr>
<tr>
<td>9110/1</td>
<td>Cystadenoma</td>
</tr>
<tr>
<td>9110/2</td>
<td>Cystadenofibroma</td>
</tr>
</tbody>
</table>

### WHO histological classification of tumours of the peritoneum

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9050/3</td>
<td>Desmoplastic small round cell tumour</td>
</tr>
<tr>
<td>8806/3</td>
<td>Epithelial tumours</td>
</tr>
<tr>
<td>8461/3</td>
<td>Primary peritoneal serous adenocarcinoma</td>
</tr>
<tr>
<td>8806/3</td>
<td>Tumour of uncertain origin</td>
</tr>
</tbody>
</table>

**Secondary tumours**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8806/3</td>
<td>Plasmacytoma</td>
</tr>
</tbody>
</table>

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

### WHO histological classification of tumours of the peritoneum

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9072/3</td>
<td>Germ cell sex cord-stromal tumours</td>
</tr>
<tr>
<td>9100/3</td>
<td>Gonadoblastoma</td>
</tr>
<tr>
<td>9080/3</td>
<td>Variant with malignant germ cell tumour</td>
</tr>
<tr>
<td>9110/3</td>
<td>Mixed germ cell-sex cord-stromal tumour</td>
</tr>
<tr>
<td>9080/0</td>
<td>Variant with malignant germ cell tumour</td>
</tr>
</tbody>
</table>

**Tumours of the rete ovarii**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9110/3</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>9110/0</td>
<td>Adenoma</td>
</tr>
<tr>
<td>9110/1</td>
<td>Cystadenoma</td>
</tr>
<tr>
<td>9110/2</td>
<td>Cystadenofibroma</td>
</tr>
</tbody>
</table>

### WHO histological classification of tumours of the peritoneum

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9050/3</td>
<td>Desmoplastic small round cell tumour</td>
</tr>
<tr>
<td>8806/3</td>
<td>Epithelial tumours</td>
</tr>
<tr>
<td>8461/3</td>
<td>Primary peritoneal serous adenocarcinoma</td>
</tr>
<tr>
<td>8806/3</td>
<td>Tumour of uncertain origin</td>
</tr>
</tbody>
</table>

**Secondary tumours**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8806/3</td>
<td>Plasmacytoma</td>
</tr>
</tbody>
</table>

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
### TNM and FIGO classification of tumours of the ovary

<table>
<thead>
<tr>
<th>TNM and FIGO classification of tumours of the ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong> – Primary Tumour</td>
</tr>
<tr>
<td><strong>TNM Categories</strong></td>
</tr>
<tr>
<td>TX: Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0: No evidence of primary tumour</td>
</tr>
<tr>
<td>T1: Tumour limited to the ovaries</td>
</tr>
<tr>
<td>T1a: IA Tumour limited to one ovary; capsule intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T1b: IB Tumour limited to both ovaries; capsule intact, no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T1c: IC Tumour limited to one or both ovaries with any of the following: capsule ruptured, tumour on ovarian surface, malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T2: Tumour involves one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>T2a: IIA Extension and/or implants on uterus and/or tube(s); no malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T2b: IIB Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T2c: IIC Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T3 and/or N1: Tumour involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis</td>
</tr>
<tr>
<td>T3a: IIA Microscopic peritoneal metastasis beyond pelvis</td>
</tr>
<tr>
<td>T3b: IIB Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td><strong>T3c and/or N1</strong> IIC Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>N</strong> – Regional Lymph Nodes*</td>
</tr>
<tr>
<td>NX: Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0: No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1: Regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>M</strong> – Distant Metastasis</td>
</tr>
<tr>
<td>MX: Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0: No distant metastasis</td>
</tr>
<tr>
<td>M1: Distant metastasis</td>
</tr>
</tbody>
</table>

**Stage Grouping**

- Stage IA: T1a N0 M0
- Stage IB: T1b N0 M0
- Stage IC: T1c N0 M0
- Stage IIA: T2a N0 M0
- Stage IIB: T2b N0 M0
- Stage IIC: T2c N0 M0
- Stage IIIA: T3a N0 M0
- Stage IIIB: T3b N0 M0
- Stage IIIC: T3c N0 M0
- Stage IV: Any T Any N M1

Note: Liver capsule metastasis is T3/stage III, liver parenchymal metastasis M1/stage IV. Pleural effusion must have positive cytology for M1/stage IV.

---

1. [TMN2002](http://tnm.uicc.org).
3. The classification applies to malignant surface epithelial-stromal tumours including those of borderline malignancy.
4. Non-epithelial ovarian cancers may also be classified using this scheme.
5. The regional lymph nodes are the hypogastric (obturator), common iliac, external iliac, lateral sacral, para-aortic, and inguinal nodes.
**Definition**
Surface epithelial-stromal tumours are the most common neoplasms of the ovary. They originate from the ovarian surface epithelium or its derivatives and occur in women of reproductive age and beyond. They are histologically composed of one or more distinctive types of epithelium, admixed with a variable amount of stroma. Their biological behaviour varies with histological type.

**Epidemiology**
Cancer of the ovary represents about 30% of all cancers of the female genital organs. In developed countries it is about as common as cancers of the corpus uteri (35%) and invasive cancer of the cervix (27%). The age-adjusted incidence rates vary from less than 2 new cases per 100,000 women in most of Southeast Asia and Africa to over 15 cases in Northern and Eastern Europe. The economically advanced countries of North America, Europe, Australia, New Zealand and temperate South America show the highest rates. In the United States more women die from ovarian cancer today than from all other pelvic gynaecological cancer sites combined (1066). Incidence rates have been either stable or have shown slow increases in most western countries, whereas they have risen steadily in parts of Eastern Asia.

**Aetiology**
Two factors consistently associated with a reduced risk of the disease are high parity and the use of oral contraceptives (1295,2474). Three recent studies have shown an increased risk of ovarian cancer in postmenopausal women treated with high-dose estrogen replacement therapy for 10 years or greater (963, 2373,2399). Very little is known of the aetiology of non-familial cases. The protective effects of pregnancies and of oral contraception suggest a direct role for ovulation in causing the disease, but no convincing mechanism linking the risk factors with malignant transformation has been proposed.

Several dietary factors have been related to ovarian cancer (819). There is emerging evidence that the Western lifestyle, in particular, obesity, is associated with an increased risk (388).

**Clinical features**

*Signs and symptoms*
Women with ovarian cancer have a poor prognosis. The mean 5-year survival rate in Europe is 32% (256). This unfavourable outcome is largely ascribed to a lack of early warning symptoms and a lack of diagnostic tests that allow early detection. As a result, approximately 70% of patients present when this cancer is in an advanced stage, i.e. it has metastasized to the upper abdomen or beyond the abdominal cavity (394). It is now recognized that the overwhelming majority of women diagnosed with ovarian cancer actually have symptoms, but they are subtle and easily confused with those of various benign entities, particularly those related to the gastrointestinal tract (1024,2106).

Physical signs associated with early stage ovarian cancer may be limited to palpation by pelvic examination of a mobile, but somewhat irregular, pelvic mass (stage I). As the disease spreads into the pelvic cavity, nodules may be found in the cul-de-sac, particularly on bimanual rectovaginal examination (stage II). Ascites may occur even when the malignancy is limited to one or both ovaries (stage IC). As the disease involves the upper abdomen, ascites may be evident. A physical examination of the abdomen may demonstrate flank bulging and fluid waves associated with the ascites. Metastatic disease is commonly found in the omentum, such that the latter may be readily identified in the presence of advanced stage (stage III) ovarian cancer as a ballottable or palpable mass in the mid-abdomen, usually superior to the umbilicus and above the palpable pelvic mass. Finally, the

---

**Fig. 2.01** Global incidence rates of ovarian cancer. Age-standardized rates (ASR) per 100,000 population and year. From Globocan 2000 (846).
disease may spread through lymphatics to either the inguinal or left supraclavicular lymph nodes, which may be readily palpable. It may advance into the pleural cavity as a malignant effusion, usually on the right side or bilateral, in which case the lung bases exhibit dullness to percussion and decreased breath sounds and egophony to auscultation (stage IV).

Advanced intra-abdominal ovarian carcinomatosis may also present with signs of intestinal obstruction including nausea, vomiting and abdominal pain.

**Genetic susceptibility**

**Familial clustering**

Numerous epidemiological investigations of ovarian cancer have attempted to quantify the risks associated with a positive family history. Whereas ovarian cancer has not been as extensively studied as breast cancer, several studies point to familial clustering. The relative risk of ovarian cancer for first degree relatives varies from 1.94 to 25.5, the latter if both a mother and sister are affected [1029,2557,2801].

**BRCA1/2**

A number of specific genes have been identified as playing a role. The most important of these, BRCA1 and BRCA2, are discussed in chapter 8. In contrast to breast cancer in which only a minority of the familial clustering could be explained by known major susceptibility loci such as BRCA1 and BRCA2, it is likely that the majority of the familial risk of ovarian cancer is explained by BRCA1 and to a lesser extent BRCA2, MLH1 and MSH2. Using statistical modelling and the results from BRCA1 and BRCA2 mutation testing in 112 families with at least two cases of ovarian cancer (allowing for insensitivity of the mutation detection assay), BRCA1 and BRCA2 accounted for nearly all of the non-chance familial aggregation [973].

**HNPCC**

Ovarian cancer is a minor feature of the hereditary nonpolyposis colon cancer syndrome caused by mutations in genes associated with DNA base mismatch repair, the most frequent of which are MLH1 and MSH2.

**Imaging**

Due to its wide availability, ultrasound (US) is the imaging method of choice to assess an ovarian lesion and to determine the presence of solid and cystic elements. The distinction between benign, borderline and malignant tumours is generally not possible by US, either alone or in combination with magnetic resonance imaging (MRI) or computed tomography (CT). None of these methods has a clearly established role in preoperative tumour staging. Surgical exploration remains the standard approach for staging [1116,1417,1522,1795,2898].

**Tumour spread and staging**

About 70-75% of patients with ovarian cancer have tumour spread beyond the pelvis at the time of diagnosis [1770]. Ovarian cancers spread mainly by local extension, by intra-abdominal dissemination and by lymphatic dissemination, but rarely also through the blood stream. The International Federation of Gynecology and Obstetrics (FIGO) Committee on Gynecologic Oncology is responsible for the staging system that is used internationally today [217]. The pTNM-system is based on the postoperative pathological staging for histological control and confirmation of the disease. [51,2976].

**Histogenesis**

The likely origin of ovarian surface epithelial-stromal tumours is the mesothelial surface lining of the ovaries and/or invaginations of this lining into the superficial ovarian cortex that form inclusion cysts [838].
Association with endometrial cancer
Several studies provide evidence of associations between ovarian and other cancers, particularly endometrial (715, 1029). The relative risk of developing endometrial cancer is about 1.5 among mothers and sisters of ovarian cancer cases, although in both studies the risk fell just short of statistical significance.

Serous tumours

Definition
Ovarian tumours characterized in their better-differentiated forms by cell types resembling those of the fallopian tube.

ICD-O codes
Serous adenocarcinoma 8441/3
Serous borderline tumour 8442/1
Benign serous tumours
Serous papillary cystadenoma 8460/0
Serous cystadenoma 8441/0
Serous surface papilloma 8461/0
Serous adenofibroma, cystadenofibroma 9014/0

Serous adenocarcinoma

Definition
An invasive ovarian epithelial neoplasm composed of cells ranging in appearance from those resembling fallopian tube epithelium in well differentiated tumours to anaplastic epithelial cells with severe nuclear atypia in poorly differentiated tumours.

Macroscopy
The tumours range from not being macroscopically detectable to over 20-cm in diameter and are bilateral in two-thirds of all cases, but only in one-third of stage I cases. Well differentiated tumours are solid and cystic with soft papillae within the cystic spaces or on the surface. The papillae tend to be softer and more confluent than in cases of borderline tumours. Rare tumours are confined to the ovarian surface. Poorly differentiated tumours are solid, friable, multinodular masses with necrosis and haemorrhage.

Histopathology
The architecture of the tumour varies from glandular to papillary to solid. The glands are typically slit-like or irregular. The papillae are usually irregularly branching and highly cellular. In poorly differentiated tumours solid areas are usually extensive and composed of poorly differentiated cells in sheets with small papillary clusters separated by myxoid or hyaline stroma. Psammoma bodies may be present in varying numbers. The stroma may be scanty or desmoplastic. Serous carcinomas may contain a variety of other cell types as a minor component (less than 10%) that may cause diagnostic problems but do not influence the outcome. Serous psammocarcinoma is a rare variant of serous carcinoma characterized by massive psammoma body formation and low grade cytological features. The epithelium is arranged in small nests with no areas of solid epithelial proliferation, and at least 75% of the epithelial nests are associated with psammoma body formation (1001).

Immunoprofile
Serous carcinomas are always cytokeratin 7 positive and cytokeratin 20 negative. They are also positive for epithelial membrane antigen, CAM5.2, AE1/AE3, B72.3 and Leu M1 and for CA125 in 85% of the cases, but negative for calretinin and other mesothelial markers.

Grading
Various grading systems have been proposed for serous carcinomas. The utilization of a three-tiered grading system is recommended since the tumour grade has important prognostic and therapeutic implications (2687).

Somatic genetics
The prevailing view of the pathogenesis of serous adenocarcinoma is that it arises directly from the ovarian surface epithelium, invaginations or epithelial inclusions and progresses rapidly (205). At present, serous carcinoma is regarded as a relatively homogeneous group of tumours from the standpoint of pathogenesis. Thus, although these neoplasms are graded as well, moderately and poorly differentiated, they are thought to represent a spectrum of differentiation reflecting progression from a low grade to a high grade malignancy. Whereas in colorectal carcinoma a
advanced stage ovarian serous carcinoma, because well defined precursor histological serous carcinomas are paralleled by recent molecular genetic findings demonstrating TP53 mutations in very small stage I serous carcinomas (2707). Thus, there appears to be more than one pathway of tumorigenesis for serous carcinoma. In one pathway, conventional serous carcinoma, a high grade neoplasm, develops “de novo” from the surface epithelium of the ovary, grows rapidly and is highly aggressive (205). These tumours, even at their earliest stage, display TP53 mutations but not KRAS mutations. In the other pathway a SBT progresses in a “stepwise” fashion through a non-invasive micropapillary stage before becoming invasive (2706) or through microinvasion in a background of typical SBT. The indolent micropapillary tumours frequently display KRAS mutations, but TP53 mutations are only rarely detected.

Genetic susceptibility

The neoplasms that develop in women with germline BRCA1 mutations are mostly serous carcinomas of the ovary, fallopian tube and peritoneum.

Prognosis and predictive factors

The overall 5-year survival is approximately 40%; however, many of those alive at 5 years are alive with disease. Up to 85% of cases present with widespread metastatic disease. Survival at 5 years in this group is 10-20%. Patients with disease confined to the ovary or pelvis have a 5-year survival of 80%. Patients with serous psammocarcinoma have a protracted clinical course and a relatively favourable prognosis; their clinical behaviour more closely resembles that of SBT than serous carcinoma of the usual type.

Serous borderline tumour with microinvasion

Definition

An ovarian serous tumour of low malignant potential exhibiting early stromal invasion characterized by the presence in the stroma of individual or clusters of neoplastic cells cytologically similar to those of the associated non-invasive tumour. One or more foci may be present; none should exceed 10 mm².

Synonyms

Serous tumour of low malignant potential with microinvasion, serous tumour of borderline malignancy with microinvasion.

Epidemiology

Present in about 10-15% of SBTs, microinvasion occurs in women ranging in age from 17-83 years with a median age of 34.5 years (203,2867).

Clinical features

Most symptomatic women present with a pelvic mass or pain. About 28% of the 39 women in the 2 major series were pregnant at the time of presentation (203,2867).

Macroscopy

The macroscopic features are similar to those of SBT without microinvasion.

Tumour spread and staging

At presentation about 60% of the neoplasms are stage I, 13% stage I B, 5% stage IC, 8% stage IIC, 10% stage III (mostly IIIC) and 2.5% stage IV (liver metastases).

Histopathology

The hallmark of serous borderline tumours with microinvasion is the presence within the tumour stroma of single cells and cell clusters with generally abundant eosinophilic cytoplasm morphologically identical to those of the adjacent non-invasive tumour. The microinvasive foci form micropapillary, solid or rarely cribriform arrangements without or with only minimal stromal or cellular reaction. These cells are often

Table 2.01: Histological criteria for the diagnosis of serous borderline tumours.

- Epithelial hyperplasia in the form of stratification, tufting, cribriform and micropapillary arrangements
- Atypia (usually mild to moderate)
- Detached cell clusters
- Variable and usually minimal mitotic activity
- Absence of destructive stromal invasion

Tumours of the ovary and peritoneum
Surface epithelial-stromal tumours

located within empty stromal spaces, but vascular space invasion occurs in 10% of cases. In 87% of the 39 reported cases the invasive cells were of the eosinophilic cell type [203,2867]. The lymph nodes were rarely assessed as part of staging for these tumours. Tumour cells, mainly of the eosinophilic cell type, were found in three nodes (obturator, external iliac, and para-aortic) from two women [203,2867].

Prognosis and predictive factors

The behaviour of SBTs with microinvasion is similar to that of SBTs without microinvasion. In one series long-term follow-up was available in 11 cases with a 5-year survival of 100% and a 10-year survival of 86% [2285]. Unilateral salpingo-oophorectomy is currently acceptable therapy for young women who wish to preserve fertility.

Serous borderline tumour

Definition

An ovarian tumour of low malignant potential exhibiting an atypical epithelial proliferation of serous type cells greater than that seen in their benign counterparts but without destructive stromal invasion.

Synonyms

Serous tumour of low malignant potential, serous tumour of borderline malignancy. The designation "atypical proliferative serous tumour" is not recommended because it discourages complete surgical staging [2285] and because long term follow up indicates that some patients with typical SBT do not follow a benign course [3946].

Epidemiology

Patients with SBT are approximately 10-15 years younger than those with serous carcinoma (i.e. 45 years vs. 60 years). About 30-50% of SBTs are bilateral.

Clinical features

Signs and symptoms

The tumour is often asymptomatic but may rarely present with abdominal enlargement or pain due to rupture of a cystic tumour or torsion. In younger women SBT has been associated with a high rate of infertility [2894a].

Macroscopy

The tumour may be cystic with a variable number of excrescences, form a solid purely surface papillary growth or have a combination of these appearances. In
contrast to carcinomas, SBTs generally lack areas of necrosis and haemorrhage. The cysts usually contain serous fluid, but occasionally it is mucinous.

**Tumour spread and staging**

Stage I SBTs are confined to the inner surface of the cyst with no spread beyond the ovary. The staging of SBT follows the TNM/FIGO system for carcinomas [51, 2976].

**Histopathology**

The hallmarks of SBT that distinguish it from a cystadenoma are the presence of epithelial hyperplasia forming papillae (with fibrodermatous stalks), micropapillae associated with "detached" or "floating" cell clusters and mild to moderate nuclear atypia. It is distinguished from serous carcinoma by the lack of destructive stromal invasion. The proliferating cells vary from uniform, small cells with hyperchromatic nuclei to larger cells displaying eosinophilic cytoplasm with variable and generally low mitotic activity. Psammoma bodies may be present but are less abundant than in serous carcinomas. SBTs are divided into typical and micropapillary types. The typical type makes up the vast majority (90%) of SBTs and has a classic branching papillary architecture and epithelial tufts overlying the papillae. The micropapillary type accounts for a small proportion (5-10%) of tumours. This type shows focal or diffuse proliferation of the tumour cells in elongated, thin micropapillae with little or no stromal support emerging directly from the lining of a cyst, from large papillae in a non-hierarchical pattern or from the surface of the ovary. The micropapillae are at least five times as long as they are wide, arising directly from papillae with a thick fibrous stalk (non-hierarchical branching creating a "Medusa head-like appearance"). Less common patterns are cribriform and almost solid proliferations of non-invasive cells overlying papillary stalks. A continuous 5-mm growth of any of these three patterns is required for the diagnosis of micropapillary SBT. Up to 30% of SBTs are associated with tumour on the outer surface of the ovary, and about two-thirds are associated with peritoneal implants [376, 2615].

**Serous surface borderline tumour**

In this variant, polypoid excrescences formed by fine papillae with features of SBT occupy the outer surface of the ovary. Serous surface borderline tumour and cystadenofibroma

In this variant, the epithelial lining of the glands and/or cysts of the adenofibroma or cystadenofibroma has the features of SBT instead of benign epithelium.

**Peritoneal implants**

Two prognostically different types of peritoneal implants have been identified, non-invasive and invasive. The former is further subdivided into desmoplastic and epithelial types. Whereas the non-invasive implants (regardless of their type) have almost no negative influence on the
implants are heterogeneous, and various involved by SBT in about 20% of cases; the typical appearance of tubal the pathologist must assess multiple samples of macroscopically "normal" appearing omentum to ascertain adequate sampling. Invasive implants should be distinguished from benign epithelial inclusions and foci of endosalpingiosis. The latter are uncommon, occurring between a fifth and a tenth as often as implants [207]. Benign epithelial inclusions are characterized by small, generally round glands lined by a single layer of flat to low columnar cells without atypia or mitotic activity, often associated with a fibrous stroma. Small rounded glands also characterize endosalpingiosis, but the latter may be papillary and the lining cells show the typical appearance of tubal epithelium (ciliated, secretory and intercalated cells).

**Lymph node involvement**

Pelvic and para-aortic lymph nodes are involved by SBT in about 20% of cases; this finding appears to be without clinical significance. These lesions may be true metastases in peripheral sinuses, mesothelial cells in sinuses misinterpreted as tumour cells or independent primary SBTs arising in Mullerian inclusion glands that are present in 25-30% of pelvic and para-aortic lymph nodes.

**Somatic genetics**

The pattern of genetic alterations described in SBTs (for review see [1159]) differs from that of invasive carcinomas, e.g. TP53 mutations are most often absent in typical [836,1408] and micropapillary SBTs [1408], but are present in up to 88% of cases of invasive serous carcinoma. Loss of heterozygosity on the long arm of the inactivated X chromosome (464) is characteristic for SBT and rare in carcinomas (for review see [838]). Chromosomal imbalances have been identified in 3 of 9 SBTs, 4 of 10 micropapillary SBTs and 9 of 11 serous carcinomas by comparative genomic hybridization; some changes in micropapillary SBT are shared with SBT and others with serous carcinomas only suggesting a relationship among them [2771]. The genetic profile indicates that SBTs are a separate category with little capacity to transform into a malignant phenotype. The situation concerning micropapillary SBTs has to be clarified.

**Histopathological criteria**

Compared to typical SBTs, it has been suggested that micropapillary SBTs have a higher frequency of bilaterality (59-71% vs. 25-30%) [1408], an increased risk of recurrence among higher stage lesions [2772], more frequent ovarian surface involvement (50-65% vs. 36%) and probably a higher frequency of advanced stage at presentation (48-66% vs. 32-35%) at least among referral cases [376,754]. Several reports based on large series of cases, however, have demonstrated no difference in survival among patients with typical SBT and those with a micropapillary pattern among specific stages [658,754,1412,2285,2727], indicating a need for further investigation of the significance of the micropapillary pattern. In addition to its indolent course, micropapillary SBT differs from conventional serous carcinoma by its lack of responsiveness to platinum-based chemotherapy [210].

**Cytophotometric predictive factors**

The most reliable approach is the application of DNA-cytometry (preferably the static variant) according to the guidelines of the 1997 ESACP consensus report [1011,1141]. About 95% of SBTs display a diploid DNA-histogram with only a few cells in the 4c region indicating their low proliferative activity and only minor genetic alterations associated with an excellent clinical outcome [1380]. On the other hand, aneuploid SBTs characterized by a stemline deviation have a high recurrence rate, and the patients die frequently of their disease. For peritoneal implants DNA-cytometry is also of prognostic importance because aneuploid implants were found.
124 Tumours of the ovary and peritoneum

Benign serous tumours

Definition
Benign tumours composed of epithelium resembling that of the fallopian tube or in some cases the surface epithelium of the ovary.

Epidemiology
Benign serous tumours of the ovary account for approximately 16% of all ovarian epithelial neoplasms. The majority of benign serous tumours arise in adults in the fourth to sixth decades, although they may occur in patients younger than twenty or older than eighty years.

Localization
Benign serous tumours arise preferentially in the cortex of the ovary or on its surface (8%). They are usually bilateral, especially in older women. Often the tumours are metachronous with intervals that range from three to fourteen years.

Macroscopy
Benign serous tumours are usually 1-10 cm in diameter but occasionally reach up to 30 cm or more. They are typically unilocular or multilocular cystic lesions, the external surface is smooth, and the inner surface may contain small papillary projections. The cyst contents are watery and very rarely opaque or bloody. Adenofibromas are solid and have a spongy sectioned surface with minute, colourless fluid-containing cysts. Cystadenofibromas contain both solid areas and cysts. Surface papillomas appear as warty excrescences of different sizes on the surface of the ovary.

Histopathology
Benign serous tumours typically are lined by an epithelium similar to that of the fallopian tube with ciliated and less frequently nonciliated secretory cells. Of special diagnostic interest are the cysts with flattened lining, some of which may represent benign serous neoplasms with a desquamated lining. The only effective method to establish their nature is the application of scanning electron microscopy, which easily detects the ciliated cells, allowing a definitive diagnosis to be made.

Histogenesis
Benign serous tumours result from the proliferation of the surface epithelium of the ovary, [272,1403,2605] producing surface papillary excrescences or invaginating into the cortex of the ovary, forming so called inclusion cysts. Some morphological data support the possibility that a number of benign serous tumours arise from remnants in the hilar region of the ovary, possibly from rete cysts [726,1403,1823].

Prognosis and predictive factors
Serous cystadenomas are benign.

Mucinous tumours

Definition
Ovarian tumours some or all of whose epithelial cells contain intracytoplasmic mucin. They may resemble those of the endocervix, gastric pylorus or intestine. In some tumours only scattered goblet cells are present in an epithelium that is otherwise non-mucinous.

ICD–O codes
Mucinous adenocarcinoma 8480/3
Mucinous cystadenocarcinofibroma 9015/3
Mucinous borderline tumour 8472/1
Mucinous cystadenoma 8470/0
Mucinous adenofibroma 9015/0

Mucinous adenocarcinoma and related tumours

Definition
A malignant epithelial tumour of the ovary that in its better differentiated areas resembles intestinal or endocervical epithelium. Ovarian mucinous adenocarcinomas differ from borderline tumours by having evidence of ovarian stromal invasion.

Macroscopy
Mucinous carcinomas are usually large, unilateral, smooth surfaced, multilocular or unilocular cystic masses containing watery or viscous mucoid material. They are bilateral in approximately 5% of cases. Haemorrhagic, necrotic, solid or papillary areas are relatively frequent, and some tumours may be predominantly solid [1613,2605]. Because areas of malignancy may be limited, generous sampling of all mucinous cystic tumours to include up to one histological section per 1-2 cm of tumour diameter with sam-
Mucinous carcinoma are an expansile, mucinous tumours contain areas of mucinous ovarian neoplasms (see Table 2.16). Invasion is assumed if there are masses have been contaminated by metastatic mucinous carcinoma that may represent a metastatic from benign to malignant neoplasia that occurs in the development of mucinous carcinomas. Recent studies strongly suggest that in the sequence of malignant transformation from benign and borderline mucinous tumours to infiltrative carcinomas in transitional stages of mucinous carcinogenesis [1613]. This hypothesis is also supported by recent molecular studies of genetic alterations in mucinous tumours {591,964,1755,1891}. An increasing frequency of codon 12/13 KRAS mutations in benign, borderline and carcinomatous mucinous ovarian tumours has been reported supporting the viewpoint that KRAS mutational activation is an early event in mucinous ovarian tumorigenesis. Mucinous borderline tumours have a higher frequency of KRAS mutations than that of mucinous cystadenomas but a lower rate than that of mucinous carcinomas [591,1755,1891]. Using microdissection, the same KRAS mutation has been detected in separate areas exhibiting different histological grades within the same neoplasm [591].

**Histopathology**

In the absence of obvious infiltration of the stroma, invasion is assumed if there are complex papillary areas or back-to-back glands lined by malignant-appearing cells with little or no discernible intervening stroma. To qualify as frankly invasive, such areas should be at least 10 mm² and at least 3 mm in each of 2 linear dimensions [1613]. Alternatively, invasion may be in the form of infiltrative glands, tubules, cords or cell nests. The stroma may resemble ovarian stroma or be desmoplastic. In most cases there are also areas that are benign or borderline in appearance (1147,1150,1228,2047,2401). Rarely, mucinous tumours contain areas of mucinous adenofibroma with malignant epithelial cells and foci of stromal invasion.

**Differential diagnosis**

The most important differential diagnosis of mucinous ovarian carcinoma is with metastatic mucinous carcinoma that may present clinically as a primary ovarian tumour. Most of these originate in the large intestine, appendix, pancreas, biliary tract, stomach or cervix {237,639,1587,1703,2377,2406,3200,3221}. Since this problem has been emphasized recently, it is likely that early reports of the histological appearance and behaviour of ovarian mucinous carcinomas have been contaminated by metastatic carcinomas masquerading as primary ovarian neoplasms (see Table 2.03). Common features that favour a primary mucinous carcinoma are an expansile pattern of invasion and a complex papillary pattern [1614]. Common features favouring a metastatic mucinous carcinoma are bilaterality, a multinodular growth pattern microscopically, histological surface involvement by epithelial cells (surface implants) and vascular space invasion [1614].

**Somatic genetics**

Tumour heterogeneity is common and probably is a reflection of the progression from benign to malignant neoplasia that occurs in the development of mucinous carcinomas. Recent studies strongly suggest that in the sequence of malignant transformation from benign and borderline mucinous tumours to infiltrative carcinomas [2047,2401], they have been termed "microinvasive," and cases with this finding have had a favourable outcome {1453,1613,1967,2047,2401,2713].

**Mucinous borderline tumour, intestinal type**

**Definition**

Ovarian tumours of low malignant potential exhibiting an epithelial proliferation of mucinous type cells greater than that seen in their benign counterparts but without evidence of stromal invasion. The epithelial component resembles intestinal epithelium, almost always contains goblet cells, usually contains neuroendocrine cells and rarely contains Paneth cells.

**Synonyms**

Mucinous tumour of low malignant potential, intestinal type; mucinous tumour of borderline malignancy, intestinal type.

**Epidemiology**

These account for 85-90% of mucinous borderline tumours.

**Macroscopy**

Mucinous borderline tumours of intestinal type are bilateral in approximately 5% of cases and usually are large, multilocular or unicocular cystic masses containing watery or viscous mucoid material.
Velvety excrescences may line the cysts. Haemorrhagic, necrotic, solid or papillary areas are occasionally present [1613,2605].

**Histopathology**

Areas resembling mucinous cystadenoma are common. In the borderline areas the cells lining the cysts are stratified (usually to no more than 3 layers) and may form filiform intracystic papillae with at least minimal stromal support. Nuclei are slightly larger with more mitotic figures than in cystadenomas. Goblet cells and sometimes Paneth cells are present. The overall appearance resembles a hyperplastic or adenomatous colonic polyp [322,653,1076,1147,1150,1613,2377,2491,2605,2713]. Some or most of the epithelial cells lining the cysts of intestinal type borderline tumours may appear cytologically malignant and may be stratified to four or more layers in a solid, papillary or cribriform pattern. Whether tumours with such foci should be classified as non-invasive carcinomas or as borderline tumours has been a subject of controversy for many years. To provide for uniformity in reporting, it has been recommended that they be classified as borderline with intraepithelial carcinoma [2605].

**Prognosis and predictive factors**

When the tumour is confined to the ovaries at initial staging, the prognosis is excellent with only rarely reported recurrences [1150]. It is likely that most tumours diagnosed as intestinal-type mucinous borderline tumour that are associated with pseudomyxoma peritonei are actually metastatic from a similar-appearing tumour in the appendix (see section on pseudomyxoma peritonei). In the remaining cases with advanced disease, the metastases are usually in the form of invasive pelvic or abdominal implants rather than pseudomyxoma peritonei. In these cases the prognosis is similar to that of ovarian mucinous carcinomas with metastases, and it is likely that areas of invasion within the ovarian tumour were not sampled [1076,1147,1150,1613,2401]. Table 2.04 summarizes the differences in appearance and outcome among neoplasms having the appearance of mucinous borderline tumours.

**Mucinous borderline tumour, endocervical-like**

**Definition**

Ovarian tumours of low malignant potential exhibiting an epithelial proliferation of mucinous type cells greater than seen in their benign counterparts but without destructive stromal invasion. The mucinous epithelial cells resemble endocervical epithelium.

**Synonyms**

Mucinous tumour of low malignant potential, endocervical-like; mucinous tumour of borderline malignancy, endocervical-like; müllerian mucinous borderline tumour.

**Epidemiology**

These tumours make up 10-15% of mucinous borderline tumours [1613,2497,2713].

**Macroscopy**

Mucinous endocervical-like borderline tumours usually are multicystic or unilocular cystic masses containing watery or viscous mucoid material. Haemorrhagic, necrotic, solid or papillary areas may be present [1613,2605]. They are smaller than the intestinal type and have fewer cysts. They are bilateral in approximately 40% of cases and sometimes arise within an endometriotic cyst [2497].

**Tumour spread and staging**

Endocervical-like borderline tumours may be associated with abdominal or pelvic implants, some of which may appear invasive [2497,2713].
Histopathology
They differ from intestinal-type borderline tumours in that the intracystic growth is composed of broad bulbous papillae similar to those of serous borderline tumours. The epithelial cells lining the papillae are columnar mucinous cells and rounded cells with eosinophilic cytoplasm; the latter are often markedly stratified with detached cell clusters. The nuclei are only slightly atypical. Characteristically, there are many acute inflammatory cells within the papillae or free-floating in extracellular spaces.

Precursor lesions
Endocervical-like borderline tumours likely arise from endometriosis (2497). At least in some cases the peritoneal implants may arise from independent foci of endometriosis with in situ transformation.

Prognosis and predictive features
Endocervical-like borderline tumours may be associated with abdominal or pelvic implants, some of which may appear invasive, but the clinical behaviour has been indolent in the relatively few cases that have been reported (2497,2713). However, more cases in this category need to be studied.

Benign mucinous tumours

Definition
Benign mucinous tumours composed of epithelium resembling endocervical or gastrointestinal epithelium. The latter almost always contains goblet cells, usually contains neuroendocrine cells and rarely contains Paneth cells.

Macroscopy
Mucinous cystadenomas are usually large, unilaterial, multimarcular or unilocular cystic masses containing watery or viscous mucoid material. Cystadenofibromas and adenofibromas are partially to almost completely solid with only small cysts (200).

Histopathology
Benign mucinous tumours consist of cystadenomas, cystadenofibromas and adenofibromas These contain glands and cysts lined by mucinous columnar epithelium (2605). Cellular stratification is minimal, and nuclei are basally located with only slight, or any, atypia. Cystadenomas may have mucin extravasation with or without a stromal reaction. An ipsilateral dermoid cyst is present in 3-5% of cases. The uncommon mucinous adenofibroma is composed predominantly of fibromatous stroma (200).

Mucinous cystic tumours with mural nodules

Rare mucinous cystic tumours contain one or more solid mural nodules in which the histological features differ markedly from the background of either an intestinal-type borderline tumour or carcinoma (2007,2288,2290,2605). The nodules are yellow, pink or red with areas of haemorrhage or necrosis and range up to 12 cm in size. They may be malignant (anaplastic carcinoma, sarcoma or carcinosarcoma) or benign (sarcoma-like). Mucinous cystic tumours containing more than 1 type of mural nodule as well as mixed nodules have been described. Anaplastic carcinosarcomatous nodules usually contain a predominant population of cytokeratin-positive, large, rounded or spindle-shaped cells with abundant eosinophilic cytoplasm and high grade malignant nuclei. The few sarcomas that have been reported have been fibrosarcomas or rhabdomyosarcomas or have not been otherwise classified. Sarcoma-like nodules are sharply circumscribed and without vascular invasion but otherwise may appear alarming, containing pleomorphic cells with bizarre nuclei and many mitotic figures, often accompanied by spindle-shaped cells, epithelium-type giant cells, acute and chronic inflammatory cells and foci of haemorrhage and necrosis. The sarcoma-like cells may be weakly or focally cytokeratin-positive, but this finding, in itself, does not indicate a carcinomatous component (2605). The distinction is important because patients with anaplastic carcinoma in a mural nodule may follow a malignant course (2290), whereas the outcome of
those with only sarcoma-like nodules is the same as the corresponding category of mucinous tumour without the nodules [163]. Although the foci of anaplastic carcinoma are found more often in advanced stage tumours, it is now apparent that when they are confined to intact stage IA tumours, they are not necessarily associated with an adverse outcome [2401].

**Mucinous cystic tumours associated with pseudomyxoma peritonei**

Since there is strong evidence that ovarian mucinous tumours associated with pseudomyxoma peritonei (PP) are almost all metastatic rather than primary, it is important that such tumours are not diagnosed as stage II or III mucinous borderline tumours or carcinomas without first excluding an appendiceal or other gastrointestinal primary. Present evidence suggests that almost all genuine ovarian mucinous borderline tumours are stage 1. The number of stage 2 and 3 tumours in this category has been greatly exaggerated by including cases in which PP is associated with an undetected primary tumour in the appendix. Also, there is probably an unwarranted apparent increase in the number of high stage ovarian mucinous carcinomas because of undetected primary intestinal mucinous carcinomas associated with the clinical syndrome of PP.

Pseudomyxoma peritonei is a clinical term used to describe the finding of abundant mucoid or gelatinous material in the pelvis and abdominal cavity surrounded by fibrous tissue. The mucus may be acellular or may contain mucinous epithelial cells. Mucinous ascites, the presence of free-floating mucinous fluid, in the peritoneal cavity, almost never leads to pseudomyxoma peritonei. Areas of pseudomyxoma peritonei should be thoroughly sampled and examined histologically. The degree of atypia (benign, borderline or malignant) of any epithelial cells that are present should be reported, as well as whether the mucin dissects into tissues with a fibrous response or is merely on the surface. Pseudomyxoma peritonei with epithelial cells that are benign or borderline-appearing has been termed "disseminated peritoneal adenomucinosis" by some authors [2409], and patients with this finding have had a benign or protracted clinical course. In cases where the epithelial cells of the pseudomyxoma peritonei appear malignant, termed "peritoneal mucinous carcinomatosis" [2409], the source has usually been the appendix or colon, and the clinical course has usually been fatal. Pseudomyxoma peritonei may be present in women without a cystic ovarian tumour or in men. In such cases the source is almost always a gastrointestinal mucinous neoplasm, most commonly from the appendix [2409]. In cases where there is an appendiceal tumour and a mucinous cystic ovarian tumour,
The origin of the pseudomyxoma peritonei has been disputed. A majority of investigators believe that the ovarian tumour(s) are secondary in almost all such cases [2294,2407,3199]. However, a synchronous origin in both organs has also been proposed [2623]. Clonality studies have demonstrated identical KRAS mutations or the lack of them in both the appendiceal and the simultaneous ovarian tumours [590, 2830]. LOH analysis has shown similar findings in three cases and divergent findings in three; this latter observation appears to indicate that some simultaneous tumours are independent primaries [590], though genetic progression of the metastatic tumours could also account for the disparity of these results. The ovarian tumours are usually classified as either mucinous cystadenomas or intestinal-type borderline tumours. The epithelial cells within them are often found floating in mucin that dissects into the ovarian stroma (pseudomyxoma ovarii). They are well differentiated and often have a tall columnar appearance with abundant mucinous cytoplasm that is positive for cytokeratin 7 in approximately one-half of the cases [1075, 2408]. The latter finding differs from that of primary ovarian mucinous cystadeno- ma or intestinal-type borderline tumours most of which are cytokeratin 7-positive. The appendiceal tumour may be quite small relative to the ovarian tumour(s) and may not be appreciated macroscopically. Thus, removal and thorough histological examination of the appendix is indicated in cases of pseudomyxoma peritonei with a mucinous cystic ovarian tumour. In cases where an appendiceal mucinous neoplasm is found, it should be considered as the primary site and the ovaries as secondary. If the appendix has not been examined histologically and the ovarian tumours are bilateral, or unilateral in the absence of an ipsilateral dermoid cyst, the appendix should also be considered primary. If an appendiceal mucinous neoplasm is not found after thorough histological examination, if the appendix had been removed previously in the absence of pseudomyxoma peritonei or if the ovarian tumour is accompanied by a dermoid cyst in the absence of either a macroscopic or histological appendiceal lesion, the ovarian tumour may be considered to be the source of the pseudomyxoma peritonei [1613]. In equivocal cases cytokeratin 7 negativity in the ovarian tumour strongly suggests that it is metastatic.

Table 2.04

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Macroscopy</th>
<th>Histopathology</th>
<th>Appearance of extravarian disease</th>
<th>Usual behaviour in cases with extravarian disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal type MBT</td>
<td>Large, smooth surfaced multilocular cyst, bilateral in 5%</td>
<td>Cysts are lined with slightly stratified intestinal type cells with mild nuclear atypia and no detached cell clusters Usually CK7 positive</td>
<td>Invasive peritoneal implants without PP This is a rare finding</td>
<td>Prognosis is poor. Cases with invasive implants are likely due to unsampled invasive areas in the ovarian tumour.</td>
</tr>
<tr>
<td>Intestinal type MBT with intraepithelial carcinoma</td>
<td>Same</td>
<td>Same, with foci of malignant-appearing nuclei and often highly stratified, solid or cribriform areas</td>
<td>Invasive peritoneal implants without PP</td>
<td>Same as above</td>
</tr>
<tr>
<td>Endocervical-like MBT</td>
<td>Smaller with fewer cysts and may be associated with endometriosis, bilateral in 40%</td>
<td>Cysts composed of complex, bulbous papillae with highly stratified, benign-appearing mucinous and eosinophilic cells, detached cell clusters and numerous neutrophils</td>
<td>Invasive or noninvasive peritoneal implants</td>
<td>Benign</td>
</tr>
<tr>
<td>Mucinous ovarian tumours associated with PP</td>
<td>Bilateral in a high percentage of cases</td>
<td>Usually resembles intestinal type of MBT often with pseudomyxoma ovarii</td>
<td>PP Often primary appendiceal tumour</td>
<td>Variable, depending on the degree of atypia of the tumour cells in PP</td>
</tr>
</tbody>
</table>

PP = Pseudomyxoma peritonei; MBT = mucinous borderline tumour
**Endometrioid tumours**

**Definition**
Tumours of the ovary, benign, low malignant potential or malignant, that closely resemble the various types of endometrioid tumours (epithelial and/or stromal) of the uterine corpus. Although an origin from endometriosis can be demonstrated in some cases, it is not required for the diagnosis.

**ICD-O codes**
- Endometrioid adenocarcinoma, not otherwise specified: 8380/3
- Variant with squamous differentiation: 8570/3
- Ciliated variant: 8383/3
- Oxyphilic variant: 8290/3
- Secretory variant: 8382/3
- Adenocarcinofibroma: 8381/3
- Malignant müllerian mixed tumour: 8950/3
- Adenosarcoma: 8933/3
- Endometrioid stromal sarcoma: 8930/3
- Endometrioid borderline tumour: 8380/1
- Cystadenoma: 8380/0
- Adenofibroma; cystadenofibroma: 8381/0

**Endometrioid adenocarcinoma**

**Definition**
A malignant epithelial tumour of the ovary that closely resembles the common variant of endometrioid carcinoma of the uterine corpus. Although an origin from endometriosis can be demonstrated in some cases, it is not required for the diagnosis.

**Epidemiology**
Endometrioid carcinomas account for 10-20% of ovarian carcinomas (1409, 2489) and occur most commonly in women in the fifth and sixth decades of life (2773).

**Aetiology**
Up to 42% of the tumours are associated with endometriosis in the same ovary or elsewhere in the pelvis (676,932,1927, 2489,2287a) and 15-20% are associated with endometrial carcinoma (1477,1479, 1683,3239). These associations suggest that some endometrioid ovarian carcinomas may have the same risk factors for their development as endometrial carcinomas (613). Patients whose tumours occur in association with endometriosis are 5-10 years younger on average than patients without associated ovarian endometriosis (2800).

**Clinical features**
Like most ovarian carcinomas, many endometrioid carcinomas are asymptomatic. Some present as a pelvic mass, with or without pain and may be associated with endocrine symptoms secondary to steroid hormone secretion by the specialized ovarian stroma (1790). Serum CA125 is elevated in over 80% of the cases (946,1603).

**Macroscopy**
The tumours, typically measuring 10-20 cm in diameter, are solid, soft, friable or cystic with a fungating mass protruding into the lumen. They are bilateral in 28% of the cases.

**Fig. 2.29** Ovarian endometrioid adenocarcinoma arising from an endometriotic cyst. **A** This solid and cystic tumour forms polypoid structures. The patient had a synchronous endometrioid adenocarcinoma of the uterine corpus. **B** Well differentiated endometrioid adenocarcinoma is seen to the right and an endometriotic cyst on the left.

**Endometrioid adenocarcinoma**

Epidemiology
Endometrioid carcinomas account for 10-20% of ovarian carcinomas (1409, 2489) and occur most commonly in women in the fifth and sixth decades of life (2773).

Aetiology
Up to 42% of the tumours are associated with endometriosis in the same ovary or elsewhere in the pelvis (676,932,1927, 2489,2287a) and 15-20% are associated with endometrial carcinoma (1477,1479, 1683,3239). These associations suggest that some endometrioid ovarian carcinomas may have the same risk factors for their development as endometrial carcinomas (613). Patients whose tumours occur in association with endometriosis are 5-10 years younger on average than patients without associated ovarian endometriosis (2800).

Clinical features
Like most ovarian carcinomas, many endometrioid carcinomas are asymptomatic. Some present as a pelvic mass, with or without pain and may be associated with endocrine symptoms secondary to steroid hormone secretion by the specialized ovarian stroma (1790). Serum CA125 is elevated in over 80% of the cases (946,1603).

Macroscopy
The tumours, typically measuring 10-20 cm in diameter, are solid, soft, friable or cystic with a fungating mass protruding into the lumen. They are bilateral in 28% of the cases.

**Tumour spread and staging**
Stage I carcinomas are bilateral in 17% of the cases (2233). The stage distribution of endometrioid carcinomas differs from that of serous carcinomas. According to the FIGO annual report, 31% of the tumours are stage I; 20%, stage II; 38%, stage III; and 11%, stage IV (2233).

**Histopathology**
Ovarian endometrioid carcinomas closely resemble endometrioid carcinomas of the uterine corpus. The well differentiated form shows round, oval or tubular glands lined by stratified nonmucin-containing epithelium. Cribriform or villoglandular patterns may be present. Squamous differentiation occurs in 30-50% of the cases, often in the form of morules (cytologically benign-appearing squamous cells) (341,2605). The designation “endometrioid carcinoma with squamous differentiation” (rather than adenocanthoma and adenosquamous carcinoma) is favoured (2604,2605). The designation “endometrioid carcinoma with squamous differentiation” (rather than adenocanthoma and adenosquamous carcinoma) is favoured (2604,2605). Aggregates of spindle-shaped epithelial cells are an occasional finding in endometrioid carcinomas (2942). Occasionally, the spindle cell nests undergo a transition to clearly recognizable squamous cells suggesting that the former may represent abortive squamous differentiation (2605). Rare examples of mucin-rich, secretory, ciliated cell and oxyphilic types have been described (759,1187,2258). In the mucin-rich variant glandular lumens and the apex of cells are occupied by mucin (2605). The secretory type contains vacuolated cells resembling those of an
early secretory endometrium (2605). The oxyphilic variant has a prominent component of large polygonal tumour cells with abundant eosinophilic cytoplasm and round central nuclei with prominent nucleoli (2258).

Occasional tumours contain solid areas punctuated by tubular or round glands or small rosette-like glands (microglandular pattern) simulating an adult granulosa cell tumour (3206). In contrast to Call-Exner bodies, however, the microglands contain intraluminal mucin. The nuclei of endometrioid carcinomas are usually round and hyperchromatic, whereas those of granulosa cell tumours are round, oval, or angular, pale and grooved. Rare cases of endometrioid carcinomas of the ovary show focal to extensive areas resembling Sertoli and Sertoli-Leydig cell tumours (2111, 2466, 3206). They contain small, well differentiated hollow tubules, solid tubules or, rarely, thin cords resembling sex cords. When the stroma is luteinized, this variant may be mistaken for a Sertoli-Leydig cell tumour, particularly in cases in which the patient is virilized. Nevertheless, typical glands of endometrioid carcinoma and squamous differentiation are each present in 75% of the tumours, facilitating their recognition as an endometrioid carcinoma (2618).

**Immunoprofile**

Endometrioid carcinomas are vimentin, cytokeratin, epithelial membrane antigen, estrogen and progesterone receptor and B72.3 positive but alpha-inhibin negative (1789).

**Grading**

Grading of endometrioid carcinoma uses the same criteria as endometrial adenocarcinoma (3238) (see chapter 4).

**Histogenesis**

Most endometrioid carcinomas are thought to arise from surface epithelial inclusions, and up to 42% are accompanied by ipsilateral ovarian or pelvic endometriosis (676, 932, 1927, 2489) that may display the entire spectrum of endometrial hyperplasia (simple, complex, typical and atypical). Atypical (ipsilateral) endometriosis occurs in up to 23% of endometrioid carcinomas (932) and may have a role in the evolution of some endometrioid carcinomas (2618).

**Somatic genetics**

Somatic mutations of beta-catenin (CTNNB1) and PTEN are the most common genetic abnormalities identified in sporadic endometrioid carcinomas. The incidence of CTNNB1 mutations ranges from 38-50% (1909, 2153). Mutations have been described in exon 3 (codons 32, 33, 37, and 41) and involve the phosphorylation sequence for glycogen synthase kinase 3β. These mutations probably render a fraction of cellular beta-catenin insensitive to APC-mediated down-regulation and are responsible for its accumulation in the nuclei of the tumour cells. Beta-catenin is immunohistochemically detectable in carcinoma cells in more than 80% of the cases. Endometrioid carcinomas with beta-catenin mutations are characteristically early stage tumours associated with a good prognosis (965). PTEN is mutated in approximately 20% of endometrioid ovarian tumours and in 46% of those with 10q23 loss of heterozygosity (LOH) (2075). PTEN mutations occur between exons 3 to 8. The majority of endometrioid carcinomas with PTEN mutations are well differentiated and stage I tumours, suggesting that in this subset of ovarian tumours PTEN inactivation is an early event (2075). The finding of 10q23 LOH and PTEN mutations in endometriotic cysts that are adjacent to endometrioid carcinomas with similar genetic alterations provides additional evidence for the precursor role of endometriosis in ovarian carcinogenesis (2543).

Microsatellite instability (MI) also occurs in sporadic endometrioid carcinomas of the ovary although less frequently than in uterine endometrioid carcinomas. The reported frequency of MI in the former tumours ranges from 12.5-19% (1055, 1909). Like endometrial carcinomas, many ovarian carcinomas with MI follow the same process of MLH1 promoter methylation and frameshift mutations at coding mononucleotide repeat microsatellites (1055).

**Simultaneous endometrioid carcinomas of the ovary and endometrium**

Endometrioid carcinoma of the ovary is associated in 15-20% of the cases with carcinoma of the endometrium (767, 822, 1479, 2651, 3239). The very good prognosis in those cases in which the tumour is
limited to both organs provides strong evidence that these neoplasms are mostly independent primaries arising as a result of a müllerian field effect (822). Less frequently, one of the carcinomas represents a metastasis from the other tumour. The criteria for distinguishing metastatic from independent primary carcinomas rely mainly upon conventional clinicopathologic findings, namely stage, size, histological type and grade of the tumours, the presence and extent of blood vessel, tubal and myometrial invasion, bilaterality and pattern of ovarian involvement, coexistence with endometrial hyperplasia or ovarian endometriosis and, ultimately, patient follow-up (762, 2286,2978). By paying attention to these findings, the precise diagnosis can be established in most cases. Occasionally, however, the differential diagnosis may be difficult or impossible as the tumours may show overlapping features. In difficult cases comparative analysis of the immunohistochemical and DNA flow cytometric features of the two neoplasms may be of some help (822,2286). The presence of identical aneuploid DNA indexes in two separate carcinomas suggests that one of them is a metastasis from the other (2286). In contrast, when the two neoplasms have different DNA indexes, the possibility of two independent primaries has to be considered (2286). The latter results, however, do not completely exclude the metastatic nature of one of the tumours, since metastatic tumours or even different parts of the same tumour may occasionally have different DNA indexes reflecting tumour progression (2728). Molecular pathology techniques can also be helpful (1788). These include LOH, (782,923,1664,2641), gene mutation (923,1664,1909) and clonal X-inactivation analyses (926). Although LOH pattern concordance in two separate carcinomas is highly suggestive of a common clonal origin (i.e. one tumour is a metastasis from the other), the finding of different LOH patterns does not necessarily indicate that they represent independent tumours. Some studies have shown varying LOH patterns in different areas of the same tumour as a consequence of tumour heterogeneity (287). Discordant PTEN mutations and different microsatellite instability (MI) patterns in the two neoplasms are suggestive of independent primary carcinomas; nevertheless, metastatic carcinomas may also exhibit gene mutations that differ from those of their corresponding primary tumours as a result of tumour progression (923). Alternatively, two independent primary carcinomas may present identical gene mutations reflecting induction of the same genetic abnormalities by a common carcinogenic agent acting in two separate sites of a single anatomic region (1786,1788). In other words, the genetic profile can be identical in independent tumours and different in metastatic carcinomas (1788). Therefore, clonality analysis is useful in the distinction of independent primary carcinomas from metastatic carcinomas provided the diagnosis does not rely exclusively on a single molecular result and the molecular data are interpreted in the light of appropriate clinical and pathologic findings (1786,1788,2283). According to FIGO when the site of origin remains in doubt after pathological examination, the primary site of the tumour should be determined by its initial clinical manifestations.

Genetic susceptibility
Most endometrioid carcinomas occur sporadically, but occasional cases develop in families with germline mutations in DNA mismatch repair genes, mainly MSH2 and MLH1 (Muir-Torre syndrome) (535). This syndrome, thought to be a variant of the hereditary nonpolyposis colon cancer syndrome, is characterized by an inherited autosomal dominant susceptibility to develop cutaneous and visceral neoplasms (796).

Prognosis and predictive factors
The 5-year survival rate (FIGO) of patients with stage I carcinoma is 78%; stage II, 63%; stage III, 24%; and stage
IV, 6% [2233]. Patients with grade 1 and 2 tumours have a higher survival rate than those with grade 3 tumours [1479]. Peritoneal foreign body granulomas to keratin found in cases of endometrioid carcinoma with squamous differentiation do not seem to affect the prognosis adversely in the absence of viable-appearing tumour cells on the basis of a small series of cases [1459]. Endometrioid carcinomas with a mixed clear cell, serous or undifferentiated carcinoma component are reported to have a worse prognosis [2941].

**Malignant müllerian mixed tumour**

**Definition**
A highly aggressive neoplasm containing malignant epithelial and mesenchymal elements.

**Synonyms**
Carcinosarcoma, malignant mesodermal mixed tumour, metaplastic carcinoma.

**Epidemiology**
Malignant müllerian mixed tumours (MMMTs) are rare, representing less than 1% of ovarian malignancies. They occur most commonly in postmenopausal women of low parity, the median age being around 60.

**Clinical features**
The clinical presentation is similar to that of carcinoma of the ovary.

**Aetiology**
An increased incidence has been reported in women who have had pelvic irradiation [3080].

**Macroscopy**
The neoplasms form large (10-20 cm diameter), partly solid and partly cystic, or, less commonly, solid, grey-brown, unilateral or bilateral, bosselated masses with foci of haemorrhage and necrosis [479]. The sectioned surface is fleshy and friable, and cartilage and bone may be apparent. The tumours are bilateral in 90% of cases.

**Tumour spread and staging**
There is extraovarian spread to the pelvic peritoneum, omentum, pelvic organs and regional lymph nodes in more than 75% of cases at the time of diagnosis.

**Histopathology**
The histological and immunoprofile are similar to those of its uterine counterpart and those occurring elsewhere in the female genital system (see chapter 4).

**Histogenesis**
MMMT is believed to develop from the ovarian surface epithelium or from foci of endometriosis and, therefore, may be regarded as a high-grade carcinoma with metaplastic sarcomatous elements. The positive tumour response to chemotheraphy directed at ovarian carcinoma also supports this viewpoint.

**Somatic genetics**
There is evidence that MMMTs are monoclonal [26,2748] as the phenotypically different elements share similar allelic losses and retentions [925] and a cell line developed from an MMMT expresses both mesenchymal and epithelial antigens [195]. Furthermore, a heterogenous pattern of allelic loss at a limited number of chromosomal loci in either the carcinoomatous or sarcomatous component of the neoplasm is consistent with either genetic progression or genetic diversion occurring during the clonal evolution of the tumour.

**Genetic susceptibility**
There is anecdotal evidence of BRCA2 mutation [2748].

**Prognosis and predictive factors**
Improved cytoreductive surgery and platinum-based chemotheraphy has resulted in a median survival of 19 months [2715] and an overall 5-year survival of 18-27% [120,1182]. The survivors almost invariably have early stage disease at the time of diagnosis, and low stage is a statistically significant indicator of outcome [120,436,1182,2749]. No other histopathological factors are significant indicators of outcome.

**Adenosarcoma**

**Definition**
A biphasic tumour characterized by a proliferation of müllerian-type epithelium with a benign or occasionally markedly atypical appearance embedded in or
overlying a dominant sarcomatous mesenchyme.

**Clinical features**
Most of the tumours reported so far have been unilateral, occurring in the 4th and 5th decades. Abdominal discomfort and distension are the usual complaints.

**Macroscopy and histopathology**
The tumour is frequently adherent to the surrounding tissue. The macroscopic and histological features are described in detail in the uterine counterpart (see chapter 4).

**Prognosis and predictive factors**
Occasional reports have linked the spread of adenosarcomas into the abdominal cavity with a poor clinical outcome. The stroma is often predominantly fibrotic, oedematous or hyalized with characteristic foci of perivascular cuffing seen only focally (sometimes, the foci are very small) and still the tumours recur and kill the patient. Unfortunately, there exist no established morphological criteria to predict such biological behaviour. However, if during the course of the disease sarcomatous overgrowth develops, signifying invasive potential, the patient requires careful monitoring. In a series of 40 cases, the 5-year survival was 64%, the 10-year survival 46% and the 15-year survival 30%.

**Clinical features**
More than 70% of the tumours are unilateral. The age range is 11-76 years with the majority of tumours occurring around the 5th and 6th decade. The clinical symptoms do not differ from those recognized for other ovarian tumours.

**Macroscopy**
Most tumours are solid and firm, but some may show variably sized cysts, sometimes filled with mucoid or haemorrhagic fluid or debris. The sectioned surface appears yellow-white or tan, sometimes interspersed with grey fibrous bundles or septa.

**Histopathology**
Roughly half of the cases of ESS are associated with either endometriosis or a similar sarcomatous lesion of the endometrial stroma or both. The dominant cell type of ESS consists of small, round to oval, or occasionally spindle shaped cells with round nuclei and scanty, sometimes barely visible pale cytoplasm. The cells may be arranged haphazardly in a diffuse pattern or may form parallel cell sheets mimicking fibroma. Hypocellular areas with a distinct oedematous appearance can be present. Lipid droplets may be present within tumour cells, which are often associated with foam cells. A hallmark of ESS is the presence of abundant small thick-walled vessels resembling spiral arteries of the late secretory endometrium. The vessels often are surrounded by whorls of neoplastic cells. Reticulin stain discloses delicate fibrils characteristically enveloping individual tumour cells. The cellularity can vary markedly within the same specimen. The tumour can be partly intersected by fibrous bands forming more or less distinct nodules. Sometimes, hyaline plaques are present. Rarely, cord-like or plexiform arrangements of tumour cells similar to the growth patterns seen in ovarian sex cord tumours such as granulosa cell tumours or thecomas are observed. In these areas reticulin fibrils are more or less absent. Rarely, glandular elements are interspersed, but they never represent a dominant feature. At its periphery the tumour exhibits a typical infiltrative growth pattern. In cases where the tumour has spread into extravarian sites, a tongue-like pattern of invasion is present.
Surface epithelial-stromal tumours

into the adjacent tissue and intravascular growth appears. Most neoplasms are low grade, whereas approximately 10% of cases are high grade and are classified as undifferentiated ovarian sarcoma. In the past, tumours with less than 10 mitoses per 10 high power fields were classified as low grade ESS, whereas tumours with more than 10 mitoses per 10 high power fields were traditionally designated high grade (3208). However, there is no evidence that mitotic rate alone alters the outcome, and all tumours with an appearance resembling that of endometrial stroma should be designated endometrioid stromal sarcoma (438), whereas those that lack endometrial stromal differentiation should be diagnosed as undifferentiated ovarian sarcoma. The latter is a high grade neoplasm that is composed of pleomorphic mesenchymal cells with distinct variability in size and shape. The nuclei are highly atypical with prominent nucleoli and occasionally resemble rhabdomyosarcoma or fibrosarcoma.

**Immunoprofile**

Immunostaining demonstrates the expression of vimentin and CD10 in ESS. Muscle-associated proteins are only focally expressed. Alpha-inhibin was negative in all cases examined (1681).

**Differential diagnosis**

ESS must be differentiated from other ovarian lesions, including some small cell tumours. The major problem is to distinguish ESS from adult granulosa cell-tumour, foci of stromal hyperplasia, ovarian fibroma or ovarian thecoma. On morphological grounds alone, it is not always possible to decide whether the ovarian lesion is a primary ESS of the ovary or a metastatic lesion from a uterine ESS. Thus, an ovarian ESS should never be diagnosed unless the uterus is carefully examined to exclude a uterine primary. Should ESS be found in both organs, it is more or less impossible to decide which tumour is the primary and which is metastatic. One criterion that establishes a primary site in the ovary is its continuity with endometriotic foci in the ovary.

**Somatic genetics**

Mutation of the TP53 tumour suppressor gene associated with overexpression of TP53 protein has been frequently observed in ovarian sarcomas. These mutations may occur on the basis of an impaired DNA repair system in these tumours (1681).

**Prognosis and predictive factors**

Since over one-half of the ESSs have already spread to pelvic or upper abdominal sites at the time of diagnosis, the tumour stage remains the major prognostic criterion (438). Whether the neoplasm is an ESS or undifferentiated ovarian sarcoma also influences the clinical course (3208). ESS often has a favourable outcome with survival in excess of 5 years even in the context of extraovarian spread. After 10 years, however, the tumour-related mortality increases, particularly if extraovarian manifestations were noted at the time of diagnosis. Tumour relapse represents an ominous prognostic sign. Undifferentiated ovarian sarcomas have a rapid course and a poor prognosis (3208). Radical panhysterectomy is the recommended therapy. Successful treatment with progesterone, non-hormonal cytostatic drugs or radiation has been reported occasionally in ESS.

**Endometrioid borderline tumour**

**Definition**

An ovarian tumour of low malignant potential composed of atypical or histologically malignant endometrioid type glands or cysts often set in a dense fibrous stroma with an absence of stromal invasion.

**Synonyms**

Endometrioid tumour of low malignant potential, endometrioid tumour of borderline malignancy.

**Epidemiology**

Endometrioid tumours with atypical epithelial proliferations and lacking stromal invasion are rare. Their precise prevalence is not known because of variation in diagnostic criteria, but reported-ly they account for 3-18% of malignant ovarian neoplasms (137,2490,2528).

**Aetiology**

These tumours appear to be predominately derived from the surface epithelium of the ovary or endometrosis.

**Clinical features**

Patients range in age from 22-77 years (201,2737). A pelvic mass is palpable in a majority of patients, and others present with uterine bleeding. The tumours are...
predominantly unilateral, but rare bilateral lesions occur.

Macroscopy
Tumours range in size from 2-40 cm, have a tan to grey-white sectioned surface that varies from solid to predominantly solid with cysts ranging from a few mm to 8 cm in diameter [201,2737]. Haemorrhage and necrosis are present mainly in larger tumours.

Histopathology
Three patterns have been described [201,2737]. The most common is adenofibromatous. Islands of crowded endometrioid glands or cysts lined by cells displaying grade 1 to, rarely, grade 3 cytological atypia proliferate in an adenofibromatous stroma. Stromal invasion is absent. Mitotic activity is usually low. Squamous metaplasia is common, and necrosis may develop in the metaplastic epithelium. The second pattern is villoglandular or papillary with an atypical cell lining similar to atypical hyperplasia of the endometrium again in a fibromatous background. The third form shows a combination of villoglandular and adenofibromatous patterns. Anywhere from 15% to over half of the patients have endometriosis in the same ovary as well as at extraovarian sites [201,2737].

Prognosis and predictive factors
The prognosis is excellent. Recurrences and metastases are rare. Even in the rare case of an extratubal event, no subsequent problems developed 9 years after surgery, radiation and chemotherapy. Since a few patients treated by unilateral salpingo-oophorectomy developed endometrioid carcinoma in the contralateral ovary, and 1 died from it, bilateral salpingo-oophorectomy would be prudent when retention of fertility is no longer an issue. Unilateral salpingo-oophorectomy along with follow-up for early detection of any subsequent ovarian or endometrial adenocarcinoma is acceptable for women of childbearing age.

Benign endometrioid tumours
Definition
Ovarian tumours with histological features of benign glands or cysts lined by well differentiated cells of endometrial type.

Epidemiology
Because of the rarity of these neoplasms no convincing epidemiological data can be quoted. The reported patients are mainly of the reproductive age.

Localization
Benign endometrioid tumours are usually unilateral, though in rare cases involvement of both ovaries is encountered.

Clinical features
Signs and symptoms
There are no specific clinical symptoms of benign endometrioid tumours. Small neoplasms are incidental findings, sometimes in the wall of an ovarian endometriotic cyst. Large tumours are manifested by pain and abdominal swelling.

Imaging
Imaging techniques, including US, CT and MRI, cannot effectively establish the specific nosological character of the process. They can visualize endometriotic foci and thus indirectly indicate the presumptive endometrioid nature of the neoplasm; otherwise the results of imaging technique show the formal characteristics, i.e. cystic or cystic-fibrous architecture of the lesion [234].

Histopathology
The histological diagnosis of endometrioid adenomas and cystadenomas is based on the presence of well differentiated, benign appearing glands or cysts lined by endometrial type cells with or without squamous differentiation. In the adenofibromatous variant fibrous stroma predominates. Though adenofibromas...
Surface epithelial-stromal tumours

**Clear cell tumours**

**Definition**
Ovarian tumours, benign, borderline or malignant, with an epithelial component consisting most commonly of clear and hobnail cells, but often containing other cell types, which rarely predominate.

**Histopathology**
Clear cell tumours may be present include cuboidal, flat, oxyphilic and rarely, signet-ring cells. Most clear cell tumours are carcinomas, and many have an adenofibromatous background. Benign and borderline clear cell tumours are rare and almost always adenofibromatous.

**ICD-O codes**
- Clear cell adenocarcinoma 8310/3
- Clear cell adenocarcinofibroma 8313/3
- Clear cell tumour of borderline malignancy 8310/1
- Clear cell adenofibroma of borderline malignancy 8313/1
- Clear cell cystadenoma 8310/0
- Clear cell cystadenofibroma 8313/0

**Clear cell adenocarcinoma**

**Definition**
A malignant ovarian tumour composed of glycogen-containing clear cells and hobnail cells and occasionally other cell types.

**Epidemiology**
The mean age of patients is 57 years.

**Aetiology**
Tumours may arise directly from the ovarian surface epithelium, from inclusion cysts or from an endometriotic cyst.

**Clinical features**
Clear cell tumours among all surface epithelial cancers have the highest association of ovarian and pelvic endometriosis and paraendocrine hypercalcaemia (2233).

**Macroscopy**
The mean diameter of clear cell adenocarcinomas is 15 cm. The tumours may be solid, but more commonly the sectioned surface reveals a thick-walled unilocular cyst with multiple yellow fleshy nodules protruding into the lumen or multiloculated cysts containing watery or mucinous fluid. Tumours associated with endometriosis typically contain chocolate-brown fluid.

**Tumour spread and staging**
Patients with clear cell adenocarcinomas present as stage I disease in 33% of cases, as stage II in 19%, as stage III in 29% and as stage IV in 9% (2233).

**Histopathology**
Clear cell adenocarcinomas display tubulocystic, papillary and solid patterns that may be pure or mixed. The most common patterns are papillary and tubulocystic. Rarely, the tumour has a reticular pattern similar to that of a yolk sac tumour. Sheets of polyhedral cells with abundant clear cytoplasm separated by a delicate fibrovascular or hyalinized stroma are characteristic of the solid pattern. The tubulocystic pattern is characterized by varying-sized tubules and cysts lined by cuboidal to flattened epithelium and occasionally hobnail cells. The papillary pattern is characterized by thick or thin papillae containing...
fibrous tissue or abundant hyaline material. The most common cell types are the clear and hobnail cells. Clear cells tend to be arranged in solid nests or masses or lining cysts, tubules and papillae, whereas hobnail cells line tubules and cysts and cover papillary structures. The clear cells tend to be rounded or polygonal with eccentric nuclei, often containing some lipid. Hobnail cells have scarce cytoplasm and contain bulbous hyperchromatic nuclei that protrude into the lumens of the tubules. Flattened or cuboidal cells are also encountered. Occasionally, oxyphilic cells with abundant eosinophilic cytoplasm, which in a few instances make up the majority of the neoplasm, are observed. Signet-ring cells often contain inspissated mucinous material in the centre of a vacuole, creating what has been referred to as a “targetoid” cell. The clear cells contain abundant glycogen, and may also contain some lipid. Mucin may be found, typically located in the lumens of tubules and cysts and is abundant within the cytoplasm of the signet-ring cells.

Immunoprofile

Clear cell adenocarcinomas stain strongly and diffusely for keratins, epithelial membrane antigen, Leu M1 and B72.3. Stains for carcinoembryonic antigen are positive in 38% of cases and for CA125 (OC-125) in 50%. There have been a few reports of clear cell adenocarcinomas containing AFP. In a patient with clear cell adenocarcinoma who developed hypercalcaemia when the tumour recurred, immunostains for parathyroid hormone-related protein were strongly positive in the recurrent carcinoma but negative in the primary carcinoma (3209).

Differential diagnosis

The differential diagnosis includes germ cell tumours, particularly yolk sac tumour, dysgerminoma and, rarely, struma ovarii, endometrioid carcinoma with secretory change and steroid cell tumours that contain prominent areas of cells with clear cytoplasm. Metastatic clear cell neoplasms from outside the female genital system are very rare. Clinical information can be particularly helpful in the differential diagnosis as germ cell tumours occur in young women, and elevated serum alpha-feto-protein (AFP) levels are always found in patients with yolk sac tumours. Histologically, the papillary structures of clear cell carcinoma are more complex than those of yolk sac tumours and contain hyalinized cores. In contrast, yolk sac tumours display a variety of distinctive features including a prominent reticular pattern and Schiller-Duval bodies. Negative immunostains for AFP are useful in excluding yolk sac tumours, although rare examples of AFP-containing clear cell carcinomas have been reported. Positive staining for EMA and diffuse strong positivity for cytokeratins exclude dysgerminoma. Immunostains for thyroglobulin are very useful in ruling out struma ovarii.

Endometrioid carcinomas with secretory change typically are composed of cells that are columnar with subnuclear and supranuclear vacuolization resembling early secretory endometrium. In contrast, the clear cell changes in clear cell carcinoma are more diffuse, the cells are polygonal, and they typically display the other characteristic patterns of clear cell carcinoma. A metaplastic squamous component may be seen in endometrioid carcinoma and is not observed in clear cell carcinoma. In contrast to clear cell carcinomas, steroid cell tumours of the ovary that contain prominent clear cytoplasm are smaller, well circumscribed, have low grade nuclear features and stain strongly for alpha-inhibin.

Grading

Nuclei in clear cell carcinomas range from grade 1 to grade 3, but pure grade...
1 tumours are extremely rare. Almost invariably high grade (grade 3) nuclei are identified. In view of this finding as well as the mixture of different architectural patterns, clear cell adenocarcinoma is not graded.

Prognosis and predictive factors
When controlled for stage, survival of women with clear cell adenocarcinoma may be slightly lower than that of patients with serous carcinoma. The five year survival is 69% for patients with stage I tumours, 55% for stage II, 14% for stage III and 4% for stage IV. There is no consensus in the literature about the value of pattern, cell type, mitotic index or grade as a prognostic indicator (395).

Borderline clear cell adenofibromatous tumour
Definition
An ovarian tumour of low malignant potential composed of atypical or histologically malignant glands or cysts lined by clear or hobnail cells set in a dense fibrous stroma with an absence of stromal invasion.

Synonyms
Clear cell adenofibromatous tumour of low malignant potential, clear cell adenofibromatous tumour of borderline malignancy.

Epidemiology
Of approximately 30 cases of neoplasms classified as borderline clear cell adenofibromatous tumour, the mean age of patients was 65 years.

Macroscopy
Adenofibromas with increasing atypia including intraepithelial carcinoma have a similar appearance to adenofibromas but in addition have areas that are softer and fleshier.

Histopathology
Borderline clear cell adenofibromatous tumours include those in which the epithelium is atypical or carcinomatous without invasion. Adenofibromatous tumours in which the glands are lined by malignant epithelium are best designated as “borderline clear cell adenofibromas with intraepithelial carcinoma”. They are similar to borderline adenofibromas; however, nuclear atypia is more marked with coarse chromatin clumping, prominent nuclei and increased mitotic activity. Occasionally, minute foci of invasion can be identified, and these tumours are designated “microinvasive”. The epithelium often displays stratification and budding, although true papillary structures are uncommon. Small solid masses of clear cells in the stroma raise the question of invasion.

Prognosis and predictive factors
With the exception of one case (202), borderline clear cell adenofibromatous tumours including those with intraepithelial carcinoma and microinvasion have a benign course following removal of the ovary (583,1285,1435, 1897,2052).

Clear cell adenofibroma
Definition
An ovarian tumour composed of histologically benign glands or cysts lined by clear or hobnail cells set in a dense fibrous stroma.

Epidemiology
Among approximately twelve reported cases of benign clear cell adenofibroma, the mean age of patients was 45.

Macroscopy
Adenofibromas have a median diameter of 12 cm and display a smooth lobulated external surface. The sectioned surface has a fine honeycomb appearance with minute cysts embedded in a rubbery stroma.

Histopathology
Clear cell adenofibromas are characterized by tubular glands lined by one or two layers of epithelium that contains polygonal, hobnail or flattened cells. The cytoplasm may be clear, slightly granular or eosinophilic. Nuclear atypia and mitotic activity are minimal. The stroma is densely fibrous.
Transitional cell tumours

Definition
Ovarian tumours composed of epithelial elements histologically resembling urothelium and its neoplasms.

Histopathology
This group of tumours includes the following:
1. Benign Brenner tumours, distinguished by a prominent stromal component accompanying transitional cell nests.
2. Borderline and malignant Brenner tumours in which a benign Brenner tumour component is associated with exuberantly proliferative, variably atypical but non-invasive transitional epithelium in the former and unequivocal stromal invasion in the latter.
3. Transitional cell carcinoma in which a malignant transitional cell tumour is not associated with a benign or borderline Brenner component.

ICD-O codes
- Transitional cell carcinoma (non-Brenner) 8120/3
- Malignant Brenner tumour 9000/3
- Borderline Brenner tumour 9000/1
- Brenner tumour 9000/0

Epidemiology
Transitional cell tumours account for 1-2% of all ovarian tumours.

Transitional cell carcinoma

Definition
An ovarian tumour that is composed of epithelial elements histologically resembling malignant urothelial neoplasms and does not have a component of benign or borderline Brenner tumour.

Epidemiology
Transitional cell carcinoma is the pure or predominant element in 6% of ovarian carcinomas (2676). The great majority of transitional cell carcinomas occur in women 50-70 years old (1110).

Clinical features
The presentation of women with transitional cell carcinoma is the same as with other malignant ovarian tumours, abdominal pain, swelling, weight loss, and bladder or bowel symptoms (139,2676).
Surface epithelial-stromal tumours

Macroscopy
Transitional cell carcinomas are bilateral in approximately 15% of cases [139] and are macroscopically indistinguishable from other surface epithelial-stromal tumours [139,2676].

Tumour spread and staging
At the time of diagnosis transitional cell carcinomas have spread beyond the ovary in over two-thirds of cases [2676].

Histopathology
Transitional cell carcinomas resemble those occurring in the urinary tract and lack a benign or borderline Brenner tumour component [139,2676]. Typically, they are papillary with multilayered transitional epithelium and a smooth luminal border ("papillary type"). A nested pattern characterized by malignant transitional cell nests irregularly distributed in fibrotic stroma ("malignant Brenner-like type") has been described [2464,2465]. As in urothelial carcinoma, foci of glandular and/or squamous differentiation may occur. Very commonly, transitional cell carcinoma is admixed with other epithelial-stromal tumours of other types, primarily serous adenocarcinoma. Transitional cell carcinomas lack the prominent stromal calcification characteristic of some benign and malignant Brenner tumours.

Immunoprofile
Ovarian transitional cell carcinomas have an immunoprofile that differs from transitional cell carcinomas of the urinary tract and closely resembles that of ovarian surface epithelial-stromal tumours. Ovarian transitional cell carcinomas are consistently uroplakin, thrombomodulin and cyokeratin 13 and 20 negative and CA125 and cytokeratin 7 positive [2115, 2371].

Grading
Transitional cell carcinomas should be graded utilizing criteria for transitional cell carcinoma of the urinary tract.

Histogenesis
The term transitional cell carcinoma is not uniformly accepted, and overlapping features with other epithelial-stromal tumours, particularly serous carcinoma, are present. It is important that strict histological criteria be applied to establish the diagnosis [2465]. Not only an architectural but also a histological resemblance to transitional epithelium is required. The frequent association with epithelial-stromal tumours of other types strongly suggests a surface epithelial origin [2465]. In addition, several immunohistochemical studies have demonstrated that the tumour lacks a urothelial phenotype [2115,2371]. Thus, the ovarian neoplasm shows histological but not immunohistochemical similarities to transitional cell carcinoma of the urinary bladder.

Prognosis and predictive factors
The overall 5-year survival rate for transitional cell carcinoma is 35%. Some, but not all, investigators have reported greater chemosensitivity and higher 5-year survival in patients whose metastases are composed purely or predominantly of transitional cell carcinoma [564, 1232,2676].
**Malignant Brenner tumour**

**Definition**
An ovarian tumour containing invasive transitional cell aggregates as well as benign nests of transitional epithelium set in a fibromatous stroma.

**Epidemiology**
The great majority of malignant Brenner tumours occur in women 50-70 years old (1110,1868,2676). Only 5% of Brenner tumours are malignant (1110,1868).

**Clinical features**
Most patients seek medical attention because of an abdominal mass or pain (139,2460,2461). A few patients present with abnormal vaginal bleeding.

**Macroscopy**
Malignant Brenner tumours are typically large with a median diameter of 16-20 cm and typically have a solid component resembling benign Brenner tumour as well as cysts containing papillary or polypoid masses (2461).

**Tumour spread and staging**
Malignant Brenner tumours are bilateral in 12% of cases (139,452). About 80% of malignant Brenner tumours are stage 1 at the time of diagnosis.

**Histopathology**
In malignant Brenner tumours there is stromal invasion associated with a benign or borderline Brenner tumour component (139). The invasive element is usually high grade transitional cell carcinoma or squamous cell carcinoma, although occasional tumours are composed of crowded, irregular islands of malignant transitional cells with low grade features (2460). Glandular elements may be admixed, but pure mucinous or serous carcinomas associated with a benign Brenner tumour component should not be diagnosed as a malignant Brenner tumour. Foci of calcification are occasionally prominent.

**Immunoprofile**
The very small number of malignant Brenner tumours studied have exhibited a benign Brenner tumour immunoprofile in that component with a variable pattern of antigen expression in the invasive component; uroplakin immunopositivity has occurred in some (2371).

**Prognosis and predictive factors**
When confined to the ovary, malignant Brenner tumours have an excellent prognosis. Patients with stage IA tumours have an 88% 5-year survival, and those with high stage malignant Brenner tumours have a better prognosis than stage matched transitional cell carcinomas (139).

**Borderline Brenner tumour**

**Synonyms**
Brenner tumour of low malignant potential, proliferating Brenner tumour (for cases with low grade features).

**Definition**
An ovarian transitional cell tumour of low malignant potential with atypical or malignant features of the epithelium but lacking obvious stromal invasion.

**Epidemiology**
Only 3-5% of Brenner tumours are borderline (1110,1868).

**Tumour spread and staging**
Borderline Brenner tumours are confined to the ovary and, with rare exceptions, have been unilateral (1110,1868,2461,3144).

**Clinical features**
Most patients seek medical attention because of an abdominal mass or pain (139,2460,2461). A few patients present with abnormal vaginal bleeding.

**Macroscopy**
Borderline Brenner tumours are typically large with a median diameter of 16-20 cm. They usually have a solid component resembling benign Brenner tumour as well as a cystic component containing a papillary or polypoid mass (2461).

**Histopathology**
Borderline Brenner tumours show a greater degree of architectural complexity than benign Brenner tumours typified by branching fibrovascular papillae surfaced by transitional epithelium often protruding into cystic spaces. The transitional epithelium manifests the same spectrum of architectural and cytological features encountered in urothelial lesions of the urinary tract. By definition, there is no stromal invasion. A benign Brenner tumour component is typically present but may be small and easily overlooked. The mitotic rate is highly variable but may be brisk, and focal necrosis is common. Mucinous metaplasia may be a prominent feature. The diagnostic criteria and terminology applied to the intermediate group of transitional cell tumours is somewhat controversial (2461,2605). Some have advocated categorizing tumours with low grade features as “proliferating” rather than borderline (2461), and others designate those resembling grade 2 or 3 transitional cell carcinoma of the urinary tract as “borderline with intraepithelial carcinoma” (2605).

**Prognosis and predictive factors**
No Brenner tumour in the intermediate category without stromal invasion has metastasized or caused the death of a patient (1110,2461).

**Benign Brenner tumour**

**Definition**
An ovarian transitional cell tumour composed of mature urothelial-like cells arranged in solid or cystic circumscribed aggregates within a predominantly fibromatous stroma.

**Epidemiology**
Benign Brenner tumours account for 4-5% of benign ovarian epithelial tumours (1409,1502,1970,2865). Most benign Brenner tumours (95%) are diagnosed in women 30-60 years old (753,905,1868,2460,2461,2676,2685,3073,3186).

**Clinical features**
The majority of patients with benign Brenner tumours are asymptomatic; over 50% of tumours are less than 2 cm and are typically discovered incidentally in ovaries removed for some other reason (753,905,2685,3073). In only 10% of cases is the tumour larger than 10 cm;
such patients may present with non-specific signs and symptoms referable to a pelvic mass. Occasionally, Brenner tumours are associated with manifestations related to the elaboration of estrogens or androgens by the stromal component of the tumour.

**Macroscopy**

The typical benign Brenner tumour is small, often less than 2 cm, but, regardless of size, is well circumscribed with a firm, white, sometimes gritty sectioned surface due to focal or extensive calcification. Small cysts are common, and a rare tumour is predominately cystic. Brenner tumours are associated with another tumour type, usually mucinous cystadenoma, in 25% of cases.

**Tumour spread and staging**

Only 7-8% of benign Brenner tumours are bilateral (753).

**Histopathology**

Benign Brenner tumours are characterized by nests and islands of transitional type epithelial cells with centrally grooved, "coffee bean" nuclei, abundant amphophilic to clear cytoplasm and distinct cell membranes growing in a dominant fibromatous stroma. The nests may be solid or exhibit central lumina containing densely eosinophilic, mucin-positive material. The lumina may be lined by transitional type cells or mucinous, ciliated or nondescript columnar cells. Variably sized cysts lined by mucinous epithelium, either pure or overlying transitional epithelium are common in benign Brenner tumours. Benign Brenner tumours with crowded transitional nests and cysts with a prominent mucinous component, sometimes with complex gland formations, are termed "metaplastic Brenner tumour" by some and not mixed epithelial tumours [2461] since the epithelial components are admixed rather than separate. Their recognition avoids confusion with borderline or malignant Brenner tumours.

**Immunoprofile**

Benign Brenner tumours show some urothelial differentiation evidenced by uroplakin expression, but they do not express thrombomodulin and have been immunonegative for cytokeratin 20 in most, but not all, studies [2085,2115, 2116,2371,2758]. Benign Brenner tumours have an endocrine cell component demonstrable with immunostains for chromogranin A, serotonin and neuron specific enolase [45,2530].

**Somatic genetics**

There is one report of a 12q14-21 amplification in a benign Brenner tumour [2207].

---

**Squamous cell lesions**

**Squamous cell carcinoma**

**Definition**

Malignant ovarian tumour composed of squamous epithelial cells that is not of germ cell origin.

**ICD-O code** 8070/3

**Epidemiology**

The age of women with squamous cell carcinoma, pure or associated with endometriosis, has ranged from 23-90 years.

**Macroscopy**

Most squamous cell carcinomas are solid, although in some instances cystic components predominate.

**Histopathology**

Histologically, squamous cell carcinomas are usually high grade and show a variety of patterns including papillary or polypoid, cystic, insular, diffusely infiltrative, verruciform or sarcomatoid. They must be distinguished from endometrioid adenocarcinomas with extensive squamous differentiation and from metastatic squamous cell carcinoma from the cervix and other sites [3198].

**Histogenesis**

Most squamous cell carcinomas arise from dermoid cysts and are classified in the germ cell tumour category. Less commonly, they occur in association with endometriosis [1624,1828,1973,2255, 2902], as a component of malignant Brenner tumour [2460] or in pure form [2255] and are considered to be surface epithelial-stromal tumours. Some pure
Tumours of the ovary and peritoneum

Squamous cell carcinomas have occurred in women with cervical squamous cell carcinoma in situ (1738).

Prognosis and predictive factors
Most tumours have spread beyond the ovary at the time of presentation, and the prognosis in the small number of reported cases is poor.

Epidermoid cyst
Definition
Benign ovarian cysts lined by squamous epithelial cells that are not clearly of germ cell origin.

Histopathology
Epidermoid cysts lined by benign keratinized squamous epithelium devoid of skin appendages and unaccompanied by teratomatous elements are rare in the ovary (823,3205). All are small (2-46 mm) and unilateral.

Histogenesis
The presence of small epithelial cell nests resembling Walthard cell nests in the walls of epidermoid cysts suggests an epithelial rather than a teratomatous origin (3205).

Mixed epithelial tumours
Definition
An ovarian epithelial tumour composed of an admixture of two or more of the five major cell types: serous, mucinous, endometrioid, clear cell and Brenner/transitional. The second or second and third cell types must comprise alone or together at least 10% of the tumour epithelium, or, in the case of a mixed Brenner-mucinous cystic tumour, both components should be macroscopically visible. A mixed epithelial tumour (MET) may be benign, borderline or malignant. Endometrioid tumours with squamous differentiation and neuroendocrine tumours associated with a surface epithelial-stromal tumour are not included in this definition.

ICD-O codes
Malignant mixed epithelial tumour 8323/3
Borderline mixed epithelial tumour 8323/1
Benign mixed epithelial tumour 8323/0

Epidemiology
The reported incidence of MET varies from 0.5-4% of surface epithelial-stromal tumours. This variability is due in part to problems in developing a standardized classification.

Tumour spread and staging
Mixed epithelial borderline tumours (MEBTs) are stage I in 93% of cases and show bilateral ovarian involvement in 22% (2496).

Histopathology
In cystadenomas the most frequent mixture is serous (ciliated) and mucinous epithelium. The mucinous epithelium should contain abundant intracytoplasmic mucin, not just apical or luminal mucin. MEBTs show papillae with detached cell clusters reminiscent of serous borderline tumours, but they generally contain a mixture of endocervical-like mucinous cells, endometrioid epithelium with focal squamous differentiation and indifferent eosinophilic epithelium. An acute inflammatory infiltrate may be seen rarely. Mixed Brenner-mucinous tumours are usually composed of a benign, and, occasionally, a borderline Brenner component; the mucinous component may be benign, borderline or malignant. A few mucinous glands within Brenner nests or histological areas of mucinous differentiation represent mucinous metaplasia in Brenner tumours, a common finding, and are not a MET. Rarely, the tumour macroscopically contains a myriad of small cysts lined by an admixture of mucinous and transitional epithelium and the term metaplastic Brenner tumour is applied (2461). For cystadenocarcinomas frequent combinations are serous and endometrioid,
serous and transitional cell carcinoma and endometrioid and clear cell.

**Grading**
The least differentiated component determines the tumour grade.

**Histogenesis**
Endometriosis, occasionally with atypia, is found in association with 53% of MEBT (2406) and up to 50% of mixed clear cell-endometrioid tumours (2511). Some cases show a transition from endometriosis to neoplastic epithelium.

**Somatic genetics**
It is impossible to make broad statements, as studies are limited to a few cases. LOH on chromosome 17, common in serous tumours, has been found in two of five mixed endometrioid-serous tumours (959). PTEN mutation, which has been associated with the endometrioid type, has also been noted in a mixed mucinous-endometrioid tumour (2075). KRAS mutations, an early event in mucinous tumours, have been noted in three mixed Brenner-mucinous tumours (589). The mucinous cystadenocarcinoma and Brenner tumour components shared amplification of 12q 14-21 in one MET, suggesting clonal relatedness (2207).

**Prognosis and predictive factors**
The behaviour of MEBT is similar to that of endocervical-like mucinous borderline tumours. The dominant cell type generally dictates behaviour. An exception is mixed endometrioid and serous carcinoma, which, even when the serous component is minor, behaves more aggressively than pure endometrioid carcinoma and similarly to their serous counterpart. Mixed endometrioid and serous carcinoma may recur as serous carcinoma (2907). This finding stresses the importance of careful sampling of an endometrioid cystadenocarcinoma to rule out a mixed serous component.

**Undifferentiated carcinoma**

**Definition**
A primary ovarian carcinoma with no differentiation or only small foci of differentiation.

**ICD-O code**
8020/3

**Epidemiology**
When applying the WHO criteria, approximately 4-5% of ovarian cancers are undifferentiated carcinoma. The frequency of undifferentiated carcinoma was 4.1% when defined as carcinomas with solid areas as the predominant component representing over 50% of the tumour (2677).

**Clinical features**
In the only large series the age of the patients ranged from 39-72 (mean, 54 years) (2677).

**Macroscopy**
Macroscopically, undifferentiated carcinoma does not have specific features. The tumours are predominantly solid, usually with extensive areas of necrosis.

**Tumour spread and staging**
According to FIGO, 6% of the patients are discovered in stage I, 3% are in stage II, 74% in stage III and 17% in stage IV; thus 91% of the tumours are discovered in stages III and IV (2677).

**Histopathology**
Histologically, undifferentiated carcinoma consists of solid groups of tumour cells with numerous mitotic figures and significant cytological atypia. Areas with a spindle cell component, microcystic pattern and focal vascular invasion can be seen. It is unusual to see an undifferentiated carcinoma without any other component of müllerian carcinoma. Usually, areas of high grade serous carcinoma are present. Foci of transitional cell carcinoma can also be seen. Undifferentiated carcinoma of the ovary does not have a specific immunophenotype.

**Diagnosis**
The main differential diagnoses are granulosa cell tumour of the adult type, transitional cell carcinoma, poorly differentiated squamous cell carcinoma, small cell carcinoma and metastatic undifferentiated carcinoma. Granulosa cell tumours may have a diffuse pattern; however, it is unusual not to have also areas with a trabecular pattern, Call-Exner bodies or areas showing sex cords. In addition, undifferentiated carci-
Sex cord-stromal tumours

Definition
Ovarian tumours composed of granulosa cells, theca cells, Sertoli cells, Leydig cells and fibroblasts of stromal origin, singly or in various combinations. Overall, sex cord-stromal tumours account for about 8% of ovarian neoplasms.

Granulosa-stromal cell tumours

Definition
Tumours containing granulosa cells, theca cells or stromal cells resembling fibroblasts or any combination of such cells.

Granulosa cell tumour group

Definition
A neoplasm composed of a pure or at least a 10% population of granulosa cells often in a fibrothecomatous background. Two major subtypes are recognized, an adult and a juvenile type.

ICD-O codes
Granulosa cell tumour group
Adult granulosa cell tumour 8620/1
Juvenile granulosa cell tumour 8622/1

Epidemiology
Granulosa cell tumours account for approximately 1.5% (range, 0.6-3%) of all ovarian tumours. The neoplasm occurs in a wide age range including newborn infants and postmenopausal women. About 5% occur prior to puberty, whereas almost 60% occur after menopause [284,2588].

Aetiology
The aetiology of these tumours is unknown. Several studies suggest that infertile women and those exposed to ovulation induction agents have an increased risk for granulosa cell tumours [2458, 2982, 3125].

Clinical features
Signs and symptoms
Granulosa cell tumours may present as an abdominal mass, with symptoms suggestive of a functioning ovarian tumour or both. About 5-15% present with symptoms suggestive of haemoperitoneum secondary to rupture of a cystic lesion [3195]. Ascites develops in about 10% of the cases. The tumour is clinically occult in 10% of the patients [829]. Granulosa cell tumours produce or store a variety of steroid hormones. When functional, most are estrogenic, but rarely androgenic activity may occur. The symptoms and clinical presentation vary depending on the patient’s age and reproductive status. In prepubertal girls, granulosa cell tumours frequently induce isosexual pseudopuberty. In women of reproductive age, the tumour may be associated with a variety of menstrual disorders related to hyperoestrogenism. In postmenopausal women, irregular uterine bleeding due to various types of endometrial hyperplasia or, rarely, well differentiated adenocarcinoma is the most common manifestation of hyperoestrogenism. A rare unicocular thin-walled cystic variant is often androgenic when functional [1971, 2059].

Imaging
Cross sectional imaging, i.e. computed tomography and magnetic resonance imaging is of value in the surgical planning and preoperative determination of resectability of patients with granulosa cell tumours [859, 1480, 1728, 1915, 2131]. In contradistinction to epithelial ovarian tumours, granulosa cell tumours have been described as predominantly solid adnexal lesions; variable amounts of cystic components may, however, be present. Enlargement of the uterus and endometrial thickening might be seen as a result of the hormone production of the tumour [859, 1480, 1728, 1915, 2131].

Adult granulosa cell tumour

Epidemiology
More than 95% of granulosa cell tumours are of the adult type, which occurs in middle aged to postmenopausal women.

Macroscopy
Adult granulosa cell tumours (AGCTs) are typically unilateral (95%) with an average size of 12.5 cm and are commonly encapsulated with a smooth or lobulated surface. The sectioned surface of the tumour...
is yellow to tan with a variable admixture of cystic and solid areas \((906,2058)\). Haemorrhage is seen in larger tumours; necrosis is focal and uncommon. A small percentage is totally cystic, either uniloculated or multiloculated \((2058,2716)\). A solid or cystic tumour with a combination of yellow tissue and haemorrhage is highly suggestive of a granulosa cell tumour.

**Histopathology**

Histologically, there is a proliferation of granulosa cells often with a stromal component of fibroblasts, theca or luteinized cells. The granulosa cells have scant cytoplasm and a round to ovoid nucleus with a longitudinal groove. The mitotic activity rarely exceeds 1-2 per 10 high power fields. When luteinized, the cells develop abundant eosinophilic or vacuolated cytoplasm, and the nuclei become round and lose their characteristic groove. The rare presence of bizarre nuclei does not have an adverse effect on the prognosis \((2890,3210)\). The tumour cells grow in a variety of patterns. The best known of these is the microfollicular pattern characterized by the presence of Call-Exner bodies. Others include the macrofollicular, characterized by large spaces lined by layers of granulosa cells, insular, trabecular, diffuse (sarcomatoid) and the moiré silk (watered silk) patterns. A fibrothecomatous stroma often surrounds the granulosa cells.

**Immunoprofile**

Granulosa cell tumours are immunoreactive for CD99, alpha-inhibin, vimentin, cytokeratin (punctate), calretinin, S-100 protein and smooth muscle actin. The tumour cells are negative for cytokeratin 7 and epithelial membrane antigen \((482, 563,889,1815,2124,2379)\).

**Differential diagnosis**

Although endometrioid carcinomas may display an abundant rosette-like arrangement of nuclei mimicking Call-Exner bodies, they often show squamous metaplasia and lack nuclear grooves. Undifferentiated carcinomas and poorly differentiated adenocarcinomas may resemble the diffuse (sarcomatoid) pattern of granulosa cell tumours. These carcinomas have abundant mitotic figures and frequently have already extended beyond the ovary at presentation. The insular and trabecular patterns of granulosa cell tumour may be mistaken for a carcinoid and vice versa. Carcinoids have uniform round nuclei with coarse chromatin, lack nuclear grooves and show chromogranin positivity. Furthermore, primary carcinoids of the ovary are usually associated with other teratomatous elements, whereas the metastatic ones are generally multi-nodular and bilateral. The diffuse pattern of granulosa cell tumours may be confused with a benign thecoma, particularly when there is luteinization. A reticulin stain is helpful since granulosa cells typically grow in sheets or aggregates bound by reticulin fibres, whereas thecomas contain an abundance of intercellular fibrils surrounding individual cells. The distinction is important since granulosa cell tumours have an aggressive potential, whereas thecomas are with rare exceptions benign. Similarly, the presence of nuclear grooves and the absence of the characteristic vascular pattern of endometrioid stromal sarcoma distinguish ASCT from the former.

**Somatic genetics**

In contrast to older studies \((1635,2862)\), recent karyotypic and fluorescence in situ hybridization analyses have shown that trisomy and tetrasomy 12 are rarely present in granulosa cell tumours \((1635, 1653,2221,2635,2862)\). The few available studies have shown trisomy 14 \((1043)\).
and structural changes in chromosome 6 with loss of 6q material (3021).

**Prognosis and predictive factors**

All granulosa cell tumours have a potential for aggressive behaviour. From 10-50% of patients develop recurrences. Some recurrences of AGCT develop as late as 20-30 years following the initial diagnosis (906,2058,2786), and long-term follow-up is required.

The most important prognostic factor is the stage of the tumour (1815). Nearly 90% of patients with granulosa cell tumour have stage I disease, however, and the prediction of tumour behaviour is most difficult in this group. Factors related to a relatively poor prognosis include age over 40 years at the time of diagnosis, large tumour size (>5cm), bilaterality, mitotic activity and atypia (906,1871,2786). There is, however, disagreement on the precise significance of some of these factors. Among adults, survival is adversely affected by tumour rupture.

**Juvenile granulosa cell tumour**

**Epidemiology**

Accounting for nearly 5% of all granulosa cell tumours, juvenile granulosa cell tumour (JGCT) is encountered predominantly during the first 3 decades of life (3195).

**Clinical features**

In prepubertal girls, approximately 80% are associated with isosexual pseudo-precocity (277,3195,3242).

**Macroscopy**

The macroscopic appearance of JGCT is not distinctive and is similar in its spectrum of appearances to the adult variant. Tumour spread and staging

JGCT presents almost always as stage I disease; less than 5% of tumours are bilateral, and only 2% have extraovarian spread.

**Histopathology**

JGCT is characterized by a nodular or diffuse cellular growth punctuated by macrofollicles of varying sizes and shapes. Their lumens contain eosinophilic or basophilic fluid. A fibrothecomatous stroma with variable luteinization and/or oedema is often evident. The typically rounded neoplastic granulosa cells have abundant eosinophilic and/or vacuolated cytoplasm; and almost all nuclei lack grooves. Mitotic figures are abundant. Cytomegaly with macronuclei, multinucleation and bizarre multilobulated nuclei is occasionally observed (2890,3210).

**Differential diagnosis**

Only the entity of small cell carcinoma associated with hypercalcaemia, which also occurs in children and young women, poses a significant diagnostic problem. The clinical presentation of JGCT with estrogenic manifestations and that of small cell carcinoma with hypercalcaemia are important clues to the precise diagnosis. Dissemination beyond the ovary is evident in 20% of these small cell carcinomas at presentation, a feature that is most unusual for a JGCT. The presence of necrosis and more eccentric nuclei in the carcinomas are additional features that can help. The presence of mucinous epithelium in 10% of cases and clusters of larger cells in most small cell carcinomas provide further support. Finally, immunostains for alpha-inhibin are positive in granulosa cell tumours but completely negative in the carcinomas. Both tumours may be negative with a variety of epithelial markers.
Genetic susceptibility
JGCTs may present as a component of a variety of non-hereditary congenital syndromes including Ollier disease (enchondromatosis) [2857,3015] and Maffucci syndrome (enchondromatosis and haemangiomatosis) [1102,2859]. Bilateral JGCT may develop in infants with features suggestive of Goldenhar (craniofacial and skeletal abnormalities) [2306] or Potter syndrome [2468].

Prognosis and predictive factors
Despite their more primitive histological appearance, only about 5% of JGCTs behave aggressively, and these usually do so within 3 years of presentation. The overall prognosis for JGCT is good with a 1.5% mortality associated with stage IA tumours; but it is poor in stage II or higher tumours [3195].

Thecoma-fibroma group

Definition
Tumours forming a continuous spectrum from those composed entirely of fibroblasts and producing collagen to those containing a predominance of theca cells.

<table>
<thead>
<tr>
<th>Thecoma</th>
<th>8600/0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteinized thecoma</td>
<td>8601/0</td>
</tr>
<tr>
<td>Fibroma, NOS</td>
<td>8810/0</td>
</tr>
<tr>
<td>Cellular fibroma</td>
<td>8810/1</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>8810/3</td>
</tr>
<tr>
<td>Stromal tumour with minor sex cord elements</td>
<td>8593/1</td>
</tr>
<tr>
<td>Sclerosing stromal tumour</td>
<td>8602/0</td>
</tr>
</tbody>
</table>

Thecoma

Definition
Thecomas are stromal tumours composed of lipid-containing cells resembling theca interna cells with a variable component of fibroblasts. Luteinized thecomas contain lutein cells in a background of thecoma or fibroma.

Epidemiology
Typical thecomas are about one-third as common as granulosa cell tumours. The great majority (84%) occur in postmenopausal women (mean age 59 years). Thecomas are rare before puberty, and only about 10% occur in women younger than 30 years [283]. The rare variant of luteinized thecoma associated with sclerosing peritonitis typically occurs in young women less than 30 years, only rarely occurring in older women [520].

Clinical features
Typical thecomas may be discovered incidentally or produce non-specific signs and symptoms of a pelvic mass. Symptoms related to estrogen production including abnormal uterine bleeding occur in about 60% of patients, and about 20% of postmenopausal women with thecoma have endometrial adenocarcinoma or rarely a malignant Müllerian mixed tumour or endometrial stromal sarcoma [2300]. Luteinized thecomas have a lower frequency of estrogenic manifestations than typical thecomas, and about 10% are associated with...
androgenic manifestations (3252). Patients with the rare variant of luteinized thecoma associated with sclerosing peritonitis present with abdominal swelling, ascites and symptoms of bowel obstruction (520).

Macroscopy
Thecomas may be small and non-palpable, but they usually measure 5-10 cm. The sectioned surface is typically solid and yellow, occasionally with cysts, haemorrhage or necrosis. Typical thecomas are almost invariably unilateral; only 3% are bilateral. Luteinized thecomas associated with sclerosing peritonitis are usually bilateral.

Histopathology
Typical thecomas are characterized by cells with uniform, bland, oval to spindle shaped nuclei with abundant, pale, vacuolated, lipid-rich cytoplasm. Individual cells are invested by reticulin. Mitoses are absent or rare. Rarely, the nuclei may be large or bizarre (3210). The fibromatous component commonly contains hyaline plaques and may be calcified. Extensively calcified thecomas tend to occur in young women (3194). Rarely, thecomas include a minor component of sex cord elements (3211). Luteinized thecomas contain lutein cells, individually or in nests, in a background often more fibromatous than thecomatous. Oedema and microcyst formation may be striking.

Immunoprofile
Thecomas are immunoreactive for vimentin and alpha-inhibin (482,562, 1499,1816,2181,2211).

Somatic genetics
Trisomy and tetrasomy 12 have been demonstrated in tumours in the thecoma-fibroma group by karyotypic analysis and fluorescence in situ hybridization (1635,1653,2221,2635,2862). This chromosomal abnormality is not, however, specific to tumours in this group since it has also been found in some benign and borderline epithelial tumours, as well as in occasional granulosa cell tumours (2209,2221).

Prognosis and predictive factors
Rarely, a typical or luteinized thecoma with nuclear atypia and mitotic activity may metastasize (1819,3074,3252), although most cases reported as "malignant thecomas" are probably fibrosarcomas or diffuse granulosa cell tumours. Patients with luteinized thecomas associated with sclerosing peritonitis may experience small bowel obstruction, and several have died of complications related to peritoneal lesions, but there has been no recurrence or metastasis of the ovarian lesion (520).

Fibroma and cellular fibroma
Definition
Fibromas are stromal tumours composed of spindle, oval or round cells producing collagen. In cellular fibromas the cells are closely packed, collagen is scanty, and the mitotic rate is increased.

Epidemiology
Fibromas account for 4% of all ovarian tumours. They are most common in middle age (mean 48 years) (709); less than 10% occur before age 30, and they occur only occasionally in children (328).
Clinical features
Fibromas may be found incidentally, but when large, patients may present with non-specific signs and symptoms of a pelvic mass. Between 10-15% of fibromas over 10 cm are associated with ascites [2519], and Meigs syndrome (ascites and pleural effusion with resolution after fibroma removal) occurs in about 1% of cases [1839].

Macroscopy
Fibromas are hard white tumours averaging 6 cm in diameter. Oedematous tumours may be soft, and cyst formation is common. Haemorrhage and necrosis are rare outside the setting of torsion. The majority of tumours are unilateral. Only 8% are bilateral, and less than 10% show focal or diffuse calcification.

Histopathology
Fibromas are composed of spindle-shaped cells with uniform, bland nuclei and scant cytoplasm that may contain small amounts of lipid or occasionally eosinophilic droplets. The cells are arranged in fascicles or in a storiform pattern. Mitoses are absent or rare. Fibromas are generally sparsely to moderately cellular with abundant intercellular collagen, hyalinized plaques and variable degrees of oedema. The cellularity may vary from area to area. About 10% of tumours are uniformly and densely cellular (attaining the cellularity of a diffuse granulosa cell tumour) and are referred to as cellular fibromas [2289]. Cellular fibromas exhibit no more than mild cytological atypia and an average of three or less mitoses per 10 high power fields. Fibromas express vimentin and may be immunoreactive for alpha-inhibin [1816, 2211].

Genetic susceptibility
Ovarian fibromas are common in females with the nevoid basal cell carcinoma syndrome, occurring in about 75% of patients having the syndrome referred to gynaecologists. Syndrome-related tumours are usually bilateral (75%), frequently multinodular, almost always calcified, sometimes massively, and tend to occur at a younger age, usually in children, adolescents, or young adults [1042,1354,2603]. Additional tumours may arise after local excision. The nevoid basal cell carcinoma syndrome has been reported in four generations of a kindred lacking other stigmata of the syndrome [728,1635,2221,2635].

Prognosis and predictive features
Rarely, cellular fibromas recur in the pelvis or upper abdomen, often after a long interval, particularly if they were adherent or ruptured at the time of diagnosis [2289]. Very rarely, fibromatous tumours with no atypical features may spread beyond the ovary [1722].

Fibrosarcoma

Definition
A rare fibroblastic tumour of the ovary that typically has 4 or more mitotic figures per 10 high power fields as well as significant nuclear atypia.

Epidemiology
Fibrosarcomas are the most common ovarian sarcoma, occurring at any age but most often in older women.

Macroscopy
Fibrosarcomas are large, solid tumours, commonly haemorrhagic and necrotic, and are usually unilateral.

Histopathology
Fibrosarcomas are densely cellular, spindle cell neoplasms with moderate to severe cytological atypia, a high mitotic rate (an average of 4 or more mitoses per 10 high power fields) with atypical division figures, haemorrhage and necrosis [90,145,2289].

Somatic genetics
Trisomy 12 as well as trisomy 8 have been reported in an ovarian fibrosarcoma [2963].

Genetic susceptibility
Ovarian fibrosarcomas are rarely associated with Maffucci syndrome [484] and the nevoid basal cell carcinoma syndrome [1517].

Prognosis and predictive factors
The majority of ovarian fibrosarcomas have had a malignant course.
Stromal tumour with minor sex cord elements

**Definition**
Stromal tumour with minor sex cord elements is a rare, fibrothecomatous tumour containing scattered sex cord elements [2605,3211]. By definition, the sex cord element must account for <10% of the composition of the tumour [2605].

**Clinical features**
This tumour may occur in women of any age. It is usually hormonally inactive, but there have been several cases associated with endometrial hyperplasia or adenocarcinoma.

**Macroscopy**
Macroscopically, the tumour is solid, not distinguishable from thecoma or fibroma, and ranges from 1-10 cm in diameter.

**Histopathology**
Histological examination demonstrates the typical features of thecoma or fibroma in which sex cord structures are intermingled with the fibrothecomatous cells. Sex cord components vary in appearance between fully differentiated granulosa cells and indifferent tubular structures resembling immature Sertoli cells.

Prognosis and predictive factors
All of the reported cases are benign.

Sclerosing stromal tumour

**Definition**
A distinctive type of benign stromal tumour characterized by cellular pseudolobules that are composed of fibroblasts and round cells and separated by hypocellular, oedematous or collagenous tissue.

**Epidemiology**
This tumour accounts for 2-6% of ovarian stromal tumours, and more than 80% occur in young women in the second and third decades [433].

**Clinical features**
Presenting symptoms include menstrual abnormalities or abdominal discomfort [433,1280a,1409a,1695a]. Hormonal manifestations are rare [433], although a few tumours have been shown to produce estrogens or androgens [614,1222,1778,2315,2964]. Virilization may occur in pregnant women [419,738,1308].

**Macroscopy**
The tumour is typically unilateral and sharply demarcated, measuring 3-17 cm in diameter. The sectioned surface is solid, grey-white with occasional yellow foci and usually contains oedematous or cystic areas.

**Histopathology**
Histological examination shows a characteristic pattern with pseudolobulation of the cellular areas separated by hypocellular areas of densely collagenous tissue.
nous or oedematous tissue. The cellular areas contain prominent thin-walled vessels with varying degrees of sclerosis admixed with both spindle and round cells, the latter may resemble luteinized theca cells or show perinuclear vacuolization. Histochemical studies show the activity of steroidogenesis-related enzymes [1575,2537] and immunoreactivity for desmin and smooth muscle actin, as well as vimentin [419,1419,2512,2637].

**Prognosis and predictive factors**

The tumour is benign, and there have been no recurrent cases.

**Signet-ring stromal tumour**

**Definition**

A rare stromal tumour composed of signet-ring cells that do not contain mucin, glycogen or lipid [697,2332, 2605,2811].

**Clinical findings**

This tumour occurs in adults and is hormonally inactive.

**Macroscopy**

Macroscopically the tumours, may be both solid and cystic or uniformly solid.

**Histopathology**

Histological examination shows a diffuse proliferation of spindle and round cells; the latter show eccentric nuclei with a single large cytoplasmic vacuole and resemble signet-ring cells. The tumour may be composed entirely of signet-ring cells or may occur as a component of an otherwise typical fibroma. With the exception of one case [697], nuclear atypia and mitotic figures are not present. Negative staining for mucin distinguishes this tumour from the Krukenberg tumour. All of the reported cases are benign.

**Sertoli-stromal cell tumours**

**Definition**

Tumours containing in pure form or in various combinations Sertoli cells, cells resembling rete epithelial cells, cells resembling fibroblasts and Leydig cells in variable degrees of differentiation.

**ICD-O codes**

- Sertoli-Leydig cell tumour group
  - Well differentiated 8631/0
  - Of intermediate differentiation 8631/1
  - With heterologous elements 8634/1
  - Poorly differentiated 8631/3
  - With heterologous elements 8634/3
  - Retiform 8633/1
  - With heterologous elements 8634/1
  - Sertoli cell tumour, NOS 8640/1

**Sertoli-Leydig cell tumour group**

**Definition**

Tumours composed of variable proportions of Sertoli cells, Leydig cells, and in the case of intermediate and poorly differentiated neoplasms, primitive gonadal stroma and sometimes heterologous elements.

**Synonym**

Androblastoma.

**Epidemiology**

Sertoli-Leydig cell tumours (SLCTs) are rare, accounting for <0.5% of ovarian neoplasms; intermediate and poorly differentiated forms are most common. SLCTs have been reported in females from 2-75 years of age with a mean age of 23-25 years in different studies [2459, 3217,3243].

![Fig. 2.73](image1.png)

Well differentiated Sertoli-Leydig cell tumour. The tumour shows well developed tubules lined by Sertoli cells and aggregates of Leydig cells.

![Fig. 2.74](image2.png)

T1 weighted MR image of a Sertoli-Leydig cell tumour that fills the abdomen.

![Fig. 2.75](image3.png)

Sertoli-Leydig cell tumour of intermediate differentiation. A The sectioned surface of the tumour shows solid, cystic and partly haemorrhagic areas. B Nests of Leydig cells are at the edge of an aggregate of Sertoli cells adjacent to an oedematous area. C Solid cords of Sertoli cells surround a cluster of Leydig cells in the centre of the field. D Leydig cells are admixed with gonadal stroma and sex cord elements.
Clinical features
Signs and symptoms
One-third of patients are virilized, and others may have estrogenic manifestations. Androgenic manifestations include amenorrhea, hirsutism, breast atrophy, clitoral hypertrophy and hoarseness, whereas estrogenic effects include isosexual pseudoprecocity and menometrorrhagia. One-half of the patients have no endocrine manifestations, and the symptoms are non-specific. Patients with poorly differentiated neoplasms are slightly more likely to present with androgenic manifestations. About 10% of cases have tumour rupture or ovarian surface involvement, and 4% have ascites [3217].

Imaging
A solid, cystic or solid and cystic mass may be identified on ultrasound, computed tomography or magnetic resonance imaging.

Macroscopy
Over 97% of SLCTs are unilateral. They may be solid, solid and cystic or, rarely, cystic. The size ranges from not detectible to 35 cm (mean 12-14 cm). Poorly differentiated tumours are larger. Solid areas are fleshy and pale yellow, pink or grey. Areas of haemorrhage and necrosis are frequent, and torsion and infarction may be seen.

Tumour spread and staging
About 2-3% of tumours have spread beyond the ovary at presentation [3217].

Histopathology
In well differentiated SLCTs, Sertoli cells are present in open or closed tubules and lack significant nuclear atypia or mitotic activity [3216]. There is a delicate fibrous stroma in which Leydig cells may be found in small clusters. In tumours of intermediate differentiation, cellular lobules composed of hyperchromatic spindle-shaped gonadal stromal cells with poorly defined cytoplasm are separated by oedematous stroma. These merge with cords and poorly developed tubules of Sertoli cells, some with atypia. With better differentiation of Sertoli cell elements, the distinction between the stromal and Sertoli cell components is more easily made. Leydig cells are found in clusters at the periphery of the cellular lobules or admixed with other elements. They may be vacuolated, contain lipofuscin or rarely have Reinke crystals. Mitotic figures are rare among the Leydig cells, which also lack cytological atypia.

In poorly differentiated tumours, a sarcomatoid stroma resembling primitive gonadal stroma is a dominant feature, and the lobulated arrangement of SLCT of intermediate differentiation is absent. Occasional tumours contain bizarre nuclei. The mitotic activity in the Sertoli and stromal elements is variable with a mean of over 20 per 10 high power fields.

Immunoprofile
Positivity is seen for vimentin, keratin and alpha-inhibin with differing intensity of expression between sex cord and stromal areas. Rarely, positivity for epithelial membrane antigen may be seen. Positivity for estrogen and progesterone receptors may also be seen in a minority of cases.

Grading
SLCTs are subdivided into well differentiated, intermediate and poorly differentiated forms based on the degree of tubular differentiation of the Sertoli cell component (decreasing with increasing grade) and the quantity of the primitive gonadal stroma (increasing with increasing grade). Leydig cells also decrease with increasing grade. Heterologous elements and/or a retiform pattern may be seen in all but the well differentiated variant.

Somatic genetics
Analysis of six SLCTs has shown limited, if any, loss of heterozygosity with 10 polymorphic DNA markers that have shown high rates of loss of heterozygosity in a variety of tumours. Three of these were assised for clonality by examining the DNA methylation pattern at a polymorphic site to the androgen receptor gene. The Leydig cells in these three cases were all polyclonal in contrast to the cells from a pure Leydig cell tumour that were monoclonal. These findings suggest that the Leydig cells in SLCTs are reactive cells of ovarian stromal origin and not a neoplastic component of the tumour [1902]. Trisomy 8 was reported as the sole karyotypic abnormality in a SLCT that metastasized [1756].

Fig. 2.76 Poorly differentiated Sertoli-Leydig cell tumour. A Heterologous elements consisting of mucinous glands are intimately associated with primitive gonadal stroma. B A nodule of primitive gonadal stroma is composed of poorly differentiated spindle-shaped cells with apoptotic bodies.
Genetic susceptibility
A familial occurrence of SLCTs in association with thyroid disease has been reported (1344) with occasional reports of other families since then. The thyroid abnormalities are usually adenomas or nodular goitres. Autosomal dominant inheritance with variable penetrance has been suggested as the method of genetic transmission. SLCT has been reported in association with cervical sarcoma botryoides in three cases (1026).

Prognosis and predictive factors
The mortality from SLCTs as a group is low and is confined to those of intermediate and poor differentiation. Poor differentiation, tumour rupture and heterologous mesenchymal elements were identified as features correlating with the development of metastases (302, 2459). In one large series none of the well differentiated tumours, 11% of those of intermediate differentiation and 59% of those that were poorly differentiated behaved in a clinically malignant fashion (3217). Presentation with stage II or higher disease is also associated with a poor outcome. However, tumours without any apparent poor prognostic factors may behave in an aggressive fashion (1903).

Presentation with stage II or higher disease is also associated with a poor outcome. However, tumours without any apparent poor prognostic factors may behave in an aggressive fashion (1903).

Sertoli-Leydig tumour with heterologous elements
Definition
A SLCT that contains either macroscopic or histological quantities of a tissue not regarded as intrinsic to the sex cord-stromal category. Such elements include epithelial (mostly mucinous) and/or mesenchymal tissues (most commonly chondroid and rhabdomyoblastic) and tumours arising from these elements.

Clinical features
The presence of heterologous elements does not alter the presentation, but 20% of patients have a slightly raised serum alpha-fetoprotein (AFP) due in some cases to hepatocytes as a heterologous element.

Macroscopy
Part or the entire cystic component of a SLCT may be mucinous in type; however, heterologous elements are only occasionally diagnosed macroscopically.

Histopathology
Heterologous elements are seen in approximately 20% of SLCTs. They occur only in those of intermediate or poor differentiation or in retiform tumours but are not identified in well-differentiated tumours. Heterologous mesenchymal elements occur in 5% of SLCTs and usually consist of cartilage, skeletal muscle or rhabdomyosarcoma. They may be admixed with the sex cord areas of the tumour or present as discrete areas. Both cartilage and skeletal...
muscle may appear cellular and of fetal type. The mucinous epithelium is usually bland intestinal or gastric-type epithelium, but sometimes shows borderline or malignant change. Argentaffin cells, goblet cells and carcinoid may be seen. The gonadal stroma may condense around areas of mucinous epithelium, a useful clue to the diagnosis of a SLCT in a tumour that appears to be a mucinous cystadenoma. Hepatocytic differentiation may be recognized by the presence of bile plugs or an acinar arrangement of hepatocytes, but immunohistochemistry is usually necessary to distinguish hepatocytes from Leydig cells [1904].

Immunoprofile
Variable positivity is seen in the sex cord elements for vimentin, keratin and alpha-inhibin. The immunoprofile of the heterologous elements is what would be expected from their constituent tissues. The mucinous elements show more extensive staining for cytokeratin 7 than for cytokeratin 20. They are positive for epithelial membrane antigen and may be focally positive for chromogranin. Leydig cells are negative for pan-keratin, CAM 5.2 and AFP but show intense positivity for vimentin and alpha-inhibin. These findings distinguish them from hepatocytes. AFP may be identified in endodermal-like structures in some cases.

Prognosis and predictive factors
The small number of cases of this tumour reported make it difficult to determine the significance of individual elements. Heterologous mesenchymal elements (skeletal muscle or cartilage) or neuro-blastoma imply a poor outcome with 8 of 10 patients dead of disease [2291]. In contrast, gastrointestinal epithelium or carcinoid as the heterologous element does not have prognostic significance [3207].

Retiform Sertoli-Leydig cell tumour and variant with retiform elements

Definition
Retiform SLCT is composed of anastomosing slit-like spaces that resemble the rete testis and comprise 90% or more of the tumour. Tumours with at least 10% but less than 90% retiform elements are classified as being of intermediate or poor differentiation and qualified “with retiform elements”.

Epidemiology
Retiform tumours tend to occur in younger patients but may occur at any age [3209]. Virilization is less common in tumours with a retiform pattern.

Macroscopy
Retiform tumours may contain papillae or polypoid structures.

Histopathology
Like heterologous elements, retiform areas occur only in SLCTS of intermediate and poor differentiation [2471,3209]. They vary from slit-like spaces to areas comprising a complex microcystic pattern. Dilated spaces may be continuous with sex cord areas of the tumour. The lining cells may be flattened and non-specific or cuboidal and sertoliform. The lumens frequently contain variably inspissated eosinophilic material resembling colloid. Within the SLCT category, retiform tumours shows the highest incidence of heterologous elements [3209].

Immunoprofile
Retiform areas stain with keratin and show moderate staining for alpha-inhibin, with a reversed pattern seen in sex cord and stromal areas of the tumour. Vimentin may show subnuclear localization in the retiform areas.

Differential diagnosis
Serous tumours, yolk sac tumours and malignant müllerian mixed tumours may resemble a retiform SLCT [3209]. The presence of primitive gonadal stroma, heterologous elements, Leydig cells and/or alpha-inhibin positivity assists in making the diagnosis.

Prognosis and predictive factors
Approximately 25% of patients with SLCTs that contain retiform elements will have an aggressive course [3209]. Many have stage II or higher disease, poor differentiation and/or heterologous elements.

Sertoli cell tumour

Definition
A neoplasm composed of Sertoli cells arranged in hollow or solid tubular formations with rare, if any, Leydig cells. Simple or complex annular tubules are dominant in those lesions that occur in association with the Peutz-Jeghers syndrome.

Epidemiology
Sertoli cell tumours are rare [2882]. Patients range in age from 2-79 years.
Clinical features

The tumours are functional in 40-60% of cases, most often estrogenic, but occasionally androgenic or rarely both. Rarely, the tumour produces progesterone. Clinical manifestations include isosexual pseudoprecocity, menometrorrhagia, amenorrhea, hirsutism, breast atrophy, clitoral hypertrophy and hoarseness. Cases with menstrual disturbances or postmenopausal bleeding may show hyperplasia or adenocarcinoma of the endometrium. A peritoneal decidua reaction may be seen. Patients with Sertoli cell tumour may have elevated levels of serum estrogen, progesterone and luteinizing hormone. Rarely, the tumour may cause hypertension due to renin production.

Macroscopy

These are unilateral neoplasms, and the ovaries are involved with equal frequency. They range in size from 1-28 cm with an average of 7-9 cm. They are well circumscribed, solid neoplasms with a smooth or lobulated external surface, a fleshy consistency and a yellow-tan sectioned surface. Areas of haemorrhage and/or cystic degeneration may be seen in larger tumours. Rare examples are totally cystic or are solid with fibrosis and ossification.

Histopathology

A variety of tubular arrangements characterize Sertoli cell tumours. The tubular pattern is either open or closed (with paired cell arrangements) and simple or complex. Simple tubules are surrounded by a basement membrane and may contain a central hyaline body. Complex tubules form multiple lumens often filled with hyaline bodies and surrounded by a thick basement membrane that may coalesce to form hyalinized areas. Diffuse and pseudopapillary patterns may be seen. In some tumours, cells distended by intracytoplasmic lipid are dominant in a pattern known as "folliculome lipidique". The Sertoli cell tumours that occur in women with the Peutz-Jeghers syndrome may have abundant eosinophilic cytoplasm, termed the oxyphilic variant. The nucleus is typically oval or spherical with a small nucleolus. The cytoplasm is clear or lightly vacuolated, stains for lipid are positive, and glycogen may be demonstrated. Mitotic figures are usually scanty (<1 per 10 high power fields), but >9 mitotic figures per 10 high power fields may be seen in tumours from younger women. The neoplasm may contain rare Leydig cells, but lacks the primitive gonadal stroma characteristic of Sertoli-Leydig cell tumours.

Immunoprofile

Sertoli cell tumours are variably positive for keratins, vimentin and alpha-inhibin. CD99 and calretinin are positive in about 50% of cases. The tumours are negative for epithelial membrane antigen.

Electron microscopy

A diagnostic feature of Sertoli cell tumour is the presence of Charcot-Böttcher (CB) filaments and Spangaro bodies. These bodies represent aggregates of intracytoplasmic microfilaments of varying size and are not present in every cell or every tumour. CB filaments have been found most frequently in the complex tubular variant, the so-called sex cord tumour with annular tubules (SCTAT).

Differential diagnosis

Sertoli cell tumours must be distinguished from struma ovarii, carcinoid and endometrioid carcinoma (see section on endometrioid carcinoma). Phenotypic females with the androgen insensitivity syndrome (AIS) may be incorrectly diagnosed as having a Sertoli cell tumour of the ovary if the syndrome has not been diagnosed preoperatively [2498]. On the other hand, Sertoli cell tumours can occur in the testes of patients with AIS. While most are benign, rare malignant Sertoli cell tumours have been reported in this setting (3165).

Genetic susceptibility

A variety of Sertoli cell phenotypes including SCTAT, oxyphilic and lipid rich (folliculome lipidique) variants have been described in patients with the Peutz-Jeghers syndrome (PJS), an autosomal dominant disease with a propensity for breast, intestinal and gynaecological neoplasia.

Prognosis and predictive factors

These tumours are typically benign. In the rare forms that behave clinically in an aggressive fashion, infiltration of the ovarian stroma, extension beyond the ovary and intravascular extension may be seen. Cytological atypia and a high
mitotic rate may be present in these tumours.

**Stromal-Leydig cell tumour**

**Definition**  
An ovarian stromal tumour composed of fibromatous stroma and clusters of Leydig cells containing crystals of Reinke.

**Clinical features**  
This tumour is virilizing in approximately one-half of the cases.

**Macroscopy**  
These extremely rare neoplasms are usually well circumscribed (302,2165,2842). The sectioned surface has been described as lobulated with a yellow-white appearance. They may be bilateral.

**Histopathology**  
Stromal-Leydig cell tumours have two components. Spindle-shaped or ovoid stromal cells identical to those of a fibroma or thecoma are present together with Leydig cells containing Reinke crystals (2789,3252). Typically, in these neoplasms the fibrothecomatous element predominates with the Leydig cell component comprising small nodular aggregates.

Definitive diagnosis requires the presence of Reinke crystals, otherwise the neoplasm would be categorized as luteinized thecoma. Since Reinke crystals may be difficult to identify and since sampling errors may occur, it has been suggested that stromal-Leydig cell tumours are more common than the literature would suggest.

**Prognosis and predictive factors**  
The clinical behaviour of stromal-Leydig cell tumours is benign, and neither clinical recurrence nor metastasis has been documented.

---

**Sex cord-stromal tumours of mixed or unclassified cell types**

**Definition**  
Sex cord-stromal tumours that do not fall in the granulosa-stromal, Sertoli-stromal or steroid cell categories.

**ICD-O codes**  
- Sex cord tumour with annular tubules: 8623/1  
- Variant associated with Peutz-Jeghers syndrome: 8623/0  
- Gynandroblastoma: 8632/1  
- Sex cord-stromal tumour, NOS: 8590/1

---

**Sex cord tumour with annular tubules**

**Definition**  
A tumour composed of sex cord (Sertoli) cells arranged in simple and complex annular tubules (2599).

**Synonym**  
Sertoli cell tumour, annular tubular variant.

**Epidemiology**  
Patients with this tumour most commonly present in the third or fourth decades, but the age ranges from 4-76 years. About one-third of cases occur in women with Peutz-Jeghers syndrome (PJS). The average age of patients with PJS is in the mid-twenties and of those unassociated with PJS in the mid-thirties.

**Clinical features**  
Nearly all women without PJS present with a palpable mass. Isosexual pseudoprecocity or other features of aberrant estrogen occurs in about 40% of cases, and, occasionally, there are progesterone effects. Those tumours that are associated with PJS are found either incidentally at autopsy or in ovaries removed as part of treatment for other gynaecological disease.

**Macroscopy**  
These are unilateral neoplasms except for those occurring in the PJS, which are usually bilateral. PJS-associated lesions are usually macroscopically undetectable; when visible, the tumourlets are multiple and <3 cm in diameter. Bilateral lesions are present in two-thirds of women. Non-PJS cases may be up to 33 cm in diameter. The sectioned surface of the tumours is solid and yellow. Calcification or cystic degeneration may be apparent.

**Histopathology**  
Regardless of the clinical setting, the annular tubules show Sertoli cells with pale cytoplasm and nuclei arranged antipodally around a single hyaline body (simple annular tubules) or multiple hyaline bodies (complex annular tubules). Classic tubular Sertoli cell arrangements may be admixed. In PJS lesions the annular tubules are typically widely scattered in the ovarian stroma without forming a distinct mass.
Tumours unassociated with PJS form masses of simple and complex tubules separated by sparse fibrous stroma. Extensive hyalinization may develop. The neoplastic cells may spill over beyond the confines of the tubules and infiltrate the surrounding stroma. Mitotic figures occasionally exceed 4 per 10 high power fields and rarely exceed 10 per 10 high power fields. Areas of well differentiated Sertoli cell tumour characterized by elongated solid tubules and/or microfollicular granulosa cell tumour are often present. Calcification of the hyaline bodies is typically found in over half of the tumours associated with PJS.

**Electron microscopy**
Ultrastructural assessment has shown Charcot-Böttcher filaments in several cases [2882]. While not required for diagnosis, their presence confirms the identification of the sex cord component as Sertoli cells.

**Histogenesis**
Although there is ultrastructural evidence supporting differentiation towards Sertoli cells in SCTAT, the histological and clinical features are sufficiently distinctive to merit its classification as a specific form of sex cord-stromal tumour.

**Prognosis and predictive factors**
All PJS-associated tumourlets have been benign. Up to 25% of SCTATs that occur in the absence of the PJS have been clinically malignant. Tumours with an infiltrative growth pattern and mitotic figures beyond the usual 3-4 per 10 high power fields are more likely to recur or otherwise behave aggressively. It is difficult, however, to predict the behaviour of individual cases. Some tumours produce müllerian inhibiting substance and/or alpha-inhibin, and these tumour markers may be useful in monitoring the course of disease in those cases [1091,2304]. Recurrences are often late and may be multiple. Spread through lymphatics may result in regional and distant lymph node involvement.

**Somatic genetics**
Germline mutations in a gene encoding serine-threonine kinase have been identified in a SCTAT associated with PJS but not in sporadic cases [548].

**Gynandroblastoma**

**Definition**
A tumour composed of an admixture of well differentiated Sertoli cell and granulosa cell components with the second cell population comprising at least 10% of the lesion.

**Clinical features**
An extremely rare tumour, gynandroblastoma generally occurs in young adults, though it may be encountered in a wide age range (96,432,1820,1996). Nearly all tumours present in stage I and may have either estrogenic or androgenic manifestations. Variable in size, they may be massive (up to 28 cm) with a predominantly solid sectioned surface showing a few cysts.

**Histopathology**
Well formed hollow tubules lined by Sertoli cells are generally admixed with rounded islands of granulosa cells growing in a microfollicular pattern. Variation from this typical histology with a juvenile granulosa cell pattern or an intermediate or poorly differentiated Sertoli-Leydig cell tumour with or without heterologous elements has been reported [1820]. The tumours are alpha-inhibin positive.

**Prognosis and predictive factors**
Almost all tumours are stage I at initial presentation and clinically benign. It is important to mention the components of the tumour in the diagnosis, in particular whether the granulosa cell component is of adult or juvenile type and also the subtype of Sertoli-Leydig cell tumour.
Unclassified sex cord-stromal tumour

Definition
Sex cord-stromal tumours in which there is no clearly predominant pattern of testicular or ovarian differentiation [2605].

Epidemiology
They account for 5-10% of tumours in the sex cord-stromal category.

Clinical features
The tumour may be estrogentic, androgentic or non-functional [2619,2701, 3196].

Histopathology
Histologically, the tumour cells show patterns and cell types that are intermediate between or common to granulosa-stromal cell tumours and Sertoli-stromal cell tumours.

Prognosis and predictive factors
The prognosis is similar to that of granulosa cell tumours and SLCTs of similar degrees of differentiation [2619].

Steroid cell tumour, not otherwise specified

Definition
These are steroid cell tumours that cannot be classified into one of the aforementioned groups. It is probable that some of these cases represent Leydig cell tumours in which Reinke crystals cannot be identified. Some may also represent large stromal luteomas where a parenchymal location can no longer be established.

Clinical features
They are usually associated with androgenic manifestations and occasionally with estrogenic effects [1163]. Rare neoplasms have also been associated with progestogenic effects, Cushing syndrome or other paraneoplastic syndromes due to hormone secretion [3218].

Macroscopy
These neoplasms are often large and are usually well circumscribed, often having a lobulated appearance. Occasional neoplasms are bilateral. The sectioned surface ranges from yellow to brown or black. Especially in large tumours, areas of haemorrhage and necrosis may be seen.

Histopathology
These neoplasms are usually composed of solid aggregates of cells with occasional nests or trabeculae. Tumour cells are polygonal with cytoplasm that is usually granular and eosinophilic but which may be vacuolated. Sometimes both cell types may be present. Cytoplasmic lipofuscin pigment may be identified. Nuclei may be bland, but in some cases there is considerable nuclear atypia and significant numbers of mitotic figures may be found. Areas of haemorrhage and necrosis can be present. Intracytoplasmic lipid can usually be identified with special stains and rarely may be so abundant as to result in a signet-ring appearance. Occasional tumours contain a considerable amount of fibrous stroma.

Immunoprofile
These neoplasms are usually immunoreactive to alpha-inhibin and variably with anti-cytokeratin antibodies and vimentin. Differential diagnosis
Luteoma of pregnancy may mimic a lipid-poor or lipid-free steroid cell tumour. The former is usually discovered in patients at caesarean section with a term pregnancy and typically occurs in multiparous Black patients in their third or fourth decade. Also in the differential diagnosis are oxyphilic variants of a number of other ovarian tumours, e.g. struma ovarii, clear cell carcinoma, primary or secondary malignant melanoma and carcinoid.

Prognosis and predictive factors
Approximately one-third of these neoplasms are clinically malignant, and they sometimes have extensive intra-abdominal spread at presentation. Malignant tumours are more likely to be larger than 7 cm diameter, contain areas of haemorrhage and necrosis, exhibit moderate to marked nuclear atypia and have a mitotic count of two or more per 10 high power fields. Occasionally, however, as with other endocrine neoplasms, the behaviour may be unpredictable, and tumours lacking these histological features may behave in a malignant fashion.

Stromal luteoma

Definition
Stromal luteomas are clinically benign steroid cell neoplasms of ovarian stro-
Sex cord-stromal tumours

Leydig cell tumours

**Clinical features**
These neoplasms typically occur in postmenopausal women (2171, 2472) (average age 58 years) but may occur in young women, pregnant women (2165) or children. They are usually associated with androgenic manifestations, but occasionally produce estrogenic effects and are associated with endometrial carcinoma (2279, 2455). In single reports ovarian Leydig cell tumours have been associated with multiple endocrine neoplasia syndrome (2630) and congenital adrenal hyperplasia (1718).

**Immunoprofile**
Leydig cell tumours of all types are intensely positive for alpha-inhibin and vimentin. There may be focal reactivity for keratins (CAM 5.2, AE1/AE3) with positivity for actin, CD68, desmin, epithelial membrane antigen and S-100 protein reported (2620).

**Prognosis and predictive factors**
The clinical behaviour of all neoplasms in the pure Leydig cell category is benign, and neither clinical recurrence nor metastasis has been documented.

**Hilus cell tumour**

**Definition**
A Leydig cell tumour arising in the ovarian hilus separated from the medullary stroma.

**Macroscopy**
Hilus cell tumours are usually small, well circumscribed lesions located at the ovarian hilus and typically have a red brown to yellow appearance on sectioning. Rarely, they are bilateral (739, 1718). When they are larger, the hilar location may no longer be apparent.

**Histopathology**
On histological examination the lesion is well circumscribed and comprised of cells with abundant cytoplasm that usually is eosinophilic but which may be clear with abundant intracytoplasmic lipid. Lipofuscin pigment is often seen, and characteristic Reinke crystals were present in 57% of cases in the largest series (2171). These are eosinophilic, rod-shaped inclusions. Occasionally, they are numerous, but they are often identified only after extensive searching.

**Prognosis and predictive factors**

**Definition**
A Leydig cell tumour that originates from the ovarian stroma and containing crystals of Reinke.

**Epidemiology**
Leydig cell tumours of non-hilar type have been reported much less often than hilus cell tumours, but their true relative frequency is unknown.

**Macroscopy**
These tumours are macroscopically well circumscribed and centered in the medullary region (2472).

**Histopathology**
They are histologically composed of steroid cells without discernible lipid and surrounded by ovarian stroma that often shows stromal hyperthecosis. Leydig cells containing demonstrable crystals of Reinke must be identified histologically in order to make the diagnosis, and lipofuscin pigment is often present.

**Histogenesis**
These tumours originate from the ovarian stroma, an origin supported by the rare non-neoplastic transformation of ovarian stromal cells to Leydig cells (2789).

Sex cord-stromal tumours 161
Tumours of the ovary
Germ cell tumours

Definition
A heterogeneous group of tumours reflecting the capacity for multiple lines of differentiation of the main stem cell system. The great majority of these neoplasms originate at different stages of development from germ cells that colonize the ovary.

Epidemiology
Germ cell tumours account for approximately 30% of primary ovarian tumours, 95% of which are mature cystic teratomas [1409,1502]. The remaining germ cell tumours are malignant and represent approximately 3% of all ovarian cancers in Western countries but have been reported to represent up to 20% of ovarian tumours in Japanese women [1970]. The median age at presentation is 18 years [883]. Malignant germ cell tumours are the most common ovarian cancer among children and adolescent females. Approximately 60% of ovarian tumours occurring in women under the age of 21 are of germ cell type, and up to one-third of them may be malignant [1555].

Aetiology
The aetiology of ovarian germ cell malignancies is unknown.

Clinical features
Signs and symptoms
Pain and a mass are the common presentations in young women [2586, 2587,2903]. Teenagers who present with abdominal masses and who have never menstruated should be evaluated for the possibility of a gonadoblastoma that has undergone malignant progression. Preoperative karyotyping of such individuals can be helpful to identify underlying chromosomal abnormalities in cases of gonadoblastoma.

Imaging
The ultrasonographic appearance of dermoid cyst ranges from a predominantly solid-appearing mass due to the echogenic aspect of sebaceous material intermixed with hair to a predominantly cystic mass [2132]. Computed tomography can accurately diagnose a teratoma because of fat attenuation within the cyst, and its complex appearance with dividing septa, hypodensity, calcified structures, and the identification of the Rokitansky protuberance [1080,2132]. Radiographic studies of fetiform teratoma demonstrate portions of skull, vertebra and limb bones within the tumour [19]. There are no diagnostic findings for other germ tumours; they often have solid and cystic components.

Histopathology
Morphologically, the different tumour types present in this group replicate in a distorted, grotesque form various stages of embryonal development from early, transient structures to mature adult tissues that in their turn may also be capable of undergoing malignant change [2248].

Histogenesis
As for histogenesis, they are believed to be from the primordial germ cells that migrate into the gonadal ridge at 6 weeks of embryonic life [2848]. A small proportion may also arise from non-germ stem cells present in the adult female genital tract [2039].

Primitive germ cell tumours
Definition
Tumours that contain malignant germ cell elements other than teratoma.

ICD-O codes
Dysgerminoma 9060/3
Yolk sac tumour 9071/3
Embryonal carcinoma 9070/3
Polyembryoma 9072/3
Non-gestational choriocarcinoma 9100/3
Mixed germ cell tumour 9085/3

Dysgerminoma
Definition
A tumour composed of a monotonous proliferation of primitive germ cells associated with connective tissue septa containing varying amount of lymphocytes and macrophages. Occasionally, syncytiotrophoblastic differentiation or somatic cysts occur. This tumour is identical to testicular seminoma.

Macroscopy
The usually well encapsulated tumour masses are apparently unilateral in 90% of cases. Macroscopic involvement of the contralateral ovary is apparent in 10% of cases, and in another 10% occult foci of dysgerminoma can be detected by biopsy [1920]. Tumours average 15 cm in maximal dimension and on section are solid, uniform or lobular and creamy white or light tan. Irregular areas of coag-

Fig. 2.87 Dysgerminoma in a 28 year old nulligravida woman. A Magnetic resonance image sagital view shows a 10 x 15 cm predominantly solid tumour with some central cystic changes. B Sectioned surface of the tumour shows a predominantly solid, multilobulated appearance with some cystic degeneration and foci of necrosis.
ulative necrosis may be present and may be associated with cystic change or macroscopic calcification. However, the presence of minute, sandy calcifications should point towards the presence of a concomitant gonadoblastoma. Focal haemorrhagic areas may be indicative of the presence of other germ cell components, possibly containing trophoblastic tissue.

**Histopathology**

The proliferating germ cells have a monotonous appearance with a polygonal shape, abundant pale cytoplasm and fairly uniform nuclei. They aggregate in cords and clumps, although sometimes the lack of cohesion between cells may lead to the formation of pseudoglandular spaces. Although the stroma is usually reduced to thin perivascular sheaths, occasionally it can be abundant. It always contains variable amounts of chronic inflammatory infiltrate, mainly composed of T lymphocytes (700) and macrophages. In fact, epithelioid granulomas are a prominent feature in a quarter of cases. Inflammation can also be present in the metastases. The mitotic rate is variable, and some tumours show anisokaryosis. Differentiation in the form of syncytiotrophoblastic cells is found in 5% of cases (3246). In these cases, beta-human chorionic gonadotropin (β-hCG)-secreting syncytiotrophoblast originates directly from dysgerminoma cells without intervening cytotrophoblast.

**Immunoprofile**

Most dysgerminomas show positivity for vimentin and placental-like alkaline phosphatase (PLAP) (1660,2011), the latter is usually found in a membranous location. An inconstant and heterogeneous cytoplasmic positivity can be found to cytokkeletal proteins such as cytokeratins (rarely), desmin, glial fibrillary acidic protein, as well as to S-100 protein and carcinoembryonic antigen (CEA). C-kit gene product (CD117) is present in dysgerminoma as it is in seminoma (2965), further supporting the similarity to its testicular counterpart.

**Precursor lesions**

There is no known precursor lesion for the vast majority of dysgerminomas, except for those arising from gonadoblastoma.

**Histogenesis**

Some dysgerminomas may subsequently be the precursors of other primitive germ cells neoplasms such as yolk sac tumour (2185).

**Prognosis and predictive factors**

Dysgerminomas respond to chemotherapy or radiotherapy. The clinical stage of the tumour is probably the only significant prognostic factor (2605). The presence of a high mitotic index and, in some
cases, anisokaryosis has no prognostic implication The behaviour of dysgerminoma with trophoblastic differentiation is identical to the usual type, but with the advantage of having β-hCG as a serum marker.

**Yolk sac tumour**

**Definition**

Yolk sac tumours are morphologically heterogeneous, primitive teratoid neoplasms differentiating into multiple endodermal structures, ranging from the primitive gut to its derivatives of extraembryonal (secondary yolk sac vesicle) and embryonal somatic type, e.g. intestine, liver [2035]. These neoplasms have many epithelial patterns and are typically immunoreactive for alpha-fetoprotein.

**Synonym and historical annotation**

Since the secondary yolk sac component represents only one of its many lines of differentiation, the current nomenclature is clearly restrictive. Perhaps the term “endodermal primitive tumours” would be more accurate in defining all the possible lines of differentiation, both epithelial and mesenchymal, that occur in these neoplasms.

The term “endodermal sinus tumour”, although still in use, is misleading, since the endodermal sinus is neither a structure present in human embryogenesis [1463] nor is it a constant feature of these tumours. The term “endodermal sinus tumour”, although still in use, is misleading, since the endodermal sinus is neither a structure present in human embryogenesis [1463] nor is it a constant feature of these neoplasms, as it only occurs in a minority of cases [1537].

**Macroscopy**

These tumours are usually well encapsulated with an average diameter of 15 cm [1537]. The sectioned tumour surface is soft and grey-yellow with frequent areas of necrosis, haemorrhage and liquefaction. Cysts can be found in the periphery forming a honeycomb appearance [2043]; rarely, they can be unicystic [522]. A relatively frequent finding is the presence of a benign cystic teratoma in the contralateral ovary [3033].

**Histopathology**

Although a marked histological heterogeneity due to numerous patterns of differentiation coexisting in the same neoplasm may occur, almost invariably characteristic areas are present that allow for the correct diagnosis.

The characteristic reticular pattern formed by a loose, basophilic, myxoid stroma harbouring a meshwork of microcystic, labyrinthine spaces lined by clear or flattened epithelial cells with various degrees of atypia and cytoplasmic PAS-positive, diastase-resistant hyaline globules permits tumour identification. Irregular but constant amounts of hyaline basement membrane material are found in relation to the epithelial cells. Both hyaline globules and the coarse aggregates of basement membrane material [2032, 2979] are good histological indicators for tumour identity. Less frequently, in 13-20% of cases, papillary fibrovascular projections lined by epithelium (Schiller-Duval bodies) are found that bear a resemblance to the structures of the choriovitelline placenta of the rat, a fact that permitted the establishment of the teratoid, endodermal identity of these tumours [2896].

**Histological variants**

Less common histological variants include the polyvesicular vitelline tumour, solid yolk sac tumour, parietal yolk sac tumour, glandular types of yolk sac tumour and hepatoid yolk sac tumour. In the polyvesicular vitelline tumour cystic, organoid change of the epithelial spaces occurs that consists of multiple dilatations lined by mesothelial-like cells that coexist with a columnar, PAS-positive epithelium [2043]. The solid yolk sac tumour shows areas of solid epithelial sheets of cells with a characteristic abundant clear cytoplasm and numerous hyaline globules. These areas may resemble anaplastic changes of dysgerminoma or even clear cell tumours [1537] but have the distinctive immunophenotype of a yolk sac tumour. Although exceptionally rare, parietal-type yolk sac tumours that are AFP-negative have been described [596, 620]. They are analogous to the experimental murine tumour of the same name and can be identified by the massive deposition of amorphous extracellular basement membrane, a material similar to the Reichert membrane of the murine parietal yolk sac.

Differentiation into organized somatic endodermal derivatives such as endodermal type gland-like structures resembling early lung and intestine as well as liver tissue can occur in a focal fashion in as many as a third of tumours [1968, 2515, 2979]. In rare instances these differentiated tissues may become the predominant elements in the tumour. Extensive differentiation of endodermal type glands characterizes the glandular variants of yolk sac tumours, which may adopt different morphological subtypes. From an embryological viewpoint the more immature type is represented by numerous dilated angular glands or papillae lined by an eosinophilic column-

---

**Table 2.05**

<table>
<thead>
<tr>
<th>Site differentiated</th>
<th>Tissue differentiated</th>
<th>Histological pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraembryonal endoderm</td>
<td>Primitive endoderm and secondary yolk sac</td>
<td>Reticular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endodermal sinus</td>
</tr>
<tr>
<td></td>
<td>Allantois</td>
<td>Polyvesicular</td>
</tr>
<tr>
<td></td>
<td>Murine-type (?) parietal yolk sac</td>
<td>Parietal</td>
</tr>
<tr>
<td>Somatic endoderm</td>
<td>Primitive intestine and lung (?)</td>
<td>Glandular</td>
</tr>
<tr>
<td></td>
<td>Early liver</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

---

**Fig. 2.89 Yolk sac tumour. Sectioned surface is predominantly solid and fleshy with areas of haemorrhage, necrosis and cyst formation.**

Germ cell tumours 165
narrow epithelium and surrounded by an oedematous, mesoblastic-type stroma that exhibits the characteristic appearance of early endoderm in both early differentiated intestine and the pseudoglandular phase of the embryonal lung (2038). Indeed, similar tumours are reported in the lung itself (1968). This gland-like aspect coupled with the presence of subnuclear vacuolization in the columnar lining mimics early secretory endometrium and endometrioid carcinoma of the ovary and, thus, was named the 'endometrioid' variant (522).

Some endometroid yolk sac tumours are highly differentiated and difficult to distinguish from grade 1 endometrioid carcinoma. Another type of glandular yolk sac tumour is composed of typical small cribriform glands resembling early intestinal differentiation. This type has been termed the intestinal-type of yolk sac tumour (533).

Extensive differentiation into hepatic tissue is another form of somatic differentiation (2515). In some yolk sac tumours extensive solid nodular areas of liver tissue can be found (2284) and can be so well formed that they reproduce their laminar structure complete with sinusoids and even haematopoiesis. Finally, since any immature teratoid tissue is considered to be capable of undergoing fully accomplished differentiation, it is possible that pure endodermal immature teratoma composed solely of AFP-secreting endodermal glands and mesenchyme may be closely related to yolk sac tumours (2042).

Predominance of mesenchymal, rather than epithelial, elements with differentiation into other components such as cartilage, bone or muscle may occur as a postchemotherapeutic conversion and be responsible for the occurrence of associated sarcomas in some cases (1854). The haematopoietic capacity of the normal secondary yolk sac may have its neoplastic counterpart in yolk sac tumours, where isolated cases of haematological disorders have been reported associated with ovarian yolk sac tumours (1782) in a similar way to those occurring in extragonadal germ cell tumours.

**Immunoprofile**

AFP is the characteristic marker of the epithelial component of yolk sac tumours, although it is not exclusive to them, as it can also be found in some ovarian tumours that are not of germ cell type. AFP is found as a dense granular cytoplasmic deposit and is absent in hyaline globules, which are rarely immunoreactive. A host of other substances can be found in yolk sac tumours recapitulating the complex functions of early endoderm, including those involved in haematopoiesis (1158,2011). The usual positivity for cytokeratins may differentiate solid yolk sac tumour from dysgerminoma. CD30 is usually positive in embryonal carcinoma (736) but is only focally positive in yolk sac tumour. Leu M1, which is positive in clear cell carcinoma, is negative in yolk sac tumour. The absence of estrogen and progesterone receptors in yolk sac tumour differentiates areas of yolk sac epithelium from associated areas of true endometrioid tumour (533).

**Prognosis and predictive factors**

Because numerous patterns of differenti-
ation may coexist in the same neoplasm, their behaviour, with some exceptions (1500), is not conditioned by specific tumour morphology but shows a generally favourable response to chemotherapy. Although the histological appearance bears little prognostic implications, mature or well differentiated glandular forms may have an indolent course even when treated by surgery alone (1500, 2284).

**Embryonal carcinoma and polyembryoma**

**Definition**
Embryonal carcinoma is a tumour composed of epithelial cells resembling those of the embryonic disc and growing in one or more of several patterns, glandular, tubular, papillary and solid. Polyembryoma is a rare tumour composed predominantly of embryoid bodies resembling early embryos.

**Epidemiology**
These rare tumours are the ovarian counterparts of their more frequent testicular homologues. Many are reported as a component of mixed germ cell tumours that originate from gonadoblastoma (see section on mixed germ cell-sex cord stromal tumours), arising in Y-chromosome containing dysgenetic gonads (and thus are technically “testicular” tumours) or even in 46 XX gonads (3253). They are multipotent stem cell tumours reproducing the primitive stages of embryonal differentiation.

**Clinical features**
Clinically, β-hCG stimulation may determine various hormonal manifestations such as precocious pseudopuberty in premenarchal girls and vaginal bleeding in adult women (1536).

**Histopathology**
Histologically, embryonal carcinoma reveals disorganized sheets of large primitive AFP and CD30-positive cells (736,1536), forming papillae or crevices which coexist with β-hCG positive syncytiotrophoblasts as well as early teratoid differentiation such as squamous, columnar, mucinous or ciliated epithelia. Its even more infrequent organoid variant is called polyembryoma due to a structural organization into blastocyst-like formations that resemble early presomatic embryos. These so-called embryoid bodies show embryonic disks with corresponding amniotic or primary yolk sac cavities and are surrounded by a mesoblast-like loose connective tissue. The surrounding tissues can differentiate into endodermal structures such as intestine or liver (2287) and trophoblast. However close the resemblance to normal early structures, the sequences of early embryonal development are not reproduced (1969).

**Non-gestational choriocarcinoma**

**Definition**
A rare germ cell tumour composed of cytotrophoblast, syncytiotrophoblast and extravillous trophoblast.
Clinical features
Clinically, hormonal manifestations such as precocious pseudopuberty and vaginal bleeding are present in children and young adults.

Macroscopy
Macroscopically, tumours are large and haemorrhagic, and large luteinized nodules or cysts due to β-hCG stimulation may appear in the uninvolved ovarian tissue.

Histopathology
Morphologically identical to gestational choriocarcinoma, primary non-gestational choriocarcinoma is rare in pure form, differentiates as an admixture of cytotrophoblast, syncytiotrophoblast and extravillous trophoblast and is usually found associated with other germ cell components [2704]. Histologically, there are fenestrated or plexiform sheets or pseudopapillae of cytotrophoblast and extravillous trophoblast admixed with numerous syncytiotrophoblasts. Tumour can be found in blood-filled spaces and sinuses. Vascular invasion is frequent. The immunophenotype is characteristic for each type of proliferating trophoblastic cell [1759] and includes cytokeratins, human placental lactogen and, above all, β-hCG.

Differential diagnosis
When found in a pure form in childbearing age, gestational choriocarcinoma, either primary in the ovary [3024] or metastatic [718] must be excluded. This may be accomplished by identifying paternal sequences by DNA analysis [1698,2655].

Prognosis and predictive factors
The distinction from gestational choriocarcinoma is important since non-gestational choriocarcinoma has a less favourable prognosis and requires more aggressive chemotherapeutic treatment regimens.

Mixed germ cell tumours
Definition
Mixed germ cell tumours are composed of at least two different germ cell elements of which at least one is primitive.

Clinical features
The value of tumour markers such as β-hCG and AFP in the diagnosis and follow-up of patients with mixed germ cell tumours containing elements of choriocarcinoma or yolk sac tumour has been proven over the years [2850]. Elevated serum levels of these markers should prompt a search for different components with extensive sampling of the tumour.

Histopathology
Histologically, the most common combination of neoplastic germ cell elements found in ovarian mixed germ cell tumours is dysgerminoma and yolk sac tumour [2850]. Additional neoplastic germ cell elements, including immature or mature teratoma, embryonal carcinoma, polyembryoma and/or choriocarcinoma, may also be present. All components of a mixed germ cell tumour and their approximate proportions should be mentioned in the diagnosis.

Most ovarian embryonal carcinomas are really malignant mixed germ cell tumours, usually admixed with yolk sac tumour and showing a large or predominant component of embryonal carcinoma [2850]. Although polyembryoma may have been the predominant malignant germ cell element within the tumour, a careful review of all the published cases of ovarian polyembryoma shows that other germ cell elements were also present [2850]. Also, ovarian choriocarcinoma of germ cell origin is in the majority of cases combined with other neoplastic germ cell elements. Immunohistochemical demonstration of β-hCG and AFP is a useful diagnostic modality in this group of tumours, as is the demonstration of PLAP in a component of dysgerminoma.

Prognosis and predictive factors
All elements in a malignant mixed germ cell tumour are capable of widespread metastatic dissemination. The metastases may be composed of a single neoplastic germ cell element or of various elements. Although these tumours are highly responsive to platinum-based chemotherapy, the therapeutic regimens should be based primarily on the most malignant elements of the tumour [2850].

Biphasic or triphasic teratomas
Definition
Tumours composed of derivatives of two or three primary germ layers (ectoderm, mesoderm, endoderm).
ICD-O codes
Immature teratoma 9080/3
Mature teratoma 9080/0
Cystic teratoma 9080/0
Dermoid cyst 9084/0

Immature teratoma
Definition
A teratoma containing a variable amount of immature, embryonal-type (generally immature neuroectodermal) tissue.

Epidemiology
Immature teratoma represents 3% of teratomas, 1% of all ovarian cancers and 20% of malignant ovarian germ cell tumours and is found either in pure form or as a component of a mixed germ cell tumour (989). It occurs essentially during the two first decade of life (from 1-46 years; average 18) (989,1174,2060).

Macroscopy
Immature teratoma is typically unilateral, large, variegated (6-35 cm; average, 18.5), predominantly solid, fleshy, and grey-tan and may be cystic with haemorrhage and necrosis (989,2060).

Histopathology
Immature teratoma is composed of variable amounts of immature embryonal-type tissues, mostly in the form of neuroectodermal rosettes and tubules, admixed with mature tissue. Neuroepithelial rosettes are lined by crowded basophilic cells with numerous mitoses (2060) and may be pigmented. Immature mesenchyme in the form of loose, myxoid stroma with focal differentiation into immature cartilage, fat, osteoid and rhabdomyoblasts is often present as well (2060). Immature endodermal structures including hepatic tissue, intestinal-type epithelium with basal vacuolization and embryonic renal tissue resembling Wilms tumour are encountered less frequently. Immature vascular structures may occur and are sometimes prominent.

Grading
Based on the quantity of the immature neuroepithelial component, primary and metastatic ovarian immature teratomas (including peritoneal implants and lymph nodes metastases) are separately graded from 1 to 3 (2060). More recently the possibility of using a two-tiered (low grade and high grade) grading system was suggested (2072). Adequate sampling of the primary tumour (one block per 1 or 2 cm of tumour) and of all resected implants is crucial, as the tumour grade may vary in different implants.

Somatic genetics
Immature teratomas grades 1-2 are

Table 2.06
Grading of ovarian immature teratomas.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tumours with rare foci of immature neuroepithelial tissue that occupy less than one low power field (40x) in any slide.</td>
</tr>
<tr>
<td>2</td>
<td>Tumours with similar elements, occupying 1 to 3 low power fields (40x) in any slide.</td>
</tr>
<tr>
<td>3</td>
<td>Tumours with large amount of immature neuroepithelial tissue occupying more than 3 low power fields (40x) in any slide.</td>
</tr>
</tbody>
</table>

Table 2.07
Management of immature teratomas according to grade of primary tumours and/or implants.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Two-tiered grading (2072)</th>
<th>Stage</th>
<th>Combination chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ovarian tumour</td>
<td>Low grade</td>
<td>Ia</td>
<td>Not required</td>
</tr>
<tr>
<td>2 or 3 ovarian tumour</td>
<td>High grade</td>
<td>Ia</td>
<td>Required</td>
</tr>
<tr>
<td>2 or 3 implants</td>
<td>High grade</td>
<td>≥ II</td>
<td>Required</td>
</tr>
<tr>
<td>0 implants*</td>
<td>High grade</td>
<td>≥ II</td>
<td>Not required</td>
</tr>
</tbody>
</table>

* Those extraovarian implants that are composed of mature tissue, essentially glia.

Fig. 2.98 A Immature teratoma, high grade. Neuroectodermal rosettes lie in a background of glial tissue. B Mitotic figures are evident within the immature neuroectodermal tissue.
Diploid in 90% of cases, whereas most (66%) of grade 3 tumours are aneuploid [165,2684]. Similarly, karyotypic abnormalities are most often seen in grade 3 tumours [165]. Immature teratomas show fewer DNA copy number changes detected by comparative genomic hybridization than other ovarian germ cell tumours and do not usually exhibit a gain of 12p or i(12p) [1518,2378].

Prognosis and predictive factors

The stage and grade of the primary tumour and the grade of its metastases are important predictive factors. Prior to the chemotherapy era, the overall survival rate of patients with grade 1, 2 and 3 neoplasms was 82%, 63% and 30%, respectively [2060].

The use of cisplatin-based combination chemotherapy has dramatically improved the survival rate of patients; 90-100% of those receiving this regimen remain disease-free [989].

The tumour grade is a crucial feature that determines behaviour and type of therapy. Patients with grade 1 tumours that are stage IA and those with mature (grade 0) implants do not require adjuvant chemotherapy. Those with grade 2 or 3 tumours, including stage IA, as well as those with immature implants require combination chemotherapy. The management of patients with grade 1 implants/metastases is not well established.

A recent report from the Pediatric Oncology Group concludes that surgery alone is curative in children and adolescents with immature teratoma of any grade, reserving chemotherapy for cases with relapse [600]. Also, in immature teratomas occurring in childhood, the presence of histological foci of yolk sac tumour rather than the grade of the immature component, per se, is the only predictor of recurrence [1174].

Mature teratoma

Definition

A cystic or, more rarely, a solid tumour composed exclusively of mature, adult-type tissues. A cyst lined by mature tissue resembling the epidermis with its appendages is clinically designated as "dermoid cyst". Homunculus or fetiform teratoma is a rare type of mature, solid teratoma containing highly organized structures resembling a malformed fetus ("homunculus" = little man).

Epidemiology

Age

Although most mature cystic teratomas occur during the reproductive years, they have a wide age distribution, from 2-80 years (mean, 32), and 5% occur in postmenopausal women [564]. Mature solid teratoma occurs mainly in the first two decades of life [199,2922].

Incidence

Mature cystic teratoma accounts for 27-44% of all ovarian tumours and up to 58% of the benign tumours [1502]. In addition to their pure form, dermoid cysts are found macroscopically within 25% of immature teratomas and in the ovary contralateral to a malignant primitive germ cell tumour in 10-15% of the cases.

Clinical features

Signs and symptoms

Most mature cystic teratomas present with a mass, but at least 25% (up to 60% in some series) are discovered incidentally [546]. Symptoms such as a pelvic mass or pain are more common when the mature teratoma is solid [199,2922]. The following complications have been described:

1. Torsion of the pedicle occurs in 10-16% of the cases, is responsible for acute abdominal pain and may be complicated by infarction, perforation or intra-abdominal haemorrhage.
2. Tumour rupture occurs in 1% of cases and can be spontaneous or traumatic. The spillage of the cyst contents into the peritoneum produces chemical peritonitis with granulomatous nodules mimicking tuberculosis or carcinomatosis. Rupture of mature teratoma containing neuroglial elements is thought to be responsible for gliomatosis peritonei characterized by peritoneal "implants" composed of mature glial tissue and does not affect the prognosis [2389]. However, a recent molecular study has demonstrated that these glial implants were heterozygous, whereas the associated mature ovarian teratomas were homozygous at the same microsatellite loci. This finding suggests that glial implants may arise from metaplasia of pluripotent müllerian stem cells rather than from implantation of the associated ovarian teratomas [845]. Similarly, peritoneal melanosis characterized by pigmentation of the peritoneum has been reported in cases of dermoid cysts.
3. Infection of the tumour occurs in 1% of cases.
(4) Haemolytic anaemia has been reported in rare cases [1020].

**Macroscopy**

Dermoid cyst is an ovoid, occasionally bilateral (8-15% of cases), cystic mass of 0.5-40 cm (average 15 cm) with a smooth external surface and is filled with sebaceous material and hair. A nodule composed of fat tissue with teeth or bone protrudes into the cyst and is termed a Rokitansky protuberance.

Mature solid teratoma is a large, solid mass with multiple cysts of varying size, a soft, cerebroid appearance and small foci of haemorrhage.

**Histopathology**

Mature teratomas are composed of adult-type tissues derived from two or three embryonic layers. Benign tumours such as struma ovarii, carcinoid, corticotroph cell adenoma, prolactinoma, naevus and glomus tumour may arise within a typical dermoid cyst [143, 1389, 2162, 2682].

Ho[...] and environmental factors in phenotypic differentiation of ovarian germ cell tumours [683].

**Prognosis and predictive factors**

Dermoid cysts with histological foci (up to 21 mm²) of immature neuroepithelial tissue have an excellent prognosis [3174]. Recurrence in the form of a dermoid cyst (3% of cases) or immature teratoma (2-2.6% of cases) in the residual ipsilateral ovary is most frequent when the initial cysts are bilateral or multiple and have ruptured [104, 3174].

**ICD-O codes**

- Struma ovarii: 9090/0
- Carcinoid: 8240/3
- Mucinous carcinoid: 8243/3
- Strumal carcinoid: 9091/1
- Ependymoma: 9391/3
- Primitive neuroectodermal tumour: 9473/3
- Glioblastoma multiforme: 9440/3
- Teratoma with malignant transformation: 9084/3
- Malignant melanoma: 8720/3
- Melanocytic naevus: 8720/0
- Sebaceous adenoma: 8410/0
- Sebaceous carcinoma: 8410/3
- Retinal anlage tumour: 9363/0

**Struma ovarii**

**Definition**

A mature teratoma composed either exclusively or predominantly of thyroid tissue. Struma ovarii may harbour changes histologically identical to thyroid adenoma, carcinoma (malignant struma ovarii) or both. Those admixed with a carcinoid (strumal carcinoid) are classified separately.

**Epidemiology**

Struma ovarii, the most common type of monodermal teratoma, accounts for 2.7% of all ovarian teratomas [3146] with...
Tumours of the ovary and peritoneum

Malignant struma ovarii represent 0.01% of all ovarian tumours and 5-10% of struma ovarii. Most patients are in their fifth decade [3146].

Clinical features

Signs and symptoms

Patients present with a palpable abdominal mass or unusual symptoms including Meigs syndrome [983], cervical thyroid hypertrophy and thyrotoxicosis (5% of cases) with high pelvic iodine uptake [2697]. An elevated serum level of thyroglobulin occurs in malignant struma ovarii [2412].

Macroscopy

The tumour is unilateral and varies from 0.5-10 cm in diameter. It has a brown solid and gelatinous sectioned surface and sometimes appears as a nodule within a dermoid cyst. Entirely cystic strumas containing green gelatinous material also occur [2831].

Histopathology

Struma ovarii is composed of normal or hyperplastic thyroid-type tissue with patterns seen in thyroid adenoma such as microfollicular, macrofollicular, trabecular and solid. Oxyphil or clear cells may be found [2832]. Cystic struma is composed of thin fibrous septa lined by flat, cuboidal cells with sparse typical thyroid follicles in the cyst wall [2831]. Immunoreactivity for thyroglobulin may be helpful in problematic cases such as cystic struma, oxyphilic or clear cell variants and a trabecular architecture that might be indistinguishable from Sertoli-Leydig cell tumours. Criteria used for malignant changes within struma ovarii are the same as those used for a diagnosis of malignancy in the thyroid gland [677,2387]. Papillary carcinomas (85% of cases) display the characteristic ground glass nuclei. However, follicular carcinomas are difficult to diagnose since struma ovarii generally lacks a capsule and has irregular margins. The thyroid tissue of struma may be uniformly malignant in some cases, undoubtedly arising in such cases from histological foci of normal-appearing thyroid tissue, which are not extensive enough in itself to qualify for the diagnosis of struma ovarii.

Prognosis and predictive factors

Tumours with the morphology of papillary or follicular thyroid cancer and extra-ovarian spread at presentation are probably the only lesions that deserve a designation of malignant struma, whilst the so-called "benign strumatisos", peritoneal implants composed of benign thyroid-type tissue, does not alter the prognosis. Factors increasing the likelihood of recurrences include the size, the presence of ascites or adhesions and solid architecture, whereas the mitotic rate and vascular invasion (identified in 15% of malignant strumas) are not prognostically helpful features [2387].

Carcinoids

Definition

These tumours contain extensive components of well differentiated neuroendocrine cells and most subtypes resemble carcinoids of the gastrointestinal tract. They may occur in pure form or within a dermoid cyst, a mucinous cystic tumour or a Brenner tumour. It should be distinguished from isolated neuroendocrine cells found within some mucinous and Sertoli-Leydig cell tumours.

Epidemiology

Ovarian carcinoids account for 0.5-1.7% of all carcinoids [2743], and the age range is 14-79 years (mean 53) [166, 2388,2390,2392].

Clinical features

Signs and symptoms

Carcinoid syndrome is a clinical sign of insular carcinoids in 30% of patients and is rare in trabecular (13%) and strumal (3.2%) carcinoids [631,2743]. Peptide YY production by the tumour cells causes severe constipation and pain with defecation in 25% of trabecular carcinoids [2658]. Strumal carcinoids may cause symptoms of functioning thyroid tissue in 8% of cases [2390].
Diagnostic procedures
Elevated urine 5-hydroxyindoleacetic acid (5-HIAA) and serum serotonin levels are found in patients with carcinoid syndrome [631,2388].

Macroscopy
Primary ovarian carcinoids are unilateral and present as a firm tan nodule (less than 5 cm) protruding into a typical dermoid cyst (32-60% of tumours) or are predominantly solid with small cysts. The sectioned surface is firm, homogeneous and tan to yellow.

Histopathology
Insular carcinoid accounts for 26-53% of cases [631,2743]) and resembles midgut derivative carcinoids. It is composed of nests of round cells with uniform nuclei and abundant eosinophilic cytoplasm enclosing small red argentaffin granules at the periphery of the nests. Acinus formation and a cribriform pattern with luminal eosinophilic secretion are present [2388].

Trabecular carcinoid accounts for 23-29% of cases [631,2743] and resembles hindgut or foregut derivative carcinoids. It exhibits wavy and anastomosing ribbons composed of columnar cells with the long axes of the cells parallel to one another and oblong nuclei with prominent nucleoli. The abundant cytoplasm is finely granular with red-orange argyrophilic granules at both poles of the nucleus [2392].

Mucinous carcinoid accounts for only 1.5% of cases [2743] and resembles goblet cell carcinoids arising in the appendix. The well differentiated mucinous carcinoid is composed of numerous small glands lined by columnar or cuboidal cells, some of which contain intracytoplasmic mucin or have a goblet cell appearance, whilst others disclose orange-red neuroendocrine granules. Individual tumour cells may contain both mucin and neuroendocrine granules. Glands may be floating within pools of mucin that also dissect the surrounding fibrous stroma with isolated signet-ring cells infiltrating the stroma. Atypical mucinous carcinoid demonstrates crowded glands or a cribriform pattern. Carcinoma arising in mucinous carcinoid exhibits large islands of tumour cells or closely packed glands with high grade nuclei, numerous mitoses and necrosis [166].

Strumal carcinoid accounts for 26-44% of cases [631,2743] and is composed of a variable proportion of thyroid tissue and carcinoid, the latter mostly having a trabecular architecture. The neuroendocrine cells invade progressively the strumal component, replacing the follicular lining cells. Glands or cysts lined by columnar epithelium with goblet cells may be found [2390].

Carcinoids with mixed patterns (essentially insular and trabecular), are classified according to the pattern that predominates [2388].

Immunoprofile
Carcinoids are immunoreactive to at least one of the neuroendocrine markers (chromogranin, synaptophysin, Leu-7) and various peptide hormones such as pancreatic polypeptide, gastrin, vasoactive intestinal peptides and glucagon [166].

Differential diagnosis
Metastatic gastrointestinal carcinoid to the ovary should be ruled out specifically when extraovarian disease is detected. Bilateral and multinodular ovarian involvement, the absence of other teratomatous components and the persistence of the carcinoid syndrome after oophorectomy favour the diagnosis of metastasis [166,2391].

Prognosis and predictive features
Almost all primary trabecular and strumal carcinoids occur in women with stage I disease and have an excellent outcome. The overall survival of patients with insular carcinoid is 95% at 5 years and 88% at 10 years [2388].

Primary ovarian mucinous carcinoid, like those in the appendix, has a more aggressive behaviour with extraovarian spread and lymph node metastases. The presence of frank carcinoma within the tumour is an important prognostic factor [166].

Neuroectodermal tumours
Definition
Tumours composed almost exclusively of neuroectodermal tissue, closely resem-
Epidemicity
Less than 40 cases are reported in patients 6-69 years old (average 28), {1077,1418,1476}.

Clinical features
The tumours usually present as a pelvic mass.

Macroscopy
Tumours are unilateral and 4-20 cm in diameter, averaging 14 cm {1476}. The sectioned surface varies from solid with friable, gray-pink tissue to cystic with papillary excrescences in their inner or outer surface {1077}.

Tumour spread and staging
The majority of patients have stage II or III disease at laparotomy usually in the form of peritoneal implants {1476}.

Histopathology
These tumours are morphologically identical to their nervous system counterparts. They may be divided into three categories as follows:
1. Well differentiated forms such as ependymoma.
2. Poorly differentiated tumours such as primitive neuroectodermal tumour (PNET), and medulloepithelioma.
3. Anaplastic forms such as glioblastoma multiforme.

Whilst ependymomas are not found in association with teratoma, other neuroectodermal tumours in the ovary may be associated with elements of mature or immature teratoma {2605}. Cases previously reported as neuroblastoma or medulloblastoma would now most likely be classified as PNETs since the morphology of all three tumours is similar with the term medulloblastoma being reserved for cerebellar and neuroblastoma for adrenal neoplasms {1474}. Medulloepithelioma, on the other hand, has a distinctive appearance characterized by papillary, tubular or trabecular arrangements of neoplastic neuroepithelium mimicking the embryonic neural tube {1474}.

Ependymomas and anaplastic tumours are immunoreactive for glial fibrillary acidic protein. The characteristic immunoprofile of PNETs, vimentin and MIC2 protein (CD99) positive and GFAP, cytokeratin, desmin. chromogranin, and inhibin negative, help to distinguish these tumours from small cell carcinoma and juvenile granulosa cell tumour.

Somatic genetics
Reverse transcription-polymerase chain reaction in a case of ovarian PNET led to the detection of EWS/FLI1 chimeric transcript, originating from the characteristic t(11;22)(q24;q12) translocation of the PNET/Ewing tumour family {1418}.

Prognosis and predictive factors
Most patients with ovarian ependymomas survive despite multiple recurrences, whereas patients with PNET and anaplastic tumours have a poor outcome {1476}.

Carcinomas
Definition
A dermoid cyst in which a secondary carcinoma develops.

Epidemiology
Malignancy arising within a mature cystic teratoma is a rare complication (1-2% of cases), mostly reported in postmenopausal women (mean 51-62 years) {1214,1429,2164}.

Clinical features
The tumour may present as a dermoid cyst or as an advanced ovarian cancer depending on tumour stage {2605}. The tumour may show adherence to surrounding pelvic structures {1214, 1429,2164}.

Macroscopy
On macroscopic examination cauliflower exophytic growth, infiltrative grey-white plaques or thickenings of the cyst wall with necrosis and haemorrhage may be seen {1214,1429,2164}.

Histopathology
The malignancy may be detectable only after histological examination, thus dermoid cysts in postmenopausal women must be adequately sampled. Any component of a mature teratoma may undergo malignant transformation. Carcinomas are the most common malignancy, with squamous cell carcinomas accounting for 80% of cases and 51% of all primary ovarian squamous cell carcinomas {1214,2255}. Adenocarcinoma is the second most common malignancy arising in dermoid cysts {1456}. Adenocarcinoma of intestinal type {2970}, Paget disease, adenosquamous carcinoma, transitional cell carcinoma {1456}, undifferentiated carcinoma, small cell carcinoma, basal cell carcinoma and carcinosarcoma {123} have been described {2605}. The malignant component invades other parts of the dermoid cyst and its wall.

Somatic genetics
Selective tissue microdissection and genetic analyses of malignant tumours...
associated with mature teratomas showed an identical homozygous genotype for the malignant component and the mature teratomatous tissues, thus demonstrating a direct pathogenetic relationship [683].

**Prognosis and predictive features**

The prognosis of squamous cell carcinoma is poor with a 15-52% overall 5-year survival and disease related death usually within 9 months. Vascular invasion is associated with a high mortality rate [1214]. Although relatively few cases have been reported, the prognosis of adenocarcinoma appears to be similar to that of squamous cell carcinoma [2970].

**Sarcomas**

Sarcomas account for 8% of cases of malignancies in dermoid cysts and are more often seen in younger patients than those with squamous cell carcinoma. Cases of leiomyosarcoma, angiosarcoma [2021], osteosarcoma [2006], chondrosarcoma, fibrosarcoma, rhabdomyosarcoma and malignant fibrous histiocytoma have been reported [2605].

**Melanocytic tumours**

Melanomas are rare, occurring much less commonly than metastatic melanoma [630]. Overall, one-half of the patients with stage I dermoid-associated melanoma are alive at 2 years [404]. Melanocytic naevi of various types may arise within a typical dermoid cyst [1544].

**Sebaceous tumours**

Sebaceous tumours are specialized neoplasms arising within an ovarian dermoid cyst that resemble various forms of cutaneous sebaceous gland tumours (sebaceous adenoma, basal cell carcinoma with sebaceous differentiation, sebaceous carcinoma). The hallmark of these lesions is the presence of large numbers of mature, foamy or bubbly sebaceous cells that stain positively with oil red O in a tumour arising within a dermoid cyst [491].

**Pituitary-type tumours**

Corticotroph cell adenoma and prolactinoma, respectively responsible for Cushing syndrome and hyperprolactinemia with amenorrhea, may arise within a typical dermoid cyst and have a benign clinical course [143, 1389, 2162].

**Retinal anlage tumours**

Pigmented progonoma and malignant tumours derived from retinal anlage within ovarian teratomas have macroscopically pigmented areas that correspond to solid nests, tubules and papillae composed of atypical cells with melanin-containing cytoplasm [1112, 1466, 2712].

**Other monodermal teratomas and related tumours**

Neural cyst of the ovary lined by a single layer of ependymal cells with white matter, astrocytes and reactive glia in the underlying wall corresponds to a monodermal teratoma with unidirectional neurogenic differentiation [894]. Similarly, endodermal variants of mature teratoma lined exclusively by respiratory epithelium [508] and ovarian epidermoid cysts [823] may fall into the category of monodermal teratoma. Mucinous cystadenomas arising within mature teratomas have a homozygous teratomatous genotype, supporting their germ cell origin [1731]. Mesodermal derived tumours such as lipoma composed of mature adipocytes with scattered benign sweat glands may occur [961]. Glomus tumour may rarely arise within a typical dermoid cyst [2682].
This group of neoplasms is composed of a mixture of germ cell and sex cord-stromal elements. They have mainly benign clinical behaviour except in cases with a malignant germ cell component.

**Gonadoblastoma**

**Definition**
A neoplasm composed of tumour cells closely resembling dysgerminoma or seminoma, intimately admixed with sex cord derivatives resembling immature Sertoli or granulosa cells and in some cases containing stromal derivatives mimicking luteinized stromal or Leydig cells devoid of Reinke crystals.

**ICD-O code**
Gonadoblastoma 9073/1

**Epidemiology**
Gonadoblastomas typically are identified in children or young adults with one-third of the tumours being detected before the age of 15.

**Aetiology**
Gonadoblastomas are frequently associated with abnormalities in the secondary sex organs. In over 90% of the cases of gonadoblastoma a Y chromosome was detected.

**Localization**
Gonadoblastoma is found more often in the right gonad than in the left and is bilateral in 38% of cases. Recent reports suggest an even higher frequency of bilateral involvement.

**Clinical features**
_Signs and symptoms_
The usual patient with a gonadoblastoma is a phenotypic female who is frequently virilized. A minority may present as phenotypic males with varying degrees of feminization.

The clinical presentation of a patient with a gonadoblastoma can vary considerably depending upon whether or not a tumour mass is present, on the nature of the underlying abnormal gonads, on the development of secondary sex organs and the occasional secretion of steroid hormones. A patient with pure gonadal dysgenesis may present with a failure to develop secondary sex organs and characteristics at puberty but has a normal height, and other congenital anomalies are absent. Those with Turner syndrome have sexual immaturity, a height of less than 150 cm and one or more congenital anomalies including neonatal lymphedema, web neck, prognathism, shield-shaped chest, widely spaced nipples, cubitus valgus, congenital nevi, coarctation of the aorta, renal anomalies, short fifth metacarpal bones and others. If a germ cell malignancy develops in the dysgenetic gonad, the patient may present with lower abdominal or pelvic pain.

**Macroscopy**
Pure gonadoblastoma varies from a histological lesion to 8 cm, and most tumours are small, measuring only a few cm. When a gonadoblastoma is overgrown by dysgerminoma or other neoplastic germ cell elements, much larger tumours are encountered. The macroscopic appearance of gonadoblastoma varies depending on the presence of hyalinization and calcification and on the overgrowth by other malignant germ cell elements.

**Histopathology**
Histologically, gonadoblastoma is a tumour composed of two main cell types, germ cells which are similar to those present in dysgerminoma or seminoma and sex cord derivatives resembling immature Sertoli or granulosa cells. The stroma in addition may contain collections of luteinized or Leydig-like cells devoid of Reinke crystals. The tumour is arranged in collections of cellular nests surrounded by connective tissue stroma. The nests are solid, usually small, oval or round, but occasionally may be larger or elongated. The cellular nests are composed of germ cells and sex cord deriv-
The connective tissue stroma surrounding the cellular nests may be scant or abundant and cellular, resembling ovarian stroma, or dense and hyalinized. It may contain luteinized or Leydig-like cells devoid of Reinke crystals [2598, 2849, 2850].

Three processes, hyalinization, calcification and overgrowth by a malignant germ cell element, usually dysgerminoma, may alter the basic histological appearance of gonadoblastoma. The hyalinization occurs by coalescence of the hyaline bodies and bands of hyaline material around the nests with replacement of the cellular contents. Calcification originates in the hyaline Call-Exner-like bodies and is seen histologically in more than 80% of cases [2598]. It tends to replace the hyalinized nests forming rounded, calcified concretions. Coalescence of such concretions may lead to the calcification of the whole lesion, and the presence of smooth, rounded, calcified bodies may be the only evidence that gonadoblastoma has been present. The term "burned-out gonadoblastoma" has been applied to such lesions [2598, 2849, 2850].

Gonadoblastoma is overgrown by dysgerminoma in approximately 50% of cases, and in an additional 10% another malignant germ cell element is present [2598, 2846, 2849, 2850]. Gonadoblastoma has never been observed in metastatic lesions or outside the gonads [2598, 2849, 2850]. In most cases the gonad of origin is indeterminate because it is overgrown by the tumour. When the nature of the gonad can be identified, it is usually a streak or a testis. The contralateral gonad, when identifiable, may be either a streak or a testis, and the latter is more likely to harbour a gonadoblastoma [2598, 2849, 2850]. Occasionally, gonadoblastoma may be found in otherwise normal ovaries [2077, 2598, 2849, 2850].

**Tumour spread and staging**

At the time of operation gonadoblastomas typically are bilateral, although at times they may be not macroscopically detectable in the gonad. Those that are overgrown by dysgerminoma or other malignant germ cell tumour may be much larger. If a malignant germ cell tumour develops, the potential for metastatic disease exists. Dysgerminomas typically spread by the lymphatic route, less frequently by peritoneal dissemination. Therefore, it is extremely important not only to remove both gonads but to perform surgical staging if at the time of operative consultation a malignant germ cell tumour is identified. The typical staging for a dysgerminoma or other malignant germ cell tumour includes pelvic and para-aortic lymph node sampling as well as peritoneal washings if no ascites is present [2586].

The operation should include omentectomy, and multiple peritoneal samplings are required. For patients with spread of a malignant germ cell tumour other than dysgerminoma, aggressive cytoreductive surgery is appropriate [2586].

**Precursor lesions**

Gonadoblastoma is almost invariably associated with an underlying gonadal disorder. When the disorder is identifiable, it is usually pure or mixed gonadal dysgenesis with a Y chromosome being detected in over 90% of the cases [2598, 2605].

**Prognosis and predictive factors**

**Clinical criteria**

Patients having gonadoblastoma without dysgerminoma or other germ cell tumour are treated by surgical excision of the gonads without additional therapy. However, if dysgerminoma and/or another malignant germ cell element is present, surgical staging and postoperative combination chemotherapy, the most popular current regimen being bleomycin, etoposide and cisplatin (BEP), are required. Other regimens include etoposide and carboplatin [2586]. Dysgerminoma is exquisitely sensitive to chemotherapy, as it was previously shown to be exquisitely responsive to radiation therapy.
Histopathological criteria
Pure gonadoblastoma may show extensive involvement of the gonad but does not behave as a malignant lesion (2598, 2849,2850). More frequently, its germ cell component gives rise to a malignant germ cell neoplasm capable of invasion and metastases. Gonadoblastoma may sometimes undergo ablation by a process of marked hyalinization and calcification. In such cases the lesion becomes innocuous, but great care must be taken to exclude the presence of viable elements, especially of germ cell lineage.

Dysgerminoma arising within gonadoblastoma tends to metastasize less frequently and at a later stage than dysgerminoma arising de novo (2598, 2849,2850). There is no satisfactory explanation for this phenomenon. The patients can be treated similarly to patients with pure dysgerminoma with a very high likelihood of complete cure.

Mixed germ cell-sex cord-stromal tumour

Definition
A neoplasm composed of intimately admixed germ cells and sex cord derivatives that has a different histological appearance from gonadoblastoma. Mixed germ cell-sex cord-stromal tumour also differs from gonadoblastoma by its occurrence in anatomically, phenotypically and genetically normal females (2844,2845,2847).

Epidemiology
Mixed germ cell-sex cord-stromal tumours usually occur in infants or children under the age of 10, but have been occasionally reported in postmenarchal women (1556,2844,2852).

Aetiology
Patients with mixed germ cell-sex cord-stromal tumour have normal gonadal development and a normal XX karyotype. The tumour is not associated with gonadal dysgenesis, and its aetiology is unknown (1556,2844,2852,3270).

Clinical features
Patients with a mixed germ cell-sex cord-stromal tumour generally present with lower abdominal pain. In almost a fourth of the cases patients have isosexual pseudoprecocity and may have vaginal bleeding and bilateral breast development (1556,2852,3270). Physical examination routinely reveals a large mass in the adnexal area or in the lower abdomen.

Macroscopy
This tumour, unlike gonadoblastoma, tends to be relatively large, measuring 7.5-18 cm and weighing 100-1,050 grams. Except for two reported cases, mixed germ cell-sex cord-stromal tumour is unilateral (1321,2849,2850). The tumour is usually round or oval and is surrounded by a smooth, grey or grey-yellow capsule. In most cases it is solid, but in some cases it may be partly cystic. The sectioned surface is grey-pink or yellow to pale brown. There is no evidence of calcification. In all cases the fallopian tube, the uterus and the external genitalia are normal.

Tumour spread and staging
Since mixed germ cell-sex cord-stromal tumours are less aggressive than gonadoblastoma and uncommonly bilateral, the routine evaluation of patients with a mixed germ cell-sex cord-stromal tumour can be less extensive. Although the tumours are often of considerable size, metastases have occurred in only two cases (124,1556). If intraoperative consultation is inconclusive, it is appropriate to limit the operation to removal of the involved gonad and to await the final pathology results before performing any definitive surgery that might impair future fertility.

Histopathology
Mixed germ cell-sex cord-stromal tumour is composed of germ cells and sex cord derivatives resembling immature Sertoli or granulosa cells intimately admixed with each other. The tumour cells form four distinctive histological patterns as follows:

1. A cord-like or trabecular pattern composed of long, narrow, ramifying cords or trabeculae that in places expand to form wider columns and larger round cellular aggregates surrounded by connective tissue stroma that varies from dense and hyalinized to loose and oedematous.
2. A tubular pattern composed of solid tubules surrounded by fine connective tissue septa and containing peripherally located smaller epithelial-like sex cord derivatives surrounding large, round germ cells with clear or slightly granular cytoplasm and large vesicular nuclei containing prominent nucleoli.
3. A haphazard pattern consisting of scattered collections of germ cells surrounded by sex cord derivatives, which may be very abundant.
4. A mixed pattern showing an admixture of the three above mentioned patterns without any predominance. The germ cells show mitotic activity and a close similarity to those of dysgerminoma, but in some cases they are better differentiated showing smaller nuclei and less marked mitotic activity. Unlike the
Mixed germ cell-sex cord-stromal tumours

Finding in gonadoblastoma, the sex cord derivatives also show mitotic activity [2847, 2849, 2850]. The composition of a mixed germ cell-sex cord-stromal tumour varies, and in some areas the sex cord elements may predominate, whereas in others there is a predominance of germ cells. The cystic spaces seen in some tumours resemble the cystic spaces seen in cystic and retiform Sertoli cell tumours and should not be confused with cysts and papillae seen in ovarian serous tumours, which they may resemble superficially [2849, 2850]. Although originally mixed germ cell-sex cord-stromal tumours were found to occur in pure form, it was later noted that approximately 10% of cases are associated with dysgerminoma or other malignant germ cell elements. This finding is by far less common than in gonadoblastoma.

The tumour is always found in normal ovaries, and whenever the unaffected contralateral gonad is examined, it is a normal ovary.

Genetic susceptibility
Familial clustering of these rare tumours has not been reported.

Prognosis and predictive factors
In the majority of cases the mixed germ cell-sex cord-stromal tumour occurs in pure form. Mixed germ cell-sex cord-stromal tumours are generally benign and are treated by unilateral oophorectomy. Preservation of fertility should be a priority in those patients that appear to have a unilateral mixed germ cell-sex cord-stromal tumour.

The association with other neoplastic germ cell elements is more common in postmenarchal subjects, but it may be seen in children in the first decade [2849, 2850]. One case of mixed germ cell-sex cord-stromal tumour was associated with para-aortic lymph node and abdominal metastases [1556]. Another patient developed intra-abdominal metastatic disease two years following the excision of a large ovarian tumour [124]. Both patients are well and disease free following surgery and chemotherapy. It is of interest that the tumour associated with the intra-abdominal recurrence showed an unusual histological pattern of sex cord tumour with annular tubules, but differed from the latter by the presence of numerous germ cells [124]. In those cases with metastatic disease, aggressive surgical cytoreduction is performed, and the BEP regimen is routinely used postoperatively.

Fig. 2.113 Mixed germ cell-sex cord-stromal tumour associated with dysgerminoma. The former is composed of clusters of germ cells and small sex-cord type cells in a dense fibrous stroma. Note the dysgerminoma in the right upper portion of the field.
Tumours and related lesions of the rete ovarii

**Definition**
A varied group of benign and malignant tumours and related lesions that originate from the rete ovarii, a vestigial structure present in the ovarian hilus and histologically identical to its testicular homologue.

**ICD-O codes**
- Rete ovarii adenocarcinoma 9110/3
- Rete ovarii adenoma 9110/0

**Clinical features**
Most lesions are incidental findings in postmenopausal patients. Sizeable cysts and tumours manifest as pelvic masses. Some cases may present with hormonal symptoms due to concomitant hilus cell hyperplasia or stromal luteinization in adenomas.

**Histopathology**
The rete is an unusual site for any type of pathology. In order to diagnose a lesion as originating in the rete, it must be located in the ovarian hilus and be composed of cuboidal or columnar non-ciliated cells arranged in retiform spaces. Areas of normal rete and hilus cells should be found in the vicinity of the tumour or show a transition (2495). Dilated areas and cysts are the most frequent histological finding, but a few solid proliferative lesions have been reported. The rete ovarii appears to be functionally related to folliculogenesis (385). Although its embryology is not fully understood, it is likely to be mesonephric in origin. Recently, attention has been focused on its morphology and immunophenotype in order to find histogenetic relationships with neoplasms of uncertain origin such as tumours of probable wolffian origin (682) and retiform Sertoli-Leydig cell tumours (1904), as well as to differentiate it from endometriosis (2494) and to identify new mesonephric identity markers (2110). These studies show constant coexpression of vimentin and cytokeratin and positivity for CD10 (2110), frequent positivity for calretinin, inhibin and CA125 and isolated positivity to A103 (melan-A) and epithelial membrane antigen (605,1450, 2495,2792).

**Immunoprofile**
Immunohistochemically, adenomas and adenocarcinomas are positive for CAM 5.2, cytokeratin 19, CA125, CD10 and occasionally for epithelial membrane antigen and estrogen and progesterone receptors.

**Adenocarcinoma**
Adenocarcinoma of the rete ovarii is

---

**Fig. 2.114** Carcinoma of the rete ovarii. The epithelial cells lining the papillae show marked atypia.

**Fig. 2.115** Adenoma of the rete ovarii. Note the tubulopapillary architecture.
exceptional. A bilateral tumour with a retiform tubulopapillary histology admixed with transitional-like areas has been reported [2495]. The patient initially had stage II disease, and the tumour recurred with elevated serum levels of CA125.

**Adenoma**
Adenoma of the rete ovarii typically occurs as an incidental finding in middle-aged or elderly women, is located in the hilus and is well circumscribed [2495]. It is composed of closely packed elongated tubules, some of which are dilated and contain simple papillae, and may show stromal luteinization or concomitant hilus cell hyperplasia. All reported adenomas have behaved in a benign fashion.

**Cystadenoma and cystadenofibroma**
One cystadenofibroma and two cystadenomas of the rete ovarii, one of which was bilateral, have been reported [2040]. In both instances they originated from the rete, involved only the ovarian medulla and were tubulopapillary cystic proliferations of clear columnar cells. The stroma was densely populated by luteinized cells, which caused irregular bleeding in both postmenopausal patients. The bilateral case had on one side a non-invasive adenoma but with marked cellular atypia and pleomorphism.

**Adenomatous hyperplasia**
Among the proliferative lesions, adenomatous hyperplasia of the rete ovarii is similar to the same lesion in the testis [1169]. It is differentiated from adenoma only by its poorly defined margins.

**Cysts**
Most cysts are unilocular with an average diameter of 8.7cm [2495] and a smooth inner surface. Histologically, they show serrated contours with crevice formation. Their lining consists of a single layer of cuboidal to columnar non-ciliated cells. Their walls contain tracts of smooth muscle and foci of hilus cells, which are sometimes hyperplastic and may be responsible for some hormonal manifestations [2496].

---

Fig. 2.116  A Adenomatous hyperplasia of the rete ovarii. Note the branching network of spaces. B Cyst of rete ovarii. The cyst lining has shallow infoldings.
Miscellaneous tumours and tumour-like conditions of the ovary

Definition
A group of benign and malignant ovarian tumours of diverse or uncertain origin.

ICD-O codes
- Small cell carcinoma, hypercalcaemic type 8041/3
- Small cell carcinoma, pulmonary type 8041/3
- Large cell neuroendocrine carcinoma 8013/3
- Adenoid cystic carcinoma 8200/3
- Basal cell tumour 8090/1
- Hepatoid carcinoma 8576/3
- Malignant mesothelioma 9050/3
- Gestational choriocarcinoma 9100/3
- Hydatidiform mole 9100/0
- Ovarian wolffian tumour 9110/1
- Wilms tumour 8960/3
- Paraganglioma 8693/1
- Myxoma 8840/0

Small cell carcinoma, hypercalcaemic type

Definition
An undifferentiated carcinoma that is usually associated with paraendocrine hypercalcaemia and is composed primarily of small cells.

Clinical features
This neoplasm typically occurs in young women and is associated with paraendocrine hypercalcaemia in approximately two-thirds of patients (3204). Most of the patients presented with abdominal swelling or pain related to their tumour; however, one patient had a neck exploration for presumed parathyroid disease with negative results before the ovarian tumour was discovered (3204).

Macroscopy
The tumours are usually large and predominantly solid, pale white to gray masses. Necrosis, haemorrhage and cystic degeneration are common.

Tumour spread and staging
In approximately 50% of the patients the tumour has spread beyond the ovary at the time of initial laparotomy.

Histopathology
On histological examination the tumours typically grow diffusely, but they may form small islands, trabeculae or cords. They frequently form follicle-like spaces that almost always contain eosinophilic fluid, and nuclei show easily discernible nucleoli. Foci of either benign or malignant mucinous epithelium are present in 10-15% of the cases. Typically, the cells of the tumour contain scant cytoplasm, but in approximately one-half of cases a component of large cells with abundant eosinophilic cytoplasm and nuclei containing prominent nucleoli is present.

Immunoprofile
Small cell carcinomas generally stain for epithelial membrane antigen but not for inhibin (2376). Variable staining of the neoplastic cells for vimentin, cytokeratin and epithelial membrane antigen is observed (46).

Cytometric studies
Flow cytometric studies of paraffin-embedded tissue has demonstrated that the neoplastic cells are diploid (755).

Electron microscopy
Electron microscopic examination has shown an epithelial appearance to the neoplasm consisting of small desmosomes and, in some cases, tight junctions (696). Dilated granular endoplasmic reticulum containing amorphous material is characteristically present within the cytoplasm (695,696). Few or no neurosecretory granules have been identified.

Differential diagnosis
Because of the young age of the patients and the presence of follicle-like spaces in the neoplasm, the differential diagnosis includes juvenile granulosa cell tumour.

<table>
<thead>
<tr>
<th>Small cell carcinoma, hypercalcaemic type</th>
<th>Juvenile granulosa cell tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I in 50% of cases</td>
<td>Stage I in greater than 97% of cases</td>
</tr>
<tr>
<td>Highly malignant</td>
<td>Usually non-aggressive</td>
</tr>
<tr>
<td>Hypercalcaemia in two-thirds of cases</td>
<td>Hypercalcaemia absent</td>
</tr>
<tr>
<td>Usually estrogenic</td>
<td>Usually estrogenic</td>
</tr>
<tr>
<td>Scant or non-specific stroma</td>
<td>Fibrothecomatous stroma common</td>
</tr>
<tr>
<td>Follicles often contain mucicarminophilic basophilic secretion</td>
<td>Follicles rarely contain mucicarminophilic basophilic secretion</td>
</tr>
<tr>
<td>Nuclei hyperchromatic</td>
<td>Rounded euchromatic nuclei</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
<td>Indistinct nucleoli</td>
</tr>
<tr>
<td>Mitoses frequent</td>
<td>Mitoses variable</td>
</tr>
<tr>
<td>Usually epithelial membrane antigen positive</td>
<td>Epithelial membrane antigen negative</td>
</tr>
<tr>
<td>Alpha-inhibin negative</td>
<td>Alpha-inhibin positive</td>
</tr>
</tbody>
</table>

Table 2.08
Comparison of small cell carcinoma of the hypercalcaemic type with juvenile granulosa cell tumour.
This tumour may also be confused with adult type granulosa cell tumours, malignant lymphoma and other small cell malignant neoplasms that involve the ovary (695). The absence of membrane immunoreactivity for MIC2 protein (CD99) serves to distinguish small cell carcinoma from primitive neuroectodermal tumour (see section on germ cell tumours).

**Histogenesis**
The histogenesis of small cell carcinoma has not been definitively established (755). It has been proposed that this tumour may be a variant of a surface epithelial-stromal tumour (2376). A study utilized a mouse xenograft model in which tumour fragments of small cell carcinoma were cultured in six subsequent generations of nude mice. The transplanted tumour morphology remained the same as that of primary tumour from the patient, and serum calcium levels were significantly higher in tumour-bearing mice compared to controls. By comparative genomic hybridization and electron microscopy the tumour appeared to be a distinct tumour entity, not related to either a germ cell tumour or epithelial ovarian cancer (3050).

**Genetic susceptibility**
The neoplasm has been familial in several instances. The tumour has occurred in three sisters, in two cousins and in a mother and daughter (3204). The familial tumours were all bilateral in contrast to the rarity of bilateral tumours in general.

**Prognosis and predictive factors**
In the largest series of patients approximately one-third of patients with stage IA disease were alive and free of tumour at last follow up (3204). Almost all the patients with a stage higher than IA died of disease.

---

**Small cell carcinoma, pulmonary type**

**Definition**
A small cell carcinoma resembling pulmonary small cell carcinomas of neuroendocrine type.

**Synonym**
Small cell carcinoma of neuroendocrine type.

**Clinical features**
Patients typically are postmenopausal and present with pelvic or abdominal masses.

**Macroscopy**
The tumours are typically large and solid with a cystic component.

**Histopathology**
The pulmonary type resembles small cell carcinoma of the lung and is associated with a surface epithelial-stromal tumour, most often endometrioid carcinoma (761). The neoplastic cells have nuclei with finely stippled chromat in, lack nucleoli and show molding. The cytoplasm is scant. Mitoses are numerous. The appearance varies somewhat depending on cellular preservation.

---

Fig. 2.117 Small cell carcinoma, hypercalcaemic type. The ovary is involved by a solid, knobby tumour that has extended through the capsule to the right.

Fig. 2.118 Small cell carcinoma, hypercalcaemic type. A Note the follicle-like space. B There is a diffuse proliferation of mitotically active small cells with enlarged nuclei that contain small nucleoli.
Immunoprofile
Immunohistochemical markers for neuron specific enolase are typically positive, and a minority of cases were positive for chromogranin (761).

Cytometric studies
The majority of neoplasms are aneuploid by flow cytometry (761).

Prognosis and predictive factors
The neoplasm is highly malignant, and the behaviour has been aggressive regardless of stage (761).

Large cell neuroendocrine carcinoma

Definition
A malignant tumour composed of large cells that show neuroendocrine differentiation.

Synonym
Undifferentiated carcinoma of non-small cell neuroendocrine type.

Clinical features
Two series of ovarian neuroendocrine carcinomas of non-small cell type have been reported (455,756). The patients were in the reproductive age group or beyond (mean 56 years) and presented with symptoms related to a pelvic mass in the majority of cases (756).

Histopathology
These tumours have in all the reported cases been associated with a tumour of surface epithelial-stromal type, either benign or malignant (455,542,756). The neuroendocrine component consisted of medium to large cells. Nuclei contained prominent nucleoli, and mitoses were frequent. The solid component stained for chromogranin, and neuropeptides were demonstrated in some cases.

Prognosis and predictive factors
This type of tumour appears to be highly aggressive; only the neuroendocrine carcinoma component was present in the metastatic sites (455).

Hepatoid carcinoma

Definition
A primary ovarian neoplasm that histologically resembles hepatocellular carcinoma and is positive for alpha-fetoprotein.

Epidemiology
Hepatoid carcinoma of the ovary is a rare tumour; only 12 cases have been reported (1798,2629,2951). It mainly occurs in postmenopausal women with a mean age of 59.6 years (range, 35-78 years).

Clinical features
The symptoms are not specific and are related to an ovarian mass (2629). Elevation of serum alpha-fetoprotein (AFP) is characteristic, and CA125 is elevated in most cases.

Macroscopy
Tumours vary from 4-20 cm in maximum dimension with no distinctive macroscopic features (1798,2629,2951). In some cases, formalin fixation reveals green-coloured areas suggestive of bile production (2629).

Histopathology
The tumour cells are arranged in sheets, cords and trabeculae with moderate to abundant amounts of eosinophilic cytoplasm and distinctive cell borders resembling hepatocellular carcinoma. Mitoses are generally conspicuous. PAS-positive, diastase-resistant hyaline globules and Hall stain-positive bile pigment can be seen. The presence of immunoreactive AFP and protein induced by vitamin K absence or antagonist II (PIVKA-II) shows functional differentiation toward hepatocytes (1307,2629). CA125 is positive in one-half of the tumours (2629).

Differential diagnosis
Metastatic hepatocellular carcinoma and hepatoid yolk sac tumour must be ruled out (3197).

Histogenesis
Tumours admixed with serous carcinoma and tumour cells positive for CA125 suggest an ovarian surface epithelial origin (1307,2610,2629).

Prognosis and predictive factors
Clinical outcome is poor. Seven out of 12 patients died between 4 months and 5 years (mean, 19 months) after initial diagnosis, and 2 patients had a tumour recurrence after 6-7 months (1798,2629,2951).

Tumours resembling adenoid cystic carcinoma and basal cell tumour

Definition
A group of primary ovarian tumours that histologically resemble certain tumours of the salivary glands or cutaneous basal cell carcinoma.
Clinical features
Adenoid cystic-like carcinoma presents typically as a pelvic mass or abdominal distension in postmenopausal women [758]. On the other hand, the two cases of adenoid cystic carcinoma occurred in the reproductive age group [837,3248]. Cases of basal cell carcinoma of the ovary also typically present as a pelvic mass but occur over a wide age range [758].

Histopathology
These neoplasms histologically resemble adenoid cystic carcinoma, basal cell tumours of salivary gland or cutaneous basal cell carcinoma and occur in several forms. The adenoid cystic-like carcinomas resemble adenoid cystic carcinoma of salivary gland but lack a myoepithelial component [758]. On the other hand a myoepithelial component has been demonstrated in the cases of adenoid cystic carcinoma [837,3248]. Cribriform patterns composed of uniform small cells surrounding round lumens and cysts were typical, and luminal mucin and hyaline cylinders were common to both forms. A surface epithelial-stromal component was present in the great majority of cases of adenoid cystic-like carcinoma [758] but was absent in the cases of adenoid cystic carcinoma [837,3248]. The cases of basal cell tumour consisted of aggregates of basaloid cells with peripheral palisading [758]. Several tumours of this type had foci of squamous differentiation or gland formation, and some showed an ameloblastoma-like pattern. A case of a monomorphic adenoma of salivary gland type described as a cribriform variant of basal cell adenoma has been reported [2492]. In none of the reported cases in this group was there evidence of a teratoma or other germ cell tumour.

Immunoprofile
Actin and S-100 protein stains were both positive in the two cases of adenoid cystic carcinoma [837,3248]; however, these stains were negative in the cases of adenoid cystic-like carcinoma [758].

Prognosis and predictive factors
The prognosis of adenoid cystic-like carcinoma is generally unfavourable and appears to depend on the degree of malignancy of the surface epithelial-stromal component. On the other hand, cases of basal cell tumour and adenoid cystic carcinoma have an excellent prognosis with relatively limited follow up.

Ovarian malignant mesothelioma
Definition
Ovarian malignant mesotheliomas (OMMs) are mesothelial tumours confined mostly or entirely to the ovarian surface and/or the ovarian hilus.

Aetiology
In the largest series there was no history of asbestos exposure [526].

Macroscopy
The tumours were typically solid and varied from 3-15 cm in maximum dimension. Most were bilateral.

Histopathology
The tumours usually involved both the serosa and the parenchyma of the ovary. The histological and immunohistochemical characteristics of the OMM are analogous to those observed in peritoneal mesotheliomas. The proliferating mesothelial tumour cells may invade and partly replace ovarian tissue and/or the hilar soft tissue.

Differential diagnosis
Just like diffuse peritoneal malignant mesotheliomas, OMMs can extensively involve one or both ovaries in a macroscopically and histologically carcinomatous growth pattern and may thus be confused with ovarian epithelial neoplasms. In this context immunohistochemical detection of thrombomodulin, calretinin, Ber-EP4 and cytokeratin 5/6 provide the most useful markers [2113].

Prognosis and predictive factors
In the absence of sufficient follow-up data for this rare neoplasm, OMM can be assumed to have a prognosis similar to its disseminated peritoneal analogue.

Fig. 2.120 Ovarian papillary mesothelioma. Note the papillary tumour growth on the surface and a haemorrhagic corpus luteum within the ovary.

Fig. 2.121 Papillary mesothelioma of the ovary. Well differentiated papillary fronds of tumour grow from the surface of the ovary.
Gestational choriocarcinoma

Definition
A rare tumour composed of both cytotrophoblast and syncytiotrophoblast that arises as a result of an ectopic ovarian pregnancy. No germ cell or common epithelial component is present.

Clinical features
Patients with choriocarcinoma have symptoms related to a large haemorrhagic mass that may rupture causing haematoperitoneum.

Macrosopy
Choriocarcinoma consists typically of a haemorrhagic mass.

Histopathology
The typical appearance is an admixture of syncytiotrophoblast and cytotrophoblast often arranged in a plexiform pattern (142,1317). The specimens must be sampled extensively to rule out a germ cell, or in the older age group, a surface epithelial component. They must be distinguished from rarely reported ovarian hydatidiform moles, which have hydropic chorionic villi with cistern formation and trophoblastic proliferation.

Prognosis and predictive factors
The prognosis of gestational choriocarcinoma is more favourable than that of the nongestational type. Single agent chemotherapy with methotrexate or actinomycin D is highly effective.

Hydatidiform mole

Definition
Hydatidiform mole is an ectopic ovarian molar pregnancy. Ovarian hydatidiform moles have hydropic chorionic villi with cistern formation and trophoblastic proliferation.

Clinical features
Patients with hydatidiform mole have symptoms related to large haemorrhagic masses that may rupture causing haematoperitoneum.

Macrosopy
Hydatidiform mole typically consists of a haemorrhagic mass; chorionic vesicles may be identified.

Histopathology
Hydatidiform moles show characteristic hydropic chorionic villi with cistern formation and trophoblastic proliferation (2821,3212).

Ovarian wolffian tumour

Definition
A tumour of presumptive wolffian origin characterized by a variety of epithelial patterns.

Synonyms
Ovarian tumour of probable wolffian origin, retiform wolffian tumour.

Localization
Although more common in the broad ligament, this tumour also occurs in the ovary (1262,3212).

Clinical features
Patients are in the reproductive age group or beyond and present with abdominal swelling or a mass (3212). Preoperative serum oestradiol levels may be elevated and return to normal postmenopausal levels after operation (1289).
Two of the patients were living and well but not always, show nuclear atypia and antigen, and epithelial membrane antigen these neoplasms {2926}.

Prognosis and predictive factors
These tumours typically are not aggressive; however, a significant minority of patients have had an aggressive course (3212). The malignant cases sometimes, but not always, show nuclear atypia and increased mitotic activity.

Wilms tumour

Definition
A primary ovarian neoplasm that has the typical features of a Wilms tumour of the kidney.

Epidemiology
Several cases of pure Wilms tumour of the ovary have been reported (1303,2506).

Clinical features
The tumour occurs in patients in the reproductive age group and beyond and presents as a rapidly growing adnexal mass.

Histopathology
They have the typical appearance of a Wilms tumour including small tubules, gliomeruloid structures and blastema. No teratomatous elements were identified.

Prognosis and predictive factors
Two of the patients were living and well 10 months and 7 years postoperatively.

Paraganglioma

Definition
A unique neuroendocrine neoplasm, usually encapsulated and benign, arising in specialized neural crest cells associated with autonomic ganglia (paraganglia).

Synonym
Phaeochromocytoma.

Clinical features
A single case of a paraganglioma of the ovary in a fifteen year old girl with hypertension has been reported (832). In addition two unpublished cases have been described (2605).

Histopathology
The tumours consist of polygonal epithelial cells arranged in nests separated by a fibrovascular stroma.

Immunoprofile
The tumour is positive for chromogranin. In addition, stains for S-100 protein can identify sustentacular cells (2605).

Biochemistry
Epinephrine and norepinephrine were extracted from the tumour (832).

Myxoma

Definition
A benign mesenchymal tumour composed of cells with bland nuclear features producing abundant basophilic intercellular ground substance.

Clinical features
Patients with ovarian myxomas present in the reproductive age group typically with an asymptomatic unilateral adnexal mass (757).

Macroscopy
The tumours are large, averaging 11 cm in diameter. The sectioned surface is soft, often with cystic degeneration.

Histopathology
Myxoma is a sharply demarcated tumour composed of spindle and stellate-shaped cells within an abundant, well vascularized myxoid background. Small foci of non-myxoid fibrous tissue or smooth muscle may be present. Lipoblasts are not identified. Mitoses are rare. The intercellular material stains with alcian blue and colloidal iron. Staining is prevented by pretreatment with hyaluronidase indicating that the material is hyaluronic acid.

Immunoprofile
Immunohistochemical stains show that the tumours are positive for vimentin and smooth muscle actin but negative for most other common immunohistochemical markers (567).

Electron microscopy
Ultrastructural features of thin filaments condensed into dense bodies also support the presence of myofibroblasts (567).

Histogenesis
Based on an immunohistochemical comparison with myxoid areas of ovarian stromal tumours, myxomas were considered to be a variant of the thecoma-fibroma group (3254).

Prognosis and predictive factors
The tumour is practically always benign although one case diagnosed originally as myxoma had a late recurrence after 19 years (2901). In that case the original tumour showed occasional mitotic figures (less than 1 per ten high power fields), slight atypia and occasional vacuolated cells. The recurrent neoplasm, but not the original, was aneuploid by DNA-flow cytometry (2901).

Malignant soft tissue tumours not specific to the ovary

Pure soft tissue sarcomas of somatic type rarely occur as primary tumours of the ovary. They typically present as a rapidly enlarging adnexal mass. Their histological appearance is similar to soft tissue tumours in other locations. Among the reported cases of pure sarcomas are...
fibrosarcoma [1517,1867], leiomyomatosarcoma [917,1416,1895,1983, 2037], malignant peripheral nerve sheath tumour [2797], lymphangiosarcoma, angiosarcoma [2021,2064], rhabdomyosarcoma [2018], osteosarcoma [1215] and chondrosarcoma [2851]. These tumours should be classified according to the WHO Histological Typing of Soft Tissue Tumours [3086].

Similarly, tumours may also arise as a component of a complex ovarian tumour such as malignant müllerian mixed tumour, adenosarcoma, immature teratoma or dermoid cyst or from heterologous elements in a Sertoli-Leydig cell tumour. Rare sarcomas of various types may be associated with surface epithelial stromal tumours, particularly serous, mucinous and clear cell adenocarcinoma. These tumours must be distinguished from metastatic sarcoma to the ovary [3222].

**Benign soft tissue tumours not specific to the ovary**

Of the remaining soft tissue tumours, leiomyomas and haemangiomas are most common. Occasional benign neural tumours, lipomas, lymphangiomas, chondromas, osteomas and ganglioneuromas have been reported. Their appearance is similar to soft tissue tumours in other locations. These tumours should be classified according to the World Health Organization Histological Typing of Soft Tissue Tumours [3086].

**Tumour-like conditions**

**Definition**
Non-neoplastic conditions that can mimic an ovarian neoplasm clinically, macroscopically and/or histologically.

**Luteoma of pregnancy**

**Definition**
Single or multiple nodules composed of lutein cells with abundant eosinophilic cytoplasm that are detected at the end of a term pregnancy.

**Synonym**
Nodular theca-lutein hyperplasia of pregnancy.

**Epidemiology**
Patients with luteoma of pregnancy are typically in their third or fourth decade and multiparous, and 80% are Black [2056,2364,2788].

**Clinical features**
Most patients are asymptomatic, and the tumour is usually found incidentally at term during caesarean section or postpartum tubal ligation [2788]. Exceptionally, a pelvic mass is palpable or obstructs the birth canal. Approximately 25% of patients are hirsute or show signs of virilization. Elevated levels of plasma testosterone and other androgens may be observed.

**Macroscopy**
The tumours vary from not being macroscopically detectable to over 20 cm. In one series the medium diameter of the tumour was between 6-7 cm [2056]. The sectioned surface is circumscribed, solid, fleshy and red to brown. In approximately one-half of cases the lesions are multiple and at least one-third are bilateral.

**Histopathology**
There is a diffuse proliferation of polygonal, eosinophilic cells that contain little or no lipid [2364]. The nuclei are round and contain prominent nucleoli. Follicle-like spaces may be present. Mitotic figures may be frequent. The tumour cells were found to be positive for alpha-inhibin, CD99, cytokeratin and vimentin [2242].

**Differential diagnosis**
The differential diagnosis includes lipid-poor steroid cell tumours, metastatic melanoma and corpus luteum of pregnancy. Steroid cell tumours occurring during pregnancy may present a difficult differential diagnosis; however, the typical clinical setting of luteoma of pregnancy would be an unusual presentation for a steroid cell tumour. The presence of follicle-like spaces or multiple nodules favours the diagnosis of luteoma of pregnancy. In contrast to luteoma of pregnancy, steroid cell tumours that have a high mitotic rate are likely to exhibit significant nuclear atypia. Metastatic melanoma may be multinodular and contain follicle-like spaces; however, the presence of melanin pigment in some cases and positive stains for S-100 protein and often HMB-45 and Melan A and negative stains for alpha-inhibin would confirm the diagno-

---

**Tumours of the ovary and peritoneum**

188
sis. Corpus luteum of pregnancy has a central cavity and a convoluted border. It is composed of granulosa-lutein and theca-lutein layers and contains hyaline or calcified bodies. Multinodularity of the tumour or bilateral presentation favour luteoma of pregnancy.

**Histogenesis**
Luteoma of pregnancy appears dependent on beta-human chorionic gonadotropin for its growth based on its clinical presentation at term and regression following the conclusion of the pregnancy.

**Prognosis and predictive factors**
The tumours regress after the conclusion of the pregnancy.

**Uncommon tumour-like conditions associated with pregnancy**
Many tumour-like conditions occur during or subsequent to a pregnancy including ovarian pregnancy, hyperreactio luteinalis, large solitary luteinized follicle cyst of pregnancy and puerperium [513], granulosa cell proliferations of pregnancy [524], hilus cell proliferation of pregnancy and ectopic decidua [505].

**Stromal hyperthecosis**

**Definition**
Stromal hyperthecosis consists of hyperplastic ovarian stroma containing clusters of luteinized stromal cells.

**Epidemiology**
The lesion typically occurs in women in the late reproductive years and beyond.

**Clinical features**
The patients may present with endocrine manifestations including virilization, obesity, hypertension and decreased glucose tolerance and may have elevated levels of plasma testosterone. Bilateral ovarian enlargement is typically encountered at laparotomy.

**Macrosopy**
The ovaries are typically enlarged and may measure up to 7 cm in greatest dimension [2605]. With rare exceptions, the lesion is bilateral. The sectioned surface is predominately solid and white to yellow. Multiple superficial cysts may be present in premenopausal women.

**Histopathology**
On histological examination hyperplastic stroma is present containing clusters of luteinized stromal cells. In premenopausal women the outer cortex may be thickened and fibrotic with luteinized follicle cysts as is observed in the polycystic ovary syndrome.

**Differential diagnosis**
The lesion is distinguished from the closely related condition of stromal hyperplasia by the absence of luteinized stromal cells in the latter. Polycystic ovarian disease typically occurs in younger women and is less distinctly virilizing. The ovaries are more cystic than is typically seen in stromal hyperthecosis.

**Somatic genetics**
Patients with acanthosis nigricans and masculinization (HAIR-AN syndrome) all had the histologic findings of premenopausal hyperthecosis in their ovaries [729].

**Prognosis and predictive factors**
The lesion is usually treated by oophorectomy, and the postoperative course is uneventful.

**Stromal hyperplasia**

**Definition**
A tumour-like proliferation of ovarian stromal cells without the presence of luteinized stromal cells.

**Clinical features**
Patients are typically menopausal or early postmenopausal. It is much less estrogenic or androgenic than stromal hyperthecosis, and patients may occasionally have obesity, hypertension or abnormal glucose metabolism [2605].

**Macrosopy**
Ill-defined white or pale yellow nodules that sometimes coalesce are present in the cortical or medullary regions of the ovary or both. In extensive cases the ovaries may be enlarged, and the architecture replaced.

**Histopathology**
The medullary and to a lesser extent the cortical regions are replaced by a nodular or diffuse densely cellular proliferation of small stromal cells with scanty amounts of collagen. In advanced cases the ovarian architecture is completely replaced and follicle derivatives are not observed.

---

**Fig. 2.125** Stromal hyperthecosis. A The ovaries are enlarged and solid with a smooth external surface and have a multilobulated sectioned surface with a few follicle cysts. B Note the clusters of luteinized stromal cells within hyperplastic ovarian stroma.

Miscellaneous tumours and tumour-like conditions of the ovary 189
Differential diagnosis
Stromal hyperplasia is distinguished from stromal hyperthecosis by the absence of luteinized stromal cells. It is distinguished from low grade endometrial stromal sarcoma by the presence of spindle shaped rather than round or oval stromal cells and the absence of mitotic figures or spiral arterioles.

Fibromatosis
Definition
Fibromatosis is a tumour-like enlargement of one or both ovaries due to a non-neoplastic proliferation of collagen-producing ovarian stroma.

Clinical features
The patients range from 13-39 years with an average of 25. The typical presentation is menstrual irregularities, amenorrhea or rarely, virilization [3214].

Macroscopy
The ovaries range from 8-14 cm and have smooth or lobulated external surfaces. The sectioned surface is typically firm and grey or white, and small cysts may be apparent. About 80% of cases are bilateral.

Histopathology
There is a proliferation of spindle-shaped fibroblasts with a variable but usually large amount of collagen. Foci of luteinized stromal cells as well as oedema may be present. Ovarian architecture is maintained, and the fibrous proliferation surrounds follicle derivatives. Nests of sex cord type cells are present in some cases [384]. Most cases show diffuse involvement of the ovaries, but occasional cases are localized.

Differential diagnosis
The lesion is distinguished from fibroma in that the latter is usually unilateral and does not incorporate follicular derivatives. However, it differs from ovarian oedema in that oedema in the latter is massive and fibrous proliferation is not observed. It differs from stromal hyperplasia in that the latter does not produce abundant collagen and is usually unilateral. The sex cord type nests may superficially resemble a Brenner tumour, but the latter shows transitional cell features and replaces the ovarian architecture.

Prognosis and predictive factors
The lesion does not spread beyond the ovaries.

Massive ovarian oedema
Definition
Formation of a tumour-like enlargement of one or both ovaries by oedema fluid.

Epidemiology
The age range is 6-33 with an average of 21 years [3214].

Clinical features
Most patients present with abdominal pain, which may be acute, and a pelvic mass. [3214]. Others may present with abnormal uterine bleeding, hirsutism or virilization. Elevated levels of plasma testosterone and other androgens may be observed. At laparotomy ovarian enlargement, which is usually unilateral, is encountered, and torsion is observed in approximately one-half of the patients.

Macroscopy
The external surface is usually white and opaque. The ovaries range from 5-35 cm in size with an average diameter of 11 cm [3214]. The sectioned surface typically exudes watery fluid.

Histopathology
On histological examination oedematous, hypocellular ovarian stroma is present, and the ovarian architecture is preserved. The outer cortex is thickened and fibrotic. Clusters of luteinized stromal cells are present in the oedematous stroma in a minority of cases, especially those that have endocrine symptoms.

Differential diagnosis
The differential diagnosis includes an oedematous fibroma and Krukenberg tumour. The diffuse nature of the process and the preservation of ovarian architecture are unlike an oedematous fibroma, which is likely to be a circumscribed mass. The distinction from Krukenberg tumour is based on the absence of signet-ring cells and the typically unilateral mass, whereas Krukenberg tumours are bilateral in the vast majority of cases. It is important for the pathologist to recognize this lesion at the time of intraoperative consultation so that fertility may be maintained in these young patients.

Histogenesis
In many cases the oedema is due to partial torsion of the ovary insufficient to cause necrosis [1390,2463].

Prognosis and predictive factors
The lesion is usually treated by oophorectomy, and the postoperative course is uneventful.

Other tumour-like conditions
A wide variety of other conditions can, on occasion, mimic an ovarian neoplasm. Those not associated with pregnancy include follicle cyst, corpus luteum cyst, ovarian remnant syndrome, polycystic ovarian disease, hilus cell hyperplasia, simple cyst, idiopathic calcification, uterus-like adnexal mass [48], spenic-gonadal fusion, endometriosis and a variety of infections.
Lymphomas and leukaemias

Malignant lymphoma

Definition
A malignant lymphoproliferative neoplasm that may be primary or secondary.

Epidemiology
Although unusual, ovarian involvement is more frequent than that of other sites in the female genital tract [1588]. The peak incidence of ovarian involvement by lymphoma is in the fourth and fifth decades, although it may occur at any age. Ovarian involvement by lymphoma may either be primary or secondary; however, the latter is much more common.

Clinical features
Lymphoma rarely presents clinically as an ovarian mass, and in most cases it is only one component of an intra-abdominal or generalized lymphoma [483]. An exception is Burkitt lymphoma, which may account for about one-half of the cases of malignant ovarian neoplasms in childhood in endemic areas [2605]. In such cases involvement of one or both ovaries is second in frequency only to jaw involvement.

Macroscopy
Lymphoma is bilateral in approximately one-half of the cases. The tumours are large and typically have an intact capsule. The sectioned surfaces are typically white, tan or grey-pink and occasionally contain foci of haemorrhage or necrosis.

Tumour spread and staging
Ovarian involvement by lymphoma is rare and is associated with simultaneous involvement of the ipsilateral tube in 25% of the cases [2119].

Histopathology
The histological appearance of ovarian lymphomas is similar to that observed at other sites; however, the neoplastic cells tend to proliferate in cords, islands and trabeculae with occasional follicle-like spaces or alveoli and often have a sclerotic stroma [2605]. In some cases ovarian follicular structures may be spared, but in others the entire ovarian architecture is obliterated. Almost any type of lymphoma may occur in the ovary; however, the most common are diffuse large B-cell, Burkitt and follicular lymphomas [1900,2119].

Differential diagnosis
Dysgerminoma is the most important and perhaps the most difficult differential diagnosis of ovarian lymphoma, particularly of the large B-cell type, which it may mimic both macroscopically and histologically [2605,3226]. Careful attention to the appearance of the cell nuclei and immunohistochemical stains for lymphoid markers and placental-like alkaline phosphatase are important in reaching the correct diagnosis. Other tumours that may be confused with lymphoma include granulocytic sarcoma, undifferentiated carcinoma, small carcinoma of the hypercalcaemic type and metastatic breast carcinoma [2605,3226].

Prognosis and predictive factors
Almost one-half (47%) of the patients with lymphoma who presented with ovarian involvement were alive at their last follow-up with a median survival of 5 years [1900].

Leukaemia

Definition
A malignant haematopoetic neoplasm that may be primary or secondary.

Epidemiology
Ovarian involvement by leukaemia may either be primary or secondary; however, the latter is much more common [428]. A series of primary granulocytic sarcomas of the female genital tract including 7 cases of the ovary was reported [2099].

Fig. 2.128 Diffuse large B-cell lymphoma of ovary. A Intermediate-power magnification shows a diffuse growth pattern. Nuclei are medium-sized to large and polymorphic. B Immunohistochemical stain is positive for CD20.
Clinical features
Rarely, a patient presents with an ovarian granulocytic sarcoma with or without haematological evidence of acute myeloid leukaemia (2099). Cases of acute lymphoblastic leukaemia, mostly in children and teenagers, are known to recur in the ovaries during haematological remission.

Macroscopy
The ovarian tumours are usually large and may be either unilateral or bilateral. They are typically solid, soft, and white, yellow or red-brown; occasionally, they may be green, and such tumours have been designated as a “chloroma” (2605).

Histopathology
Granulocytic sarcomas have a predominantly diffuse growth pattern, but sometimes a cord-like or pseudoacinar arrangement of the tumour cells is present focally (2099). They are usually composed of cells with finely dispersed nuclear chromatin and abundant cytoplasm that may be deeply eosinophilic. The identification of eosinophilic myelocytes is helpful in establishing the diagnosis; however, they are not always present.

Differential diagnosis
The most important differential diagnosis is malignant lymphoma. Histochemical stains for chloracetate esterase or immunohistochemical stains for myeloperoxidase, CD68 and CD43 will establish the diagnosis in almost all cases (2099).

Plasmacytoma

Definition
A clonal proliferation of plasma cells that is cytologically and immunophenotypically identical to plasma cell myeloma but manifests a localized growth pattern.

Histopathology
The tumour cells may be mature or immature. The mature type has eccentric nuclei with clumped chromatin, low nuclear to cytoplasmic ratios, abundant cytoplasm and a prominent perinuclear hof. The immature form is pleomorphic with frequent multinucleated cells.

Clinical findings
Ovarian plasmacytoma is a rare tumour that may present clinically with a unilateral adnexal mass. The 7 reported patients were 12–63 years old (782).

Macroscopy
The tumours were large, and the sectioned surface was white, pale yellow or grey.

Prognosis and predictive factors
One patient developed multiple myeloma 2 years after removal of the tumour.
Secondary tumours of the ovary

Definition
Malignant tumours that metastasize to the ovary from extraovarian primary neoplasms. Tumours that extend to the ovary directly from adjacent organs or tissues are also included in this category. However, most ovarian carcinomas associated with uterine cancers of similar histological type are independent primary neoplasms. General features of ovarian metastasis include: bilaterality, small multinodular surface tumours, extensive extraovarian spread, unusual patterns of dissemination, unusual histological features, blood vessel and lymphatic invasion and a desmoplastic reaction.

Synonym
Metastatic tumours.
The term Krukenberg tumour refers to a metastatic mucinous/signet-ring cell adenocarcinoma of the ovaries which typically originates from primary tumours of the G.I. tract, most often colon and stomach.

Epidemiology
Metastatic tumours to the ovary are common and occur in approximately 30% of women dying of cancer. Approximately 6-7% of all adnexal masses found during physical examination are actually metastatic ovarian tumours, frequently unsuspected by gynaecologists (1587, 2605, 2980). The metastasis often masquerades as a primary ovarian tumour and may even be the initial manifestation of the patient’s cancer. Pathologists also tend to mistake metastatic tumours for primary ovarian neoplasms even after histological examination. Carcinomas of the colon, stomach, breast and endometrium as well as lymphomas and leukaemias account for the vast majority of cases (3226). Ovarian metastases are associated with breast cancer in 32-38% of cases, with colorectal cancer in 28-35% of cases and with tumours of the genital tract (endometrium, uterine cervix, vagina, vulva) in 16% of cases. In recent years attention has been drawn to mucinous tumours of the appendix, pancreas and biliary tract that often spread to the ovary and closely simulate ovarian mucinous borderline tumours or carcinomas (590, 1848, 2406, 3199, 3200).

Aetiology
The routes of tumour spread to the ovary are variable. Lymphatic and haematogenous metastasis to the ovaries is the most common form of dissemination (1587, 2605, 2980). Direct extension is also a common manner of spread from adjacent tumours of the fallopian tube, uterus and colorectum (3226). Transtubal spread provides an explanation for some surface ovarian implants from uterine cancers. Neoplasms may also reach the ovary by the transperitoneal route from abdominal organs, such as the appendix (3199). Embolic spread often produces multiple nodules within the substance of the ovary and commonly is accompanied by prominent intravascular nests of tumour in the ovarian hilum, mesovarium and mesosalpinx.

Clinical features
Signs and symptoms
Ovarian metastases can be discovered in patients during follow-up after treatment of a primary tumour, serendipitously diagnosed during a surgical procedure for treatment of an abdominal tumour or fortuitously found at autopsy. The circumstances leading to the discovery of these metastatic lesions depends on the site of the primary tumour (951, 1802). Ovarian metastasis was detected before the breast cancer in only 1.5% of cases

Table 2.08
Metastatic tumours to the ovary.

<table>
<thead>
<tr>
<th>Clues to the diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - Bilaterality (mucinous and endometrioid-like)</td>
</tr>
<tr>
<td>2 - Small, superficial, multinodular tumours</td>
</tr>
<tr>
<td>3 - Vascular invasion</td>
</tr>
<tr>
<td>4 - Desmoplastic reaction</td>
</tr>
<tr>
<td>5 - Extensive, unusual extraovarian spread</td>
</tr>
<tr>
<td>6 - Unusual clinical history</td>
</tr>
</tbody>
</table>

Fig. 2.130 Metastatic colonic adenocarcinoma of the ovaries. A The ovaries are replaced by bilateral, multinodular metastases. Note the additional leiomyomas of the corpus uteri (centre). B This tumour shows a garland-like glandular pattern with focal segmental necrosis of glands and luminal necrotic debris. C Immunohistochemical stain for carcinoembryonic antigen is strongly positive.
In patients with a gastrointestinal cancer, the ovarian malignant growth was discovered before, or more frequently, at the same time as the gastrointestinal primary (2232). In 35% of patients with a Krukenberg tumour, the diagnosis of the digestive primary preceded the diagnosis of the ovarian metastasis (1933,2545). When a patient presents with abdominopelvic symptoms leading to suspicion of an ovarian tumour, the symptoms are non-specific and similar to those of ovarian cancer, i.e. pelvic masses, ascites or bleeding (1598,2545). Eighty percent of patients with a Krukenberg tumour had bilateral ovarian metastases, and 73% of patients with ovarian metastases from breast carcinoma had extraovarian metastases (951,2545).

Imaging
Several studies have evaluated radiological findings in patients with a Krukenberg tumour (1094,1460). When imaging features were compared, patients with a Krukenberg tumour more frequently had a solid mass with an intratumour cyst, whereas primary ovarian growths were predominantly cystic (1460). Magnetic resonance (MR) imaging seems to be more specific than computed tomography scan. Identification of hypointense solid components in an ovarian mass on T2-weighted MR images seems to be characteristic of a Krukenberg lesion, but this aspect is not specific (1094).

Macroscopy
Ovarian metastases are bilateral tumours in approximately 70% of cases (2605). They grow as superficial or parenchymatous solid nodules or, not uncommonly, as cysts. The size of ovarian metastases is variable even from one side to the other. The ovaries may be only slightly enlarged or measure 10 cm or more.

Site of origin
The frequencies of various sites of origin of secondary ovarian tumours differ among different countries according to the incidence of various cancers therein. Colonic adenocarcinoma probably accounts for most metastatic ovarian tumours that cause errors in diagnosis (1587,2605,3226). Frequently, the ovarian metastases and the primary tumour are discovered synchronously, or the intestinal tumour has been resected months or years previously.
Occasionally, the colonic adenocarcinoma is found several months to years after resection of the ovarian metastases. Rectal or sigmoid colon cancer accounts for 75% of the metastatic colon tumours to the ovary \[1587,2605,3226\]. The primary tumour can also be located in the pancreas, biliary tract or the appendix \[590,1648,2406,3199,3200\]. The Krukenberg tumour is almost always secondary to a gastric carcinoma but may occasionally originate in the intestine, appendix, breast or other sites \[367,2605,3226\]. Rarely, breast cancer metastatic to the ovary presents clinically as an ovarian mass. A much higher percentage of cases of lobular carcinoma of the breast, including those of signet-ring cell type, metastasizes to the ovary than does ductal carcinoma \[1142\]. A wide variety of other tumours may metastasize to the ovary.

**Histopathology**

The identification of surface implants, multinodularity and intravascular tumour emboli are extremely helpful histological clues in the recognition of secondary ovarian tumours that spread through the abdominal cavity and tubal lumen. The histological appearance of the metastases is variable, depending on the nature of the primary tumour.

**Differential diagnosis**

Sometimes, metastases resemble primary ovarian tumours \[2605,2980,3226\]. Metastatic colonic adenocarcinoma to the ovary may be confused with primary endometroid or mucinous carcinoma depending on whether the colonic carcinoma is predominantly mucinous or non-mucinous. Features that help to distinguish colon cancer from endometroid carcinoma include luminal necrotic debris, focal segmental necrosis of the glands, occasional presence of goblet cells and the absence of müllerian features (squamous differentiation, an adenofibromatous component or association with endometriosis). Also the nuclei lining the glands of metastatic colon carcinoma exhibit a higher degree of atypia than those of endometroid carcinoma.

Metastatic tumours may also closely resemble primary mucinous ovarian tumours. The former may be moderately differentiated or so well differentiated that they can be mistaken for mucinous borderline or less often benign ovarian tumours. Metastatic mucinous tumours to the ovary can originate in the large intestine, pancreas, biliary tract or the appendix. Features supportive of the diagnosis of a metastasis include bilaterality, histological surface involvement by epithelial cells (surface implants), irregular infiltrative growth with desmoplasia, single cell invasion, signet-ring cells, vascular invasion, coexistence of benign-appearing mucinous areas with foci showing a high mitotic rate and nuclear hyperchromasia and histological surface mucin \[1614\]. Immunostains for cytokeratin 7 and 20 should be used with caution and along with thorough consideration of all clinical information keeping in mind that no tumour shows absolute consistency in its staining with these markers \[2183\]. Krukenberg tumours must be distinguished from primary and other metastatic ovarian tumours including clear cell adenocarcinoma, mucinous (goblet cell) carcinoid and a variety of ovarian tumours that contain signet-ring-like cells filled with non-mucinous material. Ovarian clear cell adenocarcinoma may have a signet-ring cell component that simulates a Krukenberg tumour; however, the identification of a characteristic tubulocystic pattern, hobnail cells, stromal hyalinization and eosinophilic secretion are helpful in establishing the diagnosis. Mucinous carcinoid, either primary or metastatic, may contain large areas of signet-ring cells; however, teratomatous elements other than carcinoid are usually present in the former. The tubular variant of Krukenberg tumour, sometimes associated with stro-
mal luteinization, can be confused with a Sertoli-Leydig cell tumour. Positive mucicarmine and PAS-stains with diastase digestion are of great value in establishing the diagnosis of a Krukenberg tumour. Occasional Krukenberg tumours may closely resemble fibromas on macroscopic examination and may contain relatively few signet-ring cells. Bilaterality and positive mucin stains facilitate the differential diagnosis.

Distinction between a transitional cell carcinoma of the urinary tract metastatic to the ovary and a primary transitional cell carcinoma may be difficult (2100,3220). Clinical information may be necessary to resolve the issue. Renal cell carcinoma rarely metastasizes to the ovaries; however, when it does, it must be distinguished from a primary clear cell carcinoma. The metastatic tumour usually shows a sinusoidal vascular pattern, a homogenous clear cell pattern without hobnail cells, the absence of hyalinized papillae and the absence of mucin (3226).

A metastatic carcinoid can be confused with a primary carcinoid, granulosa cell tumour, Sertoli-Leydig cell tumour, Brenner tumour, adenofibroma or endometrioid carcinoma (2605,3226). Bilaterality and extraovarian extension are important features of metastatic carcinoid.

In the ovary, metastatic malignant melanoma may be confused with primary malignant melanoma; the latter is unilateral and usually associated with a dermoid cyst. When a melanoma is composed predominantly of large cells, it may resemble steroid cell lesions such as steroid cell tumour or luteoma of pregnancy; when it is composed predominantly of small cells it may be confused with a variety of other tumours characterized by small cells (3223). Positive stains for melanin, S-100 protein, melan A, and/or HMB-45 should establish the diagnosis of melanoma. Sarcomas may metastasize to the ovary from the uterus or extragenital sites and may occasionally be discovered before the primary tumour (3222). Metastastic low grade endometrial stromal sarcoma (ESS) may simulate a primary ovarian sex cord-stromal tumour. Features helpful in their distinction include the presence of extraovarian disease, bilaterality and the characteristic content of spiral arterioles in metastatic low grade ESS. Metastatic epithelioid leiomyosarcoma may have an appearance that simulates the solid tubular pattern of a Sertoli cell tumour.

Although lymphoma and leukaemia can involve the ovaries simulating various primary tumours, they rarely present clinically as an ovarian mass. In countries where Burkitt lymphoma is endemic, however, it accounts for approximately half the cases of malignant ovarian tumours in childhood. Dysgerminoma is one of the most common and difficult differential diagnoses. The appearance of the cell nuclei is very important. Immunohistochemistry for lymphoid markers and placental alkaline phosphatase are helpful. Carcinoid, granulosa cell tumour or small cell carcinoma can also resemble lymphoma. In patients with acute myeloid leukaemia, ovarian involvement in the form of granulocytic sarcoma ("chloroma") may rarely constitute the initial clinical presentation of the disease. Histological examination reveals a diffuse growth pattern with a prominent "single file" arrangement of the tumour cells. Myeloid differentiation can be demonstrated by the chloroacetate esterase stain. Immunoperoxidase stains for lysozyme, CD68, and LCA are also helpful.

Recognition of the secondary nature of an ovarian tumour depends on a complete clinical history, a careful operative search for a primary extraovarian tumour, and accurate evaluation of the macroscopic and histological features of the ovarian tumour. In rare cases the primary tumour is not found until several years after resection of the ovarian metastases (2605,3226).

**Prognosis and predictive factors**

Ovarian metastases often represent a late disseminated stage of the disease in which other haematogenous metastases are also found. The prognosis is, therefore, poor.
Peritoneal tumours

Definition
Rare neoplasms with primary manifestation in the abdominal cavity in the absence of a visceral site of origin. Both malignant and benign tumours may occur.

ICD-O code
- Peritoneal mesothelioma: 9050/3
- Multicystic mesothelioma: 9055/1
- Adenomatoid tumour: 9054/0
- Desmoplastic small round cell tumour: 8806/3
- Primary peritoneal carcinoma: 8461/3
- Primary peritoneal borderline tumour: 8463/1

Clinical features
Signs and symptoms
Patients with malignant peritoneal tumours typically present with non-specific manifestations including abdominal discomfort and distension, digestive disturbances and ascites. Less frequently, a palpable mass or pelvic pain may be evident. Benign peritoneal tumours are usually asymptomatic.

Tumour spread and staging
Malignant peritoneal tumours spread primarily by exfoliation of cancer cells from the primary site of origin. Lymphatic and haematogenous dissemination also commonly occurs. However, some tumours have been shown to arise from separate intra-abdominal sites and are believed to have a multifocal origin. The staging involves a combination of radiological and operative findings, but these tumours do not have individual staging systems given their relative infrequency. Most malignant tumours are confined to the abdominal cavity at initial presentation. Benign peritoneal tumours do not metastasize and present as an isolated lesion, often detected at the time of operation for another indication.

Mesothelial tumours
Definition
Benign or malignant mesothelial tumours that arise within the peritoneum.

Peritoneal malignant mesothelioma
Definition
Malignant mesothelial tumours that arise within the peritoneum. Epithelial mesotheliomas may be divided into diffuse, well differentiated papillary and deciduoid types. A less common variant is the sarcomatous mesothelioma, which includes the desmoplastic type.

Epidemiology
Age and sex distribution
Patients with diffuse mesotheliomas are on average 50 years old, and those with well differentiated papillary tumours are 58.

Incidence and mortality
Primary neoplasms of the peritoneum are rare compared to the wide variety of benign and malignant peritoneal müllerian proliferations that women develop. Two clinically benign to low grade proliferations, multicystic mesothelioma and well differentiated papillary mesothelioma are more common than diffuse malignant mesothelioma, and the latter is vastly less common than primary or secondary extraovarian serous carcinoma.

Aetiology
Well differentiated papillary, diffuse epithelial and deciduoid mesotheliomas appear clinically related to asbestos exposure in some cases.

Clinical features
The most common presenting features are ascites and abdominal pain.

Macroscopy
The tumour typically consists of multiple nodules measuring <1.5 cm in greatest

Fig. 2.138 Well differentiated papillary mesothelioma of the peritoneum. A Note the distinct papillary architecture of this peritoneal tumour. B Papillae with fibrous connective tissue cores are lined by a single layer of uniform mesothelial cells.
Tumours of the ovary and peritoneum

Dimension (1443). The serosal surfaces have an appearance indistinguishable from the more common peritoneal carcinomatosis or extraovarian carcinoma.

Histopathology
Well differentiated papillary and diffuse malignant mesotheliomas are the most common types. Diffuse and well differentiated papillary mesotheliomas typically are composed of characteristic uniform cells with abundant eosinophilic cytoplasm. Another variant of epithelial mesothelioma is the deciduoid type that simulates an exuberant ectopic decidual reaction (2633). Sarcomatous mesotheliomas, including the desmoplastic type, also occur but are relatively less common than in the pleura (493).

All well differentiated papillary mesotheliomas have, at least focally, a conspicuous well-developed papillary architecture or a tubulopapillary pattern. A single layer of uniform, cuboidal or flattened mesothelial cells with bland nuclear features lines the papillae and tubules. Mitoses are rare. Occasionally, mild cytological atypia is present. Extensive fibrosis associated with irregularity of the glandular elements is common, and such areas may be confused with invasive foci of malignant mesothelioma or adenocarcinoma. Psammoma bodies are present in some cases.

Differential diagnosis
The most reliable indicator of malignancy in these tumours is invasion of fat or of organ walls; however, in small biopsies invasion may be difficult to assess (493). In the peritoneal cavity entrapment of benign cells in organizing granulation tissue or between fat lobules is frequent and confusing (493). Diffuse peritoneal malignant mesothelioma may macroscopically and histologically show a carcinomatous growth pattern and may be confused with primary peritoneal serous papillary neoplasms. In this context immunohistochemical detection of calretinin in the nuclei and Ber-EP4 were the most useful markers, whereas other mesothelial markers had too low a sensitivity for practical use (2113). Well differentiated papillary mesothelioma lacks the stratification, complex papillae and the mixed cell population of low grade serous neoplasms. Similarly, it lacks the cytological atypia of diffuse malignant mesothelioma and in some instances is localized within the peritoneum. The absence of a history of a prior operation or reactive changes elsewhere and the formation of convincing papillae distinguish well differentiated papillary mesothelioma from mesothelial hyperplasia.

Prognosis and predictive factors
The diffuse epithelial mesotheliomas are typically highly aggressive; however, unlike pleural mesotheliomas, a sizeable number of tumours are relatively indolent (1443). No morphological features were found to separate the favourable and unfavourable group of these tumours. The well differentiated papillary type is often localized and has a relatively favourable outcome (383,1027) compared to the diffuse peritoneal type.

Multicystic mesothelioma

Definition
A multiloculated cystic mesothelial tumour that typically has an indolent course. In a few instances multiple recurrences occur, and the disease may progress to diffuse malignant mesothelioma (1039).

Synonym
Multilocular peritoneal inclusion cyst.

Epidemiology
The tumour most frequently occurs in young to middle aged women.

Clinical findings
Patients typically present with an abdominal or pelvic mass associated with chronic pain. Occasional tumours are found incidentally at laparotomy.

Aetiology
An association with asbestos exposure has not been reported.

Macrosopy
Typically, the lesion is a large multicystic mass that may be solitary but is more commonly either diffuse or multifocal and consists of multiple, translucent, grape-like clusters of fluid filled cysts delimited by fibrous bands. The individual cysts are usually less than 1.0 cm in diameter but may be up to 20 cm.

Tumour spread and staging
The tumour affects chiefly the pelvic peritoneum, particularly the cul-de-sac, uterus and rectum, and there may be an

Fig. 2.139 Multicystic peritoneal mesothelioma. A Note the multiple cysts lined by mesothelial cells within a fibrous stroma. B Irregular cysts are lined by a single layer of cuboidal mesothelial cells.
abdominal or retroperitoneal component. It grows along the serosa as multiple translucent, fluid-filled cysts. Occasionally, the cysts are solitary or form a free floating mass.

**Histopathology**

The tumour is made up of multiple cysts lined by one to several layers of flattened or cuboidal mesothelial cells embedded in a delicate fibrovascular stroma [3087]. The lesions typically do not have atypia or significant mitotic activity; however, the occasional presence of cytological atypia may lead to a misdiagnosis of malignancy. Hobnail-shaped cells, foci of mesothelial hyperplasia and, less frequently, squamous metaplasia may be seen. Fibrous septa are usually prominent and may occasionally produce foci with the appearance of an adenomatoid tumour. The stroma may show marked inflammatory change that make it difficult to recognize the nature of the lesion.

**Differential diagnosis**

The chief differential diagnostic consideration is malignant mesothelioma. Attention to the macroscopic appearance, i.e. multiple cysts rather than solid plaque-like necrotic masses and the usual absence of cytological atypia are sufficient to avoid the error in most cases. Cystic lymphangioma may mimic a multicystic peritoneal mesothelioma, but the cells lining the former do not express keratin.

**Histogenesis**

The majority of investigators consider this entity to be an unusual type of mesothelial neoplasm that has a tendency to recur locally and may rarely transform into a conventional mesothelioma [1039,3087]. Some investigators, however, consider the lesion to be a non-neoplastic reactive mesothelial proliferation [2456]. A case termed cystic adenomatoid mesothelioma showed a transition from a uterine adenomatoid tumour and is illustrated above.

**Prognosis and predictive factors**

These tumours have an indolent course, but approximately one-half of cases recur at intervals ranging from 1-27 years [1410,2456]. There are rare instances of multiple recurrences and of transformation into a conventional malignant mesothelioma [1039,3087]. In the largest series 8% of patients with adequate follow up died of tumour [3087].

**Adenomatoid tumour**

**Definition**

A benign tumour of the peritoneum originating from mesothelium and forming gland-like structures.

**Synonym**

Benign mesothelioma.

**Epidemiology**

Peritoneal origin of this neoplasm is very rare [571].

**Macroscopy**

Lesions are usually solitary, less than 2 cm in diameter and have a white-grey appearance.

**Histopathology**

Histologically, multiple, small, slit-like or ovoid spaces are lined by a single layer of low cuboidal or flattened epithelial-like cells. Although adenomatoid tumours can be confused with carcinomas, nuclear atypia is absent or minimal, and mitotic figures are infrequent. Notably, adenomatoid tumours have no significant intracellular mucin, as might be found in neoplasms of müllerian origin. Clinically, they are asymptomatic, and
rarely, if ever, do they recur after adequate excision (506).

**Smooth muscle tumour**

**Leiomyomatosis peritonealis disseminata**

**Definition**
A benign entity in which numerous small nodules composed of smooth muscle are present in the peritoneal cavity.

**Synonym**
Diffuse peritoneal leiomyomatosis.

**Epidemiology**
This condition is rare and occurs in women predominantly in their late reproductive years.

**Clinical findings**
With few exceptions the patients are asymptomatic. The tumours are found incidentally at the time of laparotomy for a leiomyomatous uterus or during caesarean section. At the time of operation the surgeon is likely to be alarmed since this entity may be macroscopically indistinguishable from diffuse carcinomatosis of the peritoneum. Intraoperative consultation is required to establish the diagnosis.

**Macroscopy**
The tumour typically consists of numerous small, grey-white nodules.

**Histopathology**
The tumours consist of multiple nodules of well differentiated smooth muscle arranged in an intersecting pattern. Cases may occur in conjunction with endometriosis or multicystic mesothelioma, and a single case was associated with both conditions (3268).

**Prognosis and predictive factors**
The tumours may regress spontaneously, and conservative management is appropriate.

**Tumour of uncertain origin**

**Desmoplastic small round cell tumour**

**Definition**
A malignant peritoneal tumour of uncertain origin that shows divergent differentiation and is typically composed of nodules of small cells surrounded by a prominent desmoplastic stroma.

**ICD-O code**
8806/3

**Epidemiology**
Desmoplastic small cell tumour (DSRCT) is an extremely rare malignancy that has a strong male predilection and occurs most commonly in adolescents and young adults (mean age 19 years) (984).

**Histopathology**
Histologically, DSRCT consists of sharply circumscribed aggregates of small epithelioid cells separated by fibrous stroma. The tumour cells typically are uniform with scanty cytoplasm, have indistinct cell borders, and small to medium-sized, round, oval or spindle-shaped hyperchromatic nuclei. Mitotic figures are numerous. Immunohistochemistry indicates simultaneous divergent expression within the tumour including reactivity for epithelial (keratin, epithelial membrane antigen), neural (neuron-specific enolase) and muscle/mesenchymal (desmin) markers (984).

**Histogenesis**
These tumours are malignant neoplasms of uncertain histogenesis. Their location primarily in the peritoneum suggests a possible histogenetic relationship with mesothelium. The distinctive immunophenotype suggests multilineage (984,1038).

**Somatic genetics**
DSRCT has a characteristic reciprocal chromosome translocation t(11;22)(p13;q12) which results in the fusion of the Ewing tumour (EWS) gene and the Wilms tumour (WT1) gene (900,903). The resultant chimeric EWS-WT1 transcript produces a tumour-specific fusion protein that turns the WT1 tumour suppressor gene into a dominant oncogene (2340). As a result, cytogenetic analysis can be helpful in excluding the diagnosis of other round cell tumours.

**Genetic susceptibility**
No familial clustering has been described.

**Prognosis and predictive factors**

**Clinical criteria**
Multimodality therapy with induction chemotherapy, aggressive surgical debulking and external beam radiotherapy is advocated for the initial treatment of DSRCT. However, the prognosis is over-
Histopathological criteria
Although the detection rate of micrometastases in bone marrow and body fluids has recently been shown to be higher with reverse transcriptase polymerase chain reaction of the EWS-WT1 fusion transcript, the clinical significance of molecularly-detectable micrometastases of DSRCT remains unknown (128).

Primary epithelial tumours of müllerian type

Definition
Primary epithelial tumours of the peritoneum that resemble malignant ovarian surface epithelial-stromal tumours.

Primary peritoneal carcinoma

Definition
A variety of extraovarian neoplasms that histologically resemble surface-epithelial-stromal tumours of ovarian origin.

Epidemiology
Primary peritoneal carcinoma (PPC) occurs almost exclusively in women with a median age of 62 years. The lifetime risk is estimated to be 1 case per 500 women, since approximately 15% of "typical" epithelial ovarian cancers are actually PPCs (2575,2576).

Histopathology
Histological and immunohistochemical examination of PPC is virtually indistinguishable from epithelial ovarian carcinoma. The most common histological variant is serous adenocarcinoma, but clear cell, mucinous, transitional cell and squamous cell carcinomas have all been reported to originate from the peritoneum. Rare cases of primary psammocarcinoma of the peritoneum have been described (1001). The following are required to meet the criteria for PPC:
(1). Both ovaries must be normal in size or enlarged by a benign process.
(2). The involvement in the extraovarian sites must be greater than the involvement on the surface of either ovary.
(3). The ovarian tumour involvement must be either non-existent, confined to ovarian surface epithelium without stromal invasion, or involving the cortical stroma with

whelmingly poor (1038,1547,2310).

Fig. 2.143 Desmoplastic small round cell tumour of the peritoneum. A Irregular islands of tumour cells are separated by fibrous stroma. B The tumour cells are small and round with high nuclear to cytoplasmic ratios.

Fig. 2.144 Primary peritoneal serous carcinoma. This serous tumour is composed of papillary fronds and gland-like spaces.
tumour size less than 5 x 5 mm [2575].

**Histogenesis**

PPC is believed to develop de novo from the peritoneal lining of the pelvis and abdomen [2575]. It may develop in a woman years after having bilateral oophorectomy [2262]. Some cases have been shown to originate from multiple peritoneal sites, supporting the hypothesis that cells derived from the coelomic epithelium may independently undergo malignant transformation [1954,2575,2576].

**Somatic genetics**

PPC exhibits a distinct pattern of chromosomal allelic loss compared to epithelial ovarian cancer [176,421,1259]. Overexpression of the TP53, EGFR, ERBB2, ERBB3, and ERBB4 genes has been reported, in addition to loss of normal WT1 expression [2574,2575]. TP53 gene mutations commonly occur in PPC, but KRAS mutations are very infrequent [965,2575]. PPC BRCA1 mutation carriers have a higher incidence of TP53 mutations, are less likely to exhibit ERBB2 overexpression, and are more likely to have a multifocal disease origin [2575]. This unique molecular pathogenesis of BRCA-related PPC is believed to affect the ability of current methods to reliably prevent or detect this disease prior to metastasis [1402].

**Genetic susceptibility**

Germline BRCA1 mutations occur in PPC with a frequency comparable to the BRCA1 mutation rate in ovarian cancer. Although the penetrance is unknown, PPC should be considered a possible phenotype of the familial breast and ovarian cancer syndrome [175]. The multifocal disease origin is thought to explain why PPC has been a common cause of detection failures in familial ovarian cancer screening programs. Screening strategies for these women cannot rely on ultrasonography and CA125 testing to detect early disease [1402].

**Prognosis and predictive factors**

The staging, treatment and prognosis of PPC are similar to those of epithelial ovarian cancer. Optimal surgical cytoreduction for histological grade 1 and 2 lesions are associated with longer median survival [2575]. Carboplatin or cisplatin in conjunction with paclitaxel is the current first-line recommended chemotherapy [1436]. The clinical behaviour of psammocarcinoma more closely resembles that of serous borderline tumours than that of serous carcinomas of the usual type. Patients with psammocarcinoma follow a protracted course and have a relatively favourable prognosis [1001].

**Primary peritoneal borderline tumours**

**Definition**

A variety of extraovarian neoplasms that histologically resemble borderline surface epithelial-stromal tumours of ovarian origin. By definition minimal or no ovarian surface involvement is present.

**Epidemiology**

The age in the two largest series has ranged from 16-67 years with a mean of 32 years.

**Clinical features**

Infertility and abdominal pain are the most common presenting complaints [204]. Occasional patients present with an abdominal mass. At operation the peritoneal lesions may be focal or diffuse. They commonly appear as milary granules and may be mistaken for peritoneal carcinomatosis.

**Histopathology**

The vast majority of cases are serous in type. The histological appearance is similar to that of non-invasive peritoneal implants of epithelial or desmoplastic type [278]. Psammoma bodies are a prominent feature.

**Prognosis and predictive factors**

The usual treatment is hysterectomy, bilateral salpingo-oophorectomy and omentectomy. Younger patients who desire to maintain fertility may be treated conservatively [278]. The prognosis is excellent. Occasional tumour recurrences with bowel obstruction have been described. Rarely, the patient may develop an invasive low grade serous carcinoma of the peritoneum. Rare deaths due to tumour have been reported.
Tumours of the fallopian tube are much less common than the corresponding ovarian neoplasms; however, histologically the same surface epithelial-stromal tumour subtypes are recognized. Sex cord-stromal and germ cell tumours are rare. Hydatidiform moles and gestational choriocarcinoma are uncommon complications of tubal ectopic pregnancy. The wolffian adnexal tumour is also infrequent and typically occurs in the leaves of the broad ligament.

The risk factors appear similar to those of the ovary. Fallopian tube carcinomas are a component of the hereditary breast-ovarian cancer syndrome caused by \textit{BRCA1} and \textit{BRCA2} germline mutations.
WHO histological classification of tumours of the fallopian tube

<table>
<thead>
<tr>
<th>Epithelial tumours</th>
<th>Soft tissue tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
</tr>
<tr>
<td>Serous adenocarcinoma</td>
<td>8460/3</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>8380/3</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>8310/3</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>8120/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>8020/3</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Borderline</strong></td>
<td></td>
</tr>
<tr>
<td>Borderline tumour (of low malignant potential)</td>
<td>8442/1</td>
</tr>
<tr>
<td>Serous borderline tumour</td>
<td>8442/1</td>
</tr>
<tr>
<td>Mucinous borderline tumour</td>
<td>8472/1</td>
</tr>
<tr>
<td>Endometrioid borderline tumour</td>
<td>8380/1</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Carcinoma in situ</strong></td>
<td>(specify type)</td>
</tr>
<tr>
<td>Benign tumours</td>
<td></td>
</tr>
<tr>
<td>Papilloma (specify type)</td>
<td></td>
</tr>
<tr>
<td>Cystadenoma (specify type)</td>
<td></td>
</tr>
<tr>
<td>Adenofibroma (specify type)</td>
<td></td>
</tr>
<tr>
<td>Cystadenofibroma (specify type)</td>
<td></td>
</tr>
<tr>
<td>Metaplastic papillary tumour</td>
<td></td>
</tr>
<tr>
<td>Endometrioid polyp</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour-like epithelial lesions</strong></td>
<td></td>
</tr>
<tr>
<td>Tubal epithelial hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Salpingitis isthmica nodosa</td>
<td></td>
</tr>
<tr>
<td>Endosalpingiosis</td>
<td></td>
</tr>
<tr>
<td><strong>Mixed epithelial-mesenchymal tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Malignant müllerian mixed tumour</td>
<td>8950/3</td>
</tr>
<tr>
<td>(carcinosarcoma; metaplastic carcinoma)</td>
<td></td>
</tr>
<tr>
<td>Adenosarcoma</td>
<td>8933/3</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Germ cell tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td></td>
</tr>
<tr>
<td>Mature</td>
<td>9080/0</td>
</tr>
<tr>
<td>Immature</td>
<td>9080/3</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Trophoblastic disease</strong></td>
<td></td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Placental site trophoblastic tumour</td>
<td>9104/1</td>
</tr>
<tr>
<td>Hydatidiform mole</td>
<td></td>
</tr>
<tr>
<td>Placental site nodule</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphoid and haematopoetic tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td></td>
</tr>
<tr>
<td>Leukaemia</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary tumours</strong></td>
<td></td>
</tr>
</tbody>
</table>

**WHO histological classification of tumours of the broad ligament and other uterine ligaments**

<table>
<thead>
<tr>
<th>Epithelial tumours of müllerian type</th>
<th>Secondary tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous adenocarcinoma</td>
<td>Papillary cystadenoma (with von-Hippel-Lindau disease)</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>Uterus-like mass</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>Adenosarcoma</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>Others</td>
</tr>
<tr>
<td>Borderline tumour (of low malignant potential), (specify type)</td>
<td>Malignant</td>
</tr>
<tr>
<td>Adenoma and cystadenoma (specify type)</td>
<td>Benign</td>
</tr>
<tr>
<td><strong>Miscellaneous tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Wolffian adnexal tumour</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>

1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) (9031) and the Systematized Nomenclature of Medicine (http://snomed.org).
2 Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
### TNM and FIGO classification of carcinomas of the fallopian tube

<table>
<thead>
<tr>
<th>TNM and FIGO classification</th>
<th>M</th>
<th>IV</th>
<th>Distant metastasis (excludes peritoneal metastasis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumour cannot be assessed</td>
<td>M1</td>
<td>IV</td>
<td>Distant metastasis (excludes peritoneal metastasis)</td>
</tr>
<tr>
<td>T0 No evidence of primary tumour</td>
<td>N1</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>Tis Carcinoma in situ (preinvasive carcinoma)</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T1 Tumour confined to fallopian tube(s)</td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T1a IA Tumour limited to one tube, without penetrating the serosal surface</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T1b IB Tumour limited to both tubes, without penetrating the serosal surface</td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T1c IC Tumour limited to one or both tube(s) with extension onto or through the tubal serosa, or with malignant cells in ascites or peritoneal washings</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T2 II Tumour involves one or both fallopian tube(s) with pelvic extension</td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T2a IIA Extension and/or metastasis to uterus and/or ovaries</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T2b IIB Extension to other pelvic structures</td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T2c IIC Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washings</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T3 and/or N1 III Tumour involves one or both fallopian tube(s) with peritoneal implants outside the pelvis and/or positive regional lymph nodes</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T3a IIIA Microscopic peritoneal metastasis outside the pelvis</td>
<td>N1</td>
<td>Regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T3b IIIB Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>T3c and/or N1 IIIC Peritoneal metastasis more than 2 cm in greatest dimension and/or positive regional lymph nodes</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td></td>
</tr>
</tbody>
</table>

### Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

1 [5,129,6].
2 A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
3 The regional lymph nodes are the hypogastric (obturator), common iliac, external iliac, lateral sacral, para-aortic, and inguinal nodes.

Note: Liver capsule metastasis is T3/stage III, liver parenchymal metastasis, M1/stage IV. Pleural effusion must have positive cytology for M1/stage IV.
Malignant epithelial tumours

**Definition**
A malignant epithelial tumour of the tubal mucosa, usually with glandular differentiation. In order to be considered a primary carcinoma of the fallopian tube, the tumour must be located macroscopically within the tube or its fimbriated end, and the uterus and ovary must either not contain carcinoma or, if they do, it must be clearly different from the fallopian tube lesion.

**ICD-O codes**
- Serous adenocarcinoma 8441/3
- Mucinous adenocarcinoma 8480/3
- Endometrioid adenocarcinoma 8380/3
- Clear cell adenocarcinoma 8310/3
- Transitional cell carcinoma 8120/3
- Undifferentiated carcinoma 8020/3

**Epidemiology**
Primary fallopian tube carcinomas are rare, amounting to 0.3-1.1% of gynaecological malignancies [158]. The risk factors appear similar to those of epithelial ovarian cancer. Adenocarcinoma is the most frequent tumour of the fallopian tube [2566].

**Macroscopy**
On macroscopic examination, the tube shows abnormal dilatation or nodular thickening resembling a hydrosalpinx or haematosalpinx and contains a dominant localized tumour mass. When found in the proximal part of the tube, the tumour may protrude through the fimbriated end. On the sectioned surface the adenocarcinoma usually consists of soft, grey-brown, villous or polypoid tissue.

**Tumour spread and staging**
The tumour spread is very similar to that of ovarian carcinoma and involves adjacent organs, the peritoneum and regional lymph nodes. Involvement of the adjacent ovary may make it difficult to determine whether the tumour is primary in the tube or ovary. When the origin remains unclear, the tumour is classified as tubo-ovarian carcinoma (1296).

Surgical staging is performed according to the FIGO classification system (51,2976).

**Histopathology**
All carcinoma subtypes documented in the ovaries have been identified in the fallopian tube. Serous carcinoma is the most common cellular subtype. In one series of 151 cases, 80% of the tumours were serous [158]. In other large series, about half of these carcinomas were serous, one-fourth endometrioid, one-fifth transitional cell or undifferentiated and the remainder of other cell types (75).

**Serous adenocarcinoma**
Most serous carcinomas of the tube are invasive tumours with a high histological grade. In one series 50% of the cases were grade 3 (75). Occasional serous carcinomas have an extensive inflammatory cell infiltration that may simulate a salpingitis of non-tuberculous type (472).

**Mucinous adenocarcinoma**
These tumours are extremely rare and often are associated with other mucinous neoplasms of the female genital tract (2617). Reported cases have been predominantly in situ mucinous carcinomas (2450). A case of synchronous, trifocal mucinous papillary adenocarcinoma involving the uterine cervix and both fallopian tubes has been reported [1316]. We are only aware of a single case of an invasive mucinous adenocarcinoma. The histological appearance of these tumours resembles that of ovarian mucinous carcinomas, and goblet cells may be prominent.
**Endometrioid adenocarcinoma**

Endometrioid carcinomas of the tube are characteristically non-invasive or only superficially invasive and have a generally favourable prognosis (1985). The typical variant is the most common form of endometrioid carcinoma encountered in the tube. By definition these tumours closely resemble their uterine counterparts. Endometrioid carcinomas with a prominent spindle-shaped epithelial cell component (2942) or with the glands lined exclusively by oxyphilic cells (2258) also occur in the tube. An unusual form of endometrioid carcinoma resembling the patterns seen in the wolffian adnexal tumour has been found relatively often in the fallopian tube (641, 1985). These tumours are characterized by a prominent pattern of small, closely packed cells punctured by numerous glandular spaces, a large number of which contain a dense colloid-like secretion. The finding of areas with the typical appearance of endometrioid carcinoma enables one to make the correct diagnosis.

**Clear cell adenocarcinoma**

These neoplasms constitute 2-10% of all fallopian tube carcinomas (75, 1181a, 3031). The majority of the reported cases have shown a tubulocystic pattern varying from flattened cuboidal epithelium to an irregular pattern with prominent hobnail and clear cells. A papillary pattern featuring the hobnail type of epithelium lining fibrovascular stalks has also been described (3031).

**Transitional cell carcinoma**

These carcinomas are rare in the female genital tract but occur relatively more often than in the ovary (2676). The frequency of transitional cell carcinoma of the fallopian tube in previous reports has varied from 11-43% (75, 2974). Transitional cell metaplasia of the epithelium has been suggested as a possible source of tubal carcinoma of the same cell type (750).

**Undifferentiated carcinoma**

These carcinomas fail to show evidence of either glandular or squamous differentiation. The tumour displays a diffuse growth pattern composed of sheets of small cells resembling those of small cell carcinoma of the lung. These densely cellular tumours may have a relatively conspicuous myxoid matrix. Some tumours have large epithelial cells arranged in nests surrounded by a dense lymphocytic infiltrate resembling a lymphoepithelioma-like carcinoma. Extensive tumour areas consisting predominantly of multinucleated giant cells may also be present (75).

**Hormone-producing carcinoma**

Ectopic beta-human chorionic gonadotropin (β-hCG) production has been reported in two women with serous or undifferentiated carcinoma of the tube (75, 399). Each of the tumours contained syncytiotrophoblast-like cells, many of which stained positively for β-hCG. Unusual reported cases include a renin-producing tumour (3234) and an alpha-fetoprotein producing carcinoma that had a hepatoid appearance (111).

**Miscellaneous epithelial tumours**

Rare examples of unusual neoplasms arising in the tube include cases of squamous cell (290, 470, 1747), adenosquamous, glassy cell (75, 1191) and lymphoepithelioma-like carcinoma (75).

**Genetic susceptibility**

The discovery of the BRCA1 cancer predisposition gene in 1994 and the BRCA2...
cancer predisposition gene in 1995 has allowed the identification of a group of women who are at a greatly increased risk of developing breast and ovarian cancer [8,499]. Two previous series in which 5% and 11% respectively of patients with tubal cancer also had breast carcinoma suggest an association between breast cancer and tubal carcinoma [75,2225]. Recently, several high-risk “breast-ovarian cancer families” with BRCA1 mutations and fallopian tube cancer have been reported. Additionally, a family history of fallopian tube cancer was found to be predictive of the presence of a BRCA1 mutation in a panel of 26 Canadian “breast-ovarian cancer families” [2939]. A slightly increased risk of ovarian cancer and of early-onset breast cancer was found in the first-degree relatives of the fallopian tube cancer cases [144]. Thus, fallopian tube carcinoma should be considered to be a clinical component of the hereditary breast-ovarian cancer syndrome and may be associated with BRCA1 and BRCA2 mutations. See Chapter 8.

Prognosis and predictive factors
The surgical stage is an independent prognostic factor [75,158] and is critical for determining whether adjuvant therapy is appropriate. Stage I carcinomas that occur in the tubal fimbriae appear to have a worse prognosis than stage I tubal carcinomas that are nonfimbrial [74].

Borderline epithelial tumours
Borderline epithelial tumours of the fallopian tube are rare and include cases of serous, mucinous and endometrioid types [74]. Borderline serous tumours involve the tube, including its fimbriated portion, and have histological features similar to those of the ovary [74,1421,3257]. Mucinous tumours are sometimes associated with mucinous metaplasia of the fallopian tube or the Peutz-Jeghers syndrome [1806,2617]. Patients that have multiple organ involvement or pseudomyxoma peritonei may have a metastatic lesion to the tube, and in all cases the appendix needs to be ruled out as a source.
Two examples of adenofibroma of borderline malignancy have been reported [74,3257]. One of the tumours appeared in a pregnant woman and on ultrasound was interpreted as an ectopic pregnancy; the other was detected incidentally during an elective tubal ligation. Both neoplasms were located at the fimbriated end of the fallopian tube. One tumour was of serous type and the other endometrioid. Although relatively few cases of tubal borderline tumours have had long term follow up, the prognosis appears favourable, and it has been suggested that they can be managed conservatively [3257].

Carcinoma in situ

Rare cases of tubal intraepithelial carcinoma have been reported, and one of these occurred after tamoxifen therapy of breast carcinoma [2747]. With the exception of one case in which a small papillary tumour was found [1875], the tumours are not detectable on macroscopic examination. They are characterized by replacement of the tubal epithelium by malignant glandular epithelial cells with pleomorphic nuclei [178,2835]. Florid epithelial proliferation, sometimes even with a cribiform or sieve-like pattern, may occur in association with salpingitis and should not be mistaken for carcinoma in situ [472].

Benign epithelial tumours

Polypoid adenofibromas, papillomas, benign serous cystadenoma and endometrioid tumours are rarely found in the fallopian tube, including the fimbria [74,1615]. They may be complicated by torsion, especially during pregnancy.

Papilloma and cystadenoma

Serous papilloma and cystadenoma are uncommon lesions of the fallopian tube. Papillomas may be intramural or involve the fimbriated end [74]. Papillomas typically are loosely attached to the tubal mucosa and consist of delicate branching fibrovascular stalks lined by epithelial cells that are indistinct in appearance or resemble those of the fallopian tube lining. The lesion may cause tubal obstruction [1012,1407]. Cystadenomas are similar but lack papillary features [74]. Mucinous cystadenomas also have been reported [2617].

Adenofibroma and cystadenofibroma

Fallopian tube adenofibromas and cystadenofibromas are rare. About fifteen examples of these tumours have been documented [74,3257]. The age range is from the third to the eight decade with a mean age of 49 years. Most women are asymptomatic, and the majority of the tumours are incidental findings at the time of an operation for another gynaecological disorder [3257]. The neoplasm presents as a round, solitary mass (average 0.5-3 cm) that is either intraluminal or attached to the fimbriated end or the serosal surface and may have a smooth or papillary surface. In one case the tumour was bilateral [451]. Histologically, two components are present, a connective tissue stroma without nuclear pleomorphism or mitoses and papillary structures on the surface or tubal structures lined by epithelial cells. The epithelial cell type has been serous in most of the cases but occasionally may be endometrioid [647].

Metaplastic papillary tumour

Metaplastic papillary tumour is an uncommon lesion that typically occurs as an incidental histological finding in segments of fallopian tube removed during the postpartum period for sterilization [187,1425,2504]. Only rare lesions occur in women who were not recently pregnant. The intraluminal tumour usually involves part of the mucosal circumference and is composed of variable sized papillae covered by atypical epithelial cells that superficially resemble a serous borderline tumour. The epithelial lining shows cellular budding and the presence of abundant eosinophilic cytoplasm in most of the tumour cells. Some of the cells may contain intracellular mucin, and extracellular mucin may be abundant. Mitotic figures are rarely observed.

Endometrioid polyp

Endometrial (adenomatous) polyps occur in the interstitial portion of the fallopian tube [1170,1180]. They are commonly found in radiographic studies of infertile patients. They may obstruct the lumen and result in infertility or tubal pregnancy. They are often attached to the tubal epithelium by a broad base and, thus, macroscopically resemble intrauterine endometrial polyps. They may be occasionally associated with ectopic endometrial epithelium elsewhere in the tube [342].

Tumour-like epithelial lesions

Definition

Proliferations of the tubal mucosa that simulate neoplasms.

Tubal epithelial hyperplasia

Pseudocarcinomatous hyperplasia in chronic salpingitis may mimic adenocar-
cinoma histologically because of the pseudoglandular and cribriform permeation of the tubal wall by hyperplastic epithelium and the florid mesothelial hyperplasia (472). The typically young age of the patients, the presence of marked chronic inflammation, the absence of a macroscopically detected tumour or solid epithelial proliferation, the mildness of the nuclear atypia and the paucity of mitotic figures facilitate the differential diagnosis. Recently, atypical hyperplasia of the fallopian tube has been observed in patients on tamoxifen therapy for breast cancer [2244].

**Salpingitis isthmi nodosa**

Salpingitis isthmi nodosa is a manifestation of tubal diverticulosis and is associated with female infertility and ectopic pregnancy [1064]. These nodules in the isthmus are composed of hypertrophic myosalpinx and glandular spaces lined by tubal epithelium.

**Endosalpingiosis**

Endosalpingiosis is the benign transformation of the mesothelium into tubal epithelium with ciliated and secretory cells. Psammoma bodies and atypical changes may be found [2019]. Endosalpingiosis is distinguished from endometriosis by the absence of endometrial stroma since tubal type epithelium can also occur occasionally in endometriosis. Endosalpingiosis occurs in the peritoneum and may involve the serosal surfaces of the uterus and its adnexa. Endosalpingiosis may either present as pelvic pain or may be discovered as an incidental finding [659,1591]. Rarely, endosalpingiosis can present clinically as a cystic mass and can be confused with a neoplasm on macroscopic examination [518a].

**Mixed epithelial and mesenchymal tumours**

**Definition**

Neoplasms composed of an admixture of neoplastic epithelial and mesenchymal elements. Each of these components may be either benign or malignant.

**ICD-O codes**

- Malignant müllerian mixed tumour 8950/3
- Adenosarcoma 8933/3
- **Malignant müllerian mixed tumour**

As a group, these malignancies are uncommon. The fallopian tube is the least common site for malignant müllerian mixed tumours in the female genital system, accounting for less than 4% of the reported cases [1124]. Patients are almost always postmenopausal (mean age, 57 years) and usually present with abdominal pain, atypical genital bleeding or abdominal distension [1124,1284]. The histological appearance of these tumours resembles that of ovarian malignant müllerian mixed tumour. The prognosis is poor [1124,1284,3079].

**Adenosarcoma**

This tumour is exceedingly uncommon. Only one well documented case that arose in the fimbriated end of the tube and recurred on the pelvic wall has been reported [1036]. Another example of a tubal tumour of this type was characterized by marked adenocanthotic atypia of its epithelial component [2605].

**Gestational trophoblastic disease**

**Definition**

A heterogeneous group of gestational and neoplastic conditions arising from trophoblast, including molar gestations and trophoblastic tumours.

**ICD-O codes**

- Choriocarcinoma 9100/3
- Placental site trophoblastic tumour 9104/1
- Hydatidiform mole 9100/0

**Choriocarcinoma**

Tubal choriocarcinomas account for approximately 4% of all choriocarcinomas [660]. Most of the cases are discovered by chance during an ectopic pregnancy, but about 40% present with an enlarging adnexal mass [2078]. Histological examination shows typical features of gestational choriocarcinoma. In the older literature before the advent of modern chemotherapy, choriocarcinomas associated with ectopic pregnancy were frequently very aggressive, and 75% showed metastases at the time of diagnosis. The response to modern chemotherapy generally has been encouraging [1717,1953].

**Placental site trophoblastic tumour**

This neoplasm is composed predominantly of intermediate trophoblast. It is generally benign but occasionally may be highly malignant [1540]. To date, only one case of tubal placental site trophoblastic tumour has been reported [2810].

**Hydatidiform mole**

Approximately thirty tubal hydatidiform moles have been reported [1999]; however, only four valid examples of this lesion were accepted in 1981 [2078]. Those authors concluded that the remaining “moles” were actually ectopic pregnancies with villous hydrops. This tumour usually occurs as an isolated growth, but it may be associated with an intrauterine pregnancy [1048]. The histological appearance may be that of a complete, partial or invasive mole with clear
evidence of trophoblastic proliferation in addition to hydropic swelling of the villi.

**Placental site nodule**

Placental site nodule is an asymptomatic non-neoplastic proliferation of intermediate trophoblast from a previous gestation that failed to involute. This lesion has recently been reported to occur at the site of an ectopic gestation; two were located in the fallopian tube and one in the broad ligament in direct contact with the tube [391,1514].

**Other tumours**

**Adenomatoid tumour**

**ICD-O code** 9054/0

The adenomatoid tumour is the most frequent type of benign tubal tumour and usually is found as an incidental finding in a middle-aged or elderly woman [1290]. It typically appears as a grey, white or yellow nodular swelling measuring 1-2 cm in diameter located beneath the tubal serosa. The tumour may be large enough to displace the tubal lumen eccentrically [2787]. Rare examples are bilateral [3230]. It originates from the mesothelium and is composed of gland-like structures lined by flat to cuboidal cells [2787].

**Germ cell tumours**

To date only about 50 teratomas of the tube have been reported [1242,3051, 3189]. Many of them were found incidentally, measuring 1-2 cm in diameter, and none has been diagnosed preoperatively. The patients have the risk factors for ectopic pregnancy such as prior salpingitis and tubal occlusion [1953]. A malignant mixed germ cell tumour has been reported [1652].

**Soft tissue tumours**

Primary sarcomas of the fallopian tube are exceedingly rare; approximately 37 cases have been reported in the literature in more than 100 years [1322]. The clinical signs and symptoms are usually non-specific and include lower abdominal pain and pelvic pressure. The age at diagnosis varies from 21-70 years with a median of 47 years. Leiomyosarcoma is the most common type and may arise from the tube or broad ligament [1322]. Other reported fallopian tube or broad ligament malignancies include chondrosarcoma [2245], embryonal rhabdomyosarcoma [361], myxoid liposarcoma [2708] and Ewing tumour [1692]. The prognosis is poor, although several long-term survivors have been reported [1322].

**Malignant lymphoma and leukaemia**

Tubal involvement by lymphoma is rare and is associated almost invariably with simultaneous involvement of the ipsilateral ovary [2119]. In one large series more than 25% of patients with ovarian lymphoma had tubal involvement, most often by Burkitt or Burkitt-like (small non-cleaved cell) lymphoma or diffuse large-cell lymphoma [2119]. One example of an apparent primary malignant lymphoma of the fallopian tube has been observed [2605]. The tube may also be infiltrated in cases of leukaemia [428].

**Secondary tumours**

Metastatic tumours involving the tube usually are the result of secondary spread from carcinomas of the ovary or endometrium [3145]. In most cases, the spread is by direct extension. In one study 89% of secondary carcinomas in the tube were of ovarian origin, and the remainder originated in the endometrium. Blood-borne metastases from breast carcinomas or other extrapelvic tumours may also occur [862,3145]. The authors are aware of a case of adenocarcinoma of the gallbladder metastatic to the fallopian tube [862].
**Definition**
Benign and malignant tumours that arise in the broad ligament and other uterine ligaments.

**ICD-O codes**
- Serous adenocarcinoma 8460/3
- Endometrioid adenocarcinoma 8380/3
- Mucinous adenocarcinoma 8480/3
- Clear cell adenocarcinoma 8310/3
- Wolffian adnexal tumour 9110/1
- Ependymoma 9391/3
- Papillary cystadenoma (with von Hippel-Lindau disease) 8450/0
- Adenosarcoma 8933/3

**Epithelial tumours of müllerian type**

**Definition**
Epithelial tumours of müllerian type are the most frequent neoplasms of the broad and other ligaments [2919]. In general, tumours of every müllerian cell type and of every degree of malignancy can occur in this location but are infrequent compared to their occurrence in the ovary. The criteria for malignancy and for the borderline category are the same as described for müllerian type epithelial tumours occurring in the ovary and the peritoneum.

**Carcinomas**
Less than 20 cases have been reported, of which most were of serous, endometrioid and clear cell types [127a,604a, 715a,1481a,1850a,2402a,2775a,2912a]. An association with endometriosis was observed in some endometrioid and clear cell carcinomas. The age of the patients ranged from 28-70 years. The tumours were cystic, solid or mixed, and their diameter ranged from 4.5-13 cm. All carcinomas were unilateral, but some had spread beyond the broad ligament. Due to the small number of cases and limited follow-up in many of the cases, the prognosis of these tumours cannot be established.

**Borderline tumours**
More than 30 cases, mostly serous cystic tumours (age range 19-67 years; mean age 33 years) have been reported [73,127,434,606,740,1341,1702,2626]. One mucinous tumour has been reported [1342]. The tumours measured 1-13 cm in greatest diameter, were unilateral, clearly separated from the ovary and confined to the broad ligament.

**Benign tumours**
Serous cystadenoma is the most common type [962]. As in the ovary, the distinction from non-neoplastic serous cysts is ill defined. A suggested distinction is that serous cystadenomas have a thick wall composed of cellular stroma resembling ovarian stroma and lack folds and plicae in contrast to the histology of serous cysts [1236,1335]. Several Brenner tumours ranging from 1-16 cm in diameter have occurred [1120], and they may be associated with serous or mucinous cystadenomas [169,1628,2302,3040].

**Wolffian adnexal tumour**

**Definition**
A tumour of presumptive wolffian origin characterized by a variety of epithelial patterns.

**Synonyms**
Retiform wolffian adenoma, retiform wolffian adenocarcinoma.

**Sites of involvement**
Wolffian tumours occur mainly within the leaves of the broad ligament but may appear as pedunculated lesions arising from it. Less than 50 examples have been described that are predominantly located within the area where mesonephric remnants are distributed. They occur mainly in the broad ligament but also in the mesosalpinx, the serosa of the fallopian tube, the ovary and the retroperitoneum [637,670,682,1400, 2653,2877,2926,3212].
Clinical features
Patients range in age from 15-81 years, and most present with a unilateral adnexal mass. Ultrasound studies may show an ill-defined mass [637].

Macroscopy
These predominantly solid tumours range from 0.5-18 cm in diameter. The sectioned surface may contain variably sized cysts and is yellow-tan to grey-white [2877]. The tumour is firm to rubbery and occasionally may have areas of haemorrhage and necrosis.

Tumour spread and staging
Tumour implants may be present at the time of diagnosis and indicate an aggressive tumour [637,2653].

Histopathology
The tumour shows a variable admixture of diffuse, solid and sieve-like cystic areas, with the solid pattern dominating in the majority of cases. The diffuse, solid areas show a compact proliferation of ovoid to spindle-shaped cells reflecting closed tubules bound by a basement membrane and separated by variable amounts of fibrous stroma or none at all. The round to ovoid nuclei may show indentations. The hollow tubules have a retiform or sertoliform appearance. When the closed tubules dominate, the lesion resembles a mesenchymal tumour; a PAS or reticulin stain helps unmask the tubular pattern. The cells lining the tubules are cuboidal to low columnar with a minimal amount of eosinophilic cytoplasm and round to spindle-shaped, uniform nuclei. Sieve-like areas display clusters of variably sized cysts lined by attenuated cells. Most cases do not show atypia or mitotic figures.

Immunoprofile
The tumour cells are positive for most cytokeratins and vimentin and are often positive for calretinin (91%), inhibin (68%) and CD10 [2110]. They are usually negative for epithelial membrane antigen, estrogen receptor (ER) and progesterone receptor (PR) and are negative for cytokeratin 20, 34betaE12 and glutathione S-transferase [682,2926].

Cytometry
The ploidy of a metastatic tumour was assessed and found to be diploid [2653].

Electron microscopy
At the ultrastructural level, the tubules are surrounded by basal lamina and lined by cells with complex interdigitations, desmosomes and/or tight junctions and a few microvilli along the luminal border; no cilia are identifiable [670]. The cytoplasmic organelles are not distinctive and include lysosomes, a small amount of smooth endoplasmic reticulum and a few lipid droplets.

Differential diagnosis
The main tumours in the differential diagnosis are Sertoli cell tumour, Sertoli-Leydig cell tumour, and well-differentiated endometrioid carcinoma. The presence of a sieve-like pattern and the absence of Leydig cells help distinguish wolffian tumours from all these lesions. The absence of immunoreactivity with either ER or PR also would distinguish wolffian tumours from well-differentiated endometrioid carcinomas; the latter are invariably positive for ER and PR; however, positive immunostaining does not exclude the possibility of a wolffian tumour [682].

Prognosis and predictive factors
The tumour stage as well as cytological atypia and frequent mitotic figures are important predictors of aggressive behaviour. Careful follow-up of all women with wolffian adnexal tumours is prudent [637,2653]. Most wolffian adnexal tumours are benign and adequately treated by unilateral salpingo-oophorectomy. About 10% either recur or metastasize. Recurrences and metastases to the lungs and liver have been reported within 1 year or as late as 8 years after diagnosis [637,2653]. The metastatic tumour often has more atypia compared to the primary. Some aggressive tumours have had no significant atypia or mitotic activity in either the primary or the metastatic lesion [2653].

Ependymoma
Definition
Tumours closely resembling neoplasms of the central nervous system that show ependymal differentiation.

Fig. 3.14 Wolffian adnexal tumour. A The pattern of closely packed tubules simulates a Sertoli cell tumour. B Reticulin stain accentuates the tubular pattern.
Localization
Only four ependymomas have been described in the uterine ligaments, three in the broad ligament and one in the uterosacral ligament [208,727,1068].

Clinical features
Patients were 13-48 years of age with a mean of 38 years and presented with a mass associated with lower quadrant tenderness.

Macroscopy
The tumours are solid or multicystic, soft in consistency and vary from 1 cm to massive in size. The sectioned surface shows haemorrhage and necrosis in the larger tumours.

Histopathology
The lesions are characterized by papillae lined by flat to columnar ciliated cells with central to apical, round to elongated nuclei that protrude into cystic spaces. In more cellular solid areas, the cells form true perivascular ependymal rosettes and pseudorosettes. Mitotic figures may be few or numerous. A few psammoma bodies and small nodules of mature cartilage may be present.

At the ultrastructural level the cells have cilia, blepharoplasts and intermediate filaments [208,727].

Differential diagnosis
The papillary architecture and psammoma bodies closely resemble serous papillary carcinoma. The ependymal cells are immunoreactive for glial fibrillary acidic protein, however, helping to distinguish the two lesions. The cells are also positive for cytokeratin and vimentin.

Prognosis and predictive factors
These are malignant tumours capable of spread beyond the ligaments [208,727,1068]. Two of the reported cases had spread beyond the broad or uterosacral ligament at presentation, whilst a third had two recurrences over a 24 year period.

Papillary cystadenoma associated with von Hippel-Lindau disease

Definition
A benign tumour of mesonephric origin that occurs in women with von Hippel-Lindau (VHL) disease.

Clinical features
Reported in women 20-46 years of age, one case was not only bilateral but also the first manifestation of the disease; the remaining three were unilateral [939,949,988,1505].

Imaging
Ultrasonography shows a sonolucent mass containing an echogenic region [1505]. By computed tomography the lesion appears as an adnexal mass with both water attenuation and soft tissue attenuation areas and curvilinear calcification [939].

Histopathology
Histologically, the lesion is characterized by a complex, arborizing, papillary architecture. Generally, a single layer of non-ciliated cuboidal cells with vacuolated to lightly eosinophilic cytoplasm and bland round nuclei line the papillae [939,949,988,1505]. The papillary stalks vary from cellular to oedematous and hyalinized. Atypia and necrosis are absent, and mitotic figures are rare to absent. The cells contain glycogen but not mucinous material. A prominent basement membrane is evident beneath the epithelial cells. The cyst wall is fibrous and may have small bundles of smooth muscle or focal calcification.

Genetic susceptibility
VHL disease is an autosomal dominant disorder with inherited susceptibility to a variety of benign and malignant neoplasms including haemangioblastomas of the retina and central nervous system, renal cell carcinoma, pancreatic microcystic adenomas and a variety of other cysts, adenomas and congenital abnormalities. Papillary cystadenomas of mesonephric origin are rare VHL-associated lesions that occur more often in the epididymis but also rarely in the retroperitoneum and broad ligament in women; only four examples of the latter have been documented.

Genetics
The tumour suppressor gene responsible for VHL disease has been mapped to chromosome 3p25 and subsequently identified. Genetic studies on a variety of...
cases have been described. Cases reported in the uterosacral and broad ligaments have occurred in women under 50 years of age [48].

**Macroscopy**
The lesions form a cystic mass.

**Histopathology**
The inner lining consists of benign endometrial glands and endometrial stroma with an arrangement resembling endometrium. The outer layer of the cyst wall consists of thickened smooth muscle bundles appearing similar to myometrium.

**Immunoprofile**
Lesions may express ER and PR in the endometrial and myometrial components.

**Differential diagnosis**
"Endometriometritis" is likely the same entity as uterine-like mass. "Endometriosis with smooth muscle metaplasia" is histologically related to uterus-like mass, if not the same. Adenomyoma is distinguished from uterus-like mass by lacking the uterus-like organization. A uterus-like mass lacks the classic features of endometrioid carcinoma and extraterine adenosarcoma.

**Genetics**
A deletion on the short arm of chromosome 2 has been identified.

**Prognosis and predictive factors**
Benign behaviour would be expected.

**Adenosarcoma**
A single case of a high grade adenosarcoma arising from the round ligament was reported [1396].

**Mesenchymal tumours**
Mesenchymal tumours originating from the broad and other ligaments are rare. Almost any kind of malignant or benign mesenchymal tumour may occur.

**Malignant tumours**
Sarcomas are extremely rare, the most frequent being leiomyosarcoma. [465, 689, 1192, 1608, 1630, 2210] for which the same diagnostic criteria should be applied as for its uterine counterpart. Approximately 10 cases have been reported, and the prognosis is poor. Other sarcomas reported include endometrioid stromal sarcoma arising in endometriosis [2220], embryonal rhabdomyosarcoma (occurring in children and having a poor prognosis) [991], alveolar rhabdomyosarcoma (in an adult) [558], mixed mesenchymal sarcoma [2822], myxoid liposarcoma [2708] and alveolar soft part sarcoma [2017].

**Benign tumours**
The most common tumours are leiomyomas and lipomas [340,962]. It is often difficult to determine the site of origin of leiomyomas within the broad ligament. It has been suggested that leiomyomas be designated as ligamentous only if clearly separated from the myometrium. A leiomyoma of the broad ligament was imitated by Dracunculosis [70]. Lipomas are usually small and located within the mesosalpinx [847] and may be mixed with leiomyomas. Cases of other mesenchymal tumours of the broad and round ligament have been reported including two benign mesenchymomas [2069], neurofibromas, schwannomas [246,1047,2910] and a fibroma with heterotopic bone formation [2899]. Massive ascites and bilateral pleural effusion has been described in association with broad ligament leiomyoma and with paraovarian fibroma (pseudo-Méigs syndrome) [357,384,992].

**Miscellaneous tumours**
A variety of miscellaneous tumours have been described. Many of them are of ovarian type, such as germ cell and sex cord-stromal tumours. Although the question of origin from accessory ovarian tissue may be raised, in most cases no pre-existing ovarian tissue is identified. Mature teratomas, in particular dermoid cysts, occurred bilaterally within accessory ovaries of the broad ligament [941]. A dermoid cyst containing pituitary tissue occurred in the uterosacral ligament [1179]. A yolk sac tumour was found in the broad ligament [1270]. Other reported cases included granulosa cell tumours, but some of these were in fact wolffian adnexal tumours [962,1427,2347,2997]. Several broad ligament tumours of the thecoma-fibroma group, some of which had estro-
genic effects, have been reported. Several cases of steroid cell tumour with possible origin from accessory ovaries or adrenocortical remnants have been described [38,246,253,2996]. Three phaeochromocytomas, two that caused hypertension and elevated vanillylmandelic acid levels and one non-functional tumour [54,58,122], and a carcinoid [125] have been described.

Secondary tumours

Any type of malignant tumour originating from the uterus, its adnexae, other sites within the abdomen or from any other organ of the body may spread to the uterine ligaments by direct extension, lymphatics or blood vessels. In particular, intravenous leiomyomatosis [523, 112,194,2051], diffuse uterine leiomyomatosis [2394] and endometrial stromal sarcoma from the uterus may present as a mass within the broad ligament. Although it is far more common to spread to the broad ligament from the uterus, intravenous leiomyoma may exceptionally arise in the broad ligament [1154]. Cotyledonoid dissecting leiomyoma, the Sternberg tumour, is an unusual benign uterine smooth muscle neoplasm that spreads to the broad ligament [2470]. It is characterized by dissecting growth within the uterus, degenerative changes and a rich vascular component but does not have intravascular extension.

Fig. 3.17 Cotyledonoid dissecting leiomyoma. A Viewed posteriorly, an exophytic, congested, multinodular mass resembling placental tissue arises from the right cornual region of the uterus and extends laterally. B In the extrauterine component, a cotyledonoid process composed of smooth muscle is covered by connective tissue containing congested vessels.
CHAPTER 4

Tumours of the Uterine Corpus

The uterine corpus represents the second most common site for malignancy of the female genital system. These neoplasms are divided into epithelial, mesenchymal, mixed epithelial and mesenchymal tumours and trophoblastic tumours.

Endometrial carcinoma occurs predominantly in developed countries and is frequently associated with obesity. Two major types are distinguished. Type I is estrogen-dependent and develops through the hyperplasia-carcinoma sequence. Type II is not estrogen-dependent and develops independently of endometrial hyperplasia. It occurs in older women and is more aggressive.

Carcinosarcoma is still classified morphologically as a mixed epithelial and mesenchymal tumour, although it is considered monoclonal, with immunohistochemical and molecular studies strongly supporting its inclusion in the epithelial group. Its prognosis is worse than that of other members of the epithelial category.

Gestational trophoblastic disease is approximately 10-fold more common in the developing than in developed countries. Risk factors include a history of prior gestational trophoblastic disease, a diet low in vitamin A and blood group A women married to group O men.
### WHO histological classification of tumours of the uterine corpus

<table>
<thead>
<tr>
<th>Epithelial tumours and related lesions</th>
<th>Dissecting leiomyoma</th>
<th>Intravenous leiomyomatosis</th>
<th>Metastasizing leiomyoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>8380/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant with squamous differentiation</td>
<td>8570/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villous glandular variant</td>
<td>8262/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretory variant</td>
<td>8382/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliated cell variant</td>
<td>8383/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous adenocarcinoma</td>
<td>8441/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>8310/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed cell adenocarcinoma</td>
<td>8323/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>8120/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>8041/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>8020/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonatypical hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex (adenomatous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial polyp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen-related lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesenchymal tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial stromal and related tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial stromal sarcoma, low grade</td>
<td>8931/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial stromal nodule</td>
<td>8930/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated endometrial sarcoma</td>
<td>8930/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth muscle tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyoscarcoma</td>
<td>8890/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid variant</td>
<td>8891/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid variant</td>
<td>8896/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth muscle tumour of uncertain malignant potential</td>
<td>8897/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyoma, not otherwise specified</td>
<td>8899/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotically active variant</td>
<td>8892/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular variant</td>
<td>8892/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic cellular variant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid variant</td>
<td>8891/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid</td>
<td>8896/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical variant</td>
<td>8893/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoleiomyoma variant</td>
<td>8892/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth pattern variants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse leiomyomatosis</td>
<td>8890/1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
TNM and FIGO classification of non-trophoblastic tumours of the uterine corpus

<table>
<thead>
<tr>
<th>TNM and FIGO classification¹,²,³</th>
<th>Note: * FIGO recommends that Stage I patients given primary radiation therapy can be clinically classified as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T – Primary Tumour</strong></td>
<td>Stage I: Tumour confined to corpus uteri</td>
</tr>
<tr>
<td>TNM</td>
<td>Stage IA: Length of uterine cavity 8cm or less</td>
</tr>
<tr>
<td>FIGO</td>
<td>Stage IB: Length of uterine cavity more than 8cm</td>
</tr>
<tr>
<td><strong>Categories</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Stages</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (preinvasive carcinoma)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to corpus uteri</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour limited to endometrium</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour invades less than one half of myometrium</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour invades one half or more of myometrium</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades cervix but does not extend beyond uterus</td>
</tr>
<tr>
<td>T2a</td>
<td>Endocervical glandular involvement only</td>
</tr>
<tr>
<td>T2b</td>
<td>Cervical stromal invasion</td>
</tr>
<tr>
<td>T3 and/or N1</td>
<td>Local and/or regional spread as specified in T3a, b, N1, and FIGO IIIA, B, C below</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumour involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings</td>
</tr>
<tr>
<td>T3b</td>
<td>Vaginal involvement (direct extension or metastasis)</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades bladder mucosa and/or bowel mucosa</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa)</td>
</tr>
</tbody>
</table>

Note: The presence of bullous edema is not sufficient evidence to classify a tumour as T4.

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IC</td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

¹ (51,2976).
² A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
³ The classification applies to carcinomas and malignant mixed mesodermal tumours.
⁴ The regional lymph nodes are the pelvic (hypogastric [obturator, internal iliac], common and external iliac, parametrial, and sacral) and the para-aortic nodes.
TNM and FIGO classification of gestational trophoblastic tumours

### TNM and FIGO classification

<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>T–Primary Tumour</th>
<th>M – Distant Metastasis</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>T</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>M0</td>
<td>Unknown</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>M0</td>
<td>Low</td>
</tr>
<tr>
<td>IB</td>
<td>T1</td>
<td>M0</td>
<td>High</td>
</tr>
<tr>
<td>IIA</td>
<td>T2</td>
<td>M0</td>
<td>Low</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>M0</td>
<td>High</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
<td>M1a</td>
<td>Unknown</td>
</tr>
<tr>
<td>IIIA</td>
<td>Any T</td>
<td>M1a</td>
<td>Low</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>M1b</td>
<td>High</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>M1b</td>
<td>Low</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>M1b</td>
<td>High</td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to uterus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour extends to other genital structures: vagina, ovari, broad ligament, fallopian tube by metastasis or direct extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to lung(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Other distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Metastasis cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to lung(s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Stage grouping

<table>
<thead>
<tr>
<th>Prognostic score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 40</td>
<td>≥ 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Hydatidiform mole</td>
<td>Abortion</td>
<td>Term pregnancy</td>
<td></td>
</tr>
<tr>
<td>Months from index pregnancy</td>
<td>&lt;4</td>
<td>4–&lt;7</td>
<td>7–12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Pretreatment serum β-hCG (IU/ml)</td>
<td>&lt; 10⁵</td>
<td>10⁵–&lt;10⁶</td>
<td>10⁶–10⁷</td>
<td>&gt;10⁹</td>
</tr>
<tr>
<td>Largest tumour size, including uterus</td>
<td>&lt;3 cm</td>
<td>3–5 cm</td>
<td>≥5 cm</td>
<td></td>
</tr>
<tr>
<td>Site of metastasis</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastrointestinal tract</td>
<td>Liver, brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>1–4</td>
<td>5–8</td>
<td>&gt;8</td>
<td></td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Risk Categories

- Total prognostic score 7 or less = low risk
- Total score 8 or more = high risk

---

1. (51,2976)
2. A help desk for specific questions about the TNM classification is available at [http://tnm.uicc.org](http://tnm.uicc.org)
3. The classification applies to choriocarcinoma (9108/3), invasive hydatidiform mole (9101/1), and placental site trophoblastic tumour (9104/1).
**Endometrial carcinoma**

**Definition**
A primary malignant epithelial tumour, usually with glandular differentiation, arising in the endometrium that has the potential to invade into the myometrium and to spread to distant sites.

**ICD-O codes**
- Endometrioid adenocarcinoma 8380/3
  - Variant with squamous differentiation 8570/3
  - Villoglandular variant 8262/3
  - Ciliated cell variant 8383/3
  - Mucinous adenocarcinoma 8480/3
  - Serous adenocarcinoma 8441/3
  - Clear cell adenocarcinoma 8310/3
  - Mixed adenocarcinoma 8323/3
  - Squamous cell carcinoma 8070/3
  - Transitional cell carcinoma 8120/3
  - Small cell carcinoma 8041/3
  - Undifferentiated carcinoma 8020/3

**Epidemiology**
Endometrial carcinoma is the most common malignant tumour of the female genital system in developed countries, where estrogen-dependent neoplasms account for 80-85% of cases and the non-estrogen dependent tumours make up the remaining 10-15% of cases. The estrogen-dependent tumours are low grade, i.e. well or moderately differentiated and predominantly of endometrioid type. Patients with this form of endometrial cancer frequently are obese, diabetic, nulliparous, hypertensive or have a late menopause. Obesity is an independent risk factor (388), and in Western Europe, is associated with up to 40% of endometrial cancer (241a). On the other hand, patients with a large number of births, old age at first birth, a long birth period and a short premenopausal delivery-free period have a reduced risk of postmenopausal endometrial cancer, emphasizing the protective role of progesterone in the hormonal background of this disease (1212). In contrast, the non-estrogen dependent type occurs in older postmenopausal women; the tumours are high grade and consist predominantly of histological subtypes such as serous or clear cell as well as other carcinomas that have high grade nuclear features. They lack an association with exogenous or endogenous hyperoestrinism or with endometrial hyperplasia and have an aggressive behaviour (497,2005,2646).

**Pathogenesis**
Endometrial cancer is made up of a biologically and histologically diverse group of neoplasms that are characterized by a different pathogenesis. Estrogen-dependent tumours (type I) are low grade and frequently associated with endometrial hyperplasias, in particular atypical hyperplasia. Unopposed estrogenic stimulation is the driving force behind this group of tumours. It may be the result of anovulatory cycles that occur in young women with the polycystic ovary syndrome or due to normally occurring anovulatory cycles at the time of menopause. The iatrogenic use of unopposed estrogens as hormone replacement therapy in older women also is a predisposing factor for the development of endometrial cancer. The second type (type II) of endometrial cancer appears less related to sustained estrogen stimulation.

**Clinical features**

**Signs and symptoms**
Although endometrial carcinoma and related lesions can be incidental findings in specimens submitted to the pathologist for other reasons (for example, endometrial biopsy for infertility or hysterectomy for uterine prolapse), in the great majority of cases they present clinically with abnormal uterine bleeding. Since most of these lesions are seen in postmenopausal women, the most common presentation is postmenopausal bleeding, but earlier in life the usual clinical finding is menometrorrhagia (1104). The most common type of endometrial carcinoma, endometrioid adenocarcinoma, may be manifested by such clinical findings as obesity, infertility and late menopause, since it is often related either to exogenous estrogen...
administration or to endogenous hyperoestrinism [2276,2648,2805]. Endometrial hyperplasia and atypical hyperplasia have similar clinical associations.

**Imaging**

Transvaginal ultrasound (US) is the imaging technique of choice for the assessment of the endometrium in symptomatic patients, e.g. in cases of postmenopausal bleeding [133]. In postmenopausal women without hormonal replacement an endometrial thickness of 5 mm is regarded as the upper normal limit [133,2650]. The presence of endometrial thickening on ultrasound or cross sectional imaging is, however, a nonspecific finding. It may be due to endometrial hyperplasia, polyps or carcinoma. The final diagnosis usually needs to be determined by endometrial sampling [133]. Whereas currently magnetic resonance imaging (MRI) has no established role in screening for endometrial pathology, it is regarded as the best imaging technique for preoperative staging of endometrial carcinoma proven by endometrial sampling. MRI was shown to be superior to ultrasound or cross sectional imaging [2691]. The typical carcinoma is exophytic and has a shaggy, frequently ulcerated surface beneath which a soft or firm white tumour may extend shallowly or deeply into the underlying myometrium. In advanced cases the tumour may penetrate the serosa or extend into the cervix. An estimate of the extent of tumour may be requested preoperatively or operative ly in order to determine the extent of the surgical procedure to be performed [594]. In occasional cases no tumour may be visible macroscopically, with carcinoma identified only at histological examination.

**Tumour spread and staging**

The staging of uterine tumours is by the TNM/FIGO classification [51,2976].

**Endometrioid adenocarcinoma**

**Definition**

A primary endometrial adenocarcinoma containing glands resembling those of the normal endometrium.

**Histopathology**

All but a few rare endometrial carcinomas are adenocarcinomas, and the most common of these is the endometrioid type [2691]. Endometrioid adenocarcinoma represents a spectrum of histological differentiation from a very well differentiated carcinoma difficult to distinguish from atypical complex hyperplasia to minimally differentiated tumours that can be confused not only with undifferentiated carcinoma but with various sarcomas as well. A highly characteristic feature of endometrioid adenocarcinoma is the presence of at least some glandular or villoglandular structures lined by simple to pseudostratified columnar cells that have their long axes arranged perpendicularly to the basement membrane with at least somewhat elongated nuclei that are also polarized in the same direction. As the glandular differentiation decreases and is replaced by solid nests and sheets of cells, the tumour is classified as less well differentiated (higher grade). Deep myometrial invasion and lymph node metastases are both more frequent in higher grade carcinomas, and survival rates are correspondingly lower [574,1359]. It should be noted that:

1. Only those cells which are considered to be of glandular type are considered in the grading schema, so that solid nests of cells showing squamous or morular differentiation do not increase the tumour grade.
2. Bizarre nuclear atypia should raise the grade by one, e.g. from 1 to 2 or 2 to 3.
3. It should be emphasized that the presence of bizarre nuclei occurring in even a predominantly glandular tumour may indicate serous or clear cell rather than endometrioid differentiation [2691]. The distinction of very well differentiated

---

**Fig. 4.02** Well differentiated endometrioid adenocarcinoma. A Invasion is indicated by back to back glands, complex folds and stromal disappearance. B The neoplastic glands are lined by columnar cells with relatively uniform nuclei; note the altered stroma in the top of the field.

222 Tumours of the uterine corpus
endometrioid adenocarcinoma from atypical complex hyperplasia is best provided by stromal disappearance between adjacent glands, i.e. confluent, cribriform or villoglandular patterns [1433,1689,2688,2691]. Other features that may be helpful include a stromal desmoplastic response and/or tumour necrosis. Stromal foamy cells may be associated with adenocarcinoma or its precursors.

Variants of endometrioid adenocarcinoma

Endometrial proliferations may exhibit a variety of differentiated epithelial types including squamous/morules, mucinous, ciliated, cleared or eosinophilic cells, and architectural variations including papillary formations. These cell types are often called metaplasias and may be encountered in benign, premalignant and malignant epithelia. When prominent in a carcinoma the neoplasm is termed a "special variant" carcinoma.

Variant with squamous differentiation

From 20-50% or more of endometrioid adenocarcinomas contain varying amounts of neoplastic epithelium showing squamous differentiation. Although the distinction between endometrioid adenocarcinoma with and without squamous differentiation is not clinically important, the recognition of squamous differentiation is nevertheless essential because the squamous or morular elements should not be considered a part of the solid component that increases the grade of an endometrioid carcinoma. The criteria for squamous differentiation [2691] are as follows:

1. Keratinization demonstrated with standard staining techniques.
2. Intercellular bridges and/or
3. Three or more of the following four criteria:
   a. Sheet-like growth without gland formation or palisading.
   b. Sharp cell margins.
   c. Eosinophilic and thick or glassy cytoplasm.
   d. A decreased nuclear to cytoplasmic ratio as compared with foci elsewhere in the same tumour.

Villoglandular variant

This type is the next most commonly encountered endometrioid adenocarcinoma variant and is usually seen involving part of a low grade endometrioid carcinoma but not the entire tumour. In this pattern numerous villous fronds are seen, but their central cores are delicate, and cells with the usual cytological features (including stratification perpendicular to the basement membrane) line the villi. These features are in contrast to the more complex papillary architecture and high grade nuclear features that are typical of serous and clear cell adenocarcinomas growing in a papillary pattern.

Secretory variant

Occasional endometrioid adenocarcinomas are composed of glands lined by epithelium with voluminous, usually subnuclear, glycogen vacuoles reminiscent of early secretory endometrium. These tumours have minimal nuclear atypia and are diagnosable as carcinoma only by virtue of a confluent, cribriform or villoglandular pattern. As with the other variants, this pattern may be seen as the only one in an endometrioid adenocarci-
nomas or may coexist with the usual endometrioid pattern within a single tumour.

Ciliated cell variant

Although occasional ciliated cells may be seen in many endometrioid adenocarcinomas, the diagnosis of the ciliated cell variant is made only when ciliated cells line the majority of the malignant glands. Defined in this manner, this is a rare variant, and the glands often have a strong resemblance to tubal epithelium.

Mucinous adenocarcinoma

Definition

A primary adenocarcinoma of the endometrium in which most of the tumour cells contain prominent intracytoplasmic mucin.

Epidemiology

Mucinous adenocarcinoma comprises up to 9% of all cases of surgical stage I endometrial carcinoma [2454]. However, in most published series it is a relatively rare type of endometrial carcinoma [1842].

Histopathology

Both endometrioid and clear cell adenocarcinomas may have large amounts of intraluminal mucin, but only mucinous adenocarcinoma contains the mucin within the cytoplasm. The mucin is usually easily visible with hematoxylin and eosin staining but may also be demonstrated with a mucicarmine or other mucin stain.

Variants

Some mucinous adenocarcinomas have a microglandular pattern and may be difficult to distinguish from microglandular hyperplasia of the endocervix in a biopsy specimen [2066]. These neoplasms have been reported as microglandular carcinomas [3224,3241]. Rare mucinous adenocarcinomas of the endometrium may show intestinal differentiation, containing numerous goblet cells.

Differential diagnosis

The main differential diagnosis of the usual endometrial mucinous adenocarcinoma is with a primary mucinous adenocarcinoma of the endocervix. The distinction may be particularly difficult in a biopsy or curettage specimen but is crucial for therapy and may have to be resolved by clinical and imaging studies. Some studies have claimed that immunohistochemistry is useful in determining the site of origin of an adenocarcinoma in such a specimen, with endometrial carcinomas being vimentin and estrogen receptor-positive and carcinoembryonic antigen-negative and the opposite findings for endocervical adenocarcinomas [3180]. Others have found, however, that this distinction is based more on differentiation (endometrioid vs. mucinous) than on site of origin [1393].

Grading

Mucinous adenocarcinomas are theoretically graded in the same way as endometrioid adenocarcinomas, but in practice almost all of them are grade 1.

Prognosis and predictive factors

The prognosis appears to be similar to that of other low grade endometrial adenocarcinomas and thus is generally favourable.

Serous adenocarcinoma

Definition and historical annotation

A primary adenocarcinoma of the endometrium characterized by a complex pattern of papillae with cellular budding and not infrequently containing psammoma bodies. Although long recognized as a common type of adenocarcinoma of the ovary, serous adenocarcinoma was first characterized as a common endometrial tumour in the early 1980s [1186,1590].

Clinical features

Serous carcinoma typifies the so-called type II endometrial carcinoma, which dif-
fers from the prototypical type I endometrioid adenocarcinoma by its lack of association with exogenous or endogenous hyperoestrinism, its lack of association with endometrial hyperplasia and its aggressive behaviour (497, 2005, 2646).

Histopathology
Serous adenocarcinoma is usually, but not always, characterized by a papillary architecture with the papillae having broad fibrovascular cores, secondary and even tertiary papillary processes and prominent sloughing of the cells. The cells and nuclei are generally rounded rather than columnar and lack a perpendicular orientation to the basement membrane. The nuclei are typically poorly differentiated, are often apically rather than basally situated and usually have large, brightly eosinophilic macronucleoli. Mitoses, often atypical and bizarre, and multinucleated cells are commonly present, as are solid cell nests and foci of necrosis. Psammoma bodies are found in about 30% of cases and may be numerous. When the tumour grows in a glandular pattern, the glands are generally complex and "labyrinthine." Serous carcinoma is considered a high grade carcinoma by definition and is not graded.

Precursor lesions
A putative precursor of serous adenocarcinoma is serous endometrial intraepithelial carcinoma, which has also been called endometrial carcinoma in situ and surface serous carcinoma (79, 975, 2764, 3256). This lesion is characterized by a noninvasive replacement of benign (most commonly atrophic) endometrial surface and glandular epithelium by highly malignant cells that resemble those of invasive serous carcinoma. Serous endometrial intraepithelial carcinoma has been proposed as the precursor or in situ phase of serous carcinoma, and in most reported studies it has co-existed with invasive serous and, occasionally, clear cell, adenocarcinoma. Clinically, serous endometrial intraepithelial carcinoma has a significance very similar to that of invasive serous adenocarcinoma since it can also be associated with disseminated disease outside the uterus (usually in the peritoneal cavity) even in the absence of invasive carcinoma in the endometrium (79, 160, 975, 2764, 3105, 3256).

Prognosis and predictive factors
This tumour has a tendency to develop deep myometrial invasion and extensive lymphatic invasion, and patients commonly present with extrauterine spread at the time of diagnosis. However, even in the absence of a large or deeply invasive tumour extrauterine spread is common, as are recurrence and a fatal outcome (160, 1370, 3106).

Clear cell adenocarcinoma
Definition
An adenocarcinoma composed mainly of clear or hobnail cells arranged in solid, tubulocystic or papillary patterns or a combination of these patterns.

Epidemiology
The other major type II carcinoma of the endometrium is clear cell adenocarcinoma. It is less common than serous carcinoma (1-5%, as opposed to 5-10% of all endometrial carcinomas) but occurs in the same, predominantly older, patient population.

Tumour spread and staging
Similar to serous adenocarcinoma, patients with clear cell adenocarcinoma are frequently diagnosed in advanced clinical stages.

Histopathology
Histologically, clear, glycogen-filled cells and hobnail cells that project individually into lumens and papillary spaces characterize the typical clear cell adenocarcinoma. Unlike similarly glycogen-rich secretory endometrioid adenocarcinomas, clear cell adenocarcinoma contains large, highly pleomorphic nuclei, often with bizarre and multinucleated forms. The architectural growth pattern may be tubular, papillary, tubulocystic or solid and most frequently consists of a mixture of two or more of these patterns. Although psammoma bodies are present in approximately one-third of serous adenocarcinomas, they are rarely seen in clear cell adenocarcinomas. Occasionally, the tumour cells have granular...
eosinophilic (oncocytic) cytoplasm rather than the more characteristic clear cytoplasm [2258,2678]. This cell type may comprise the entire tumour and make it difficult to recognize as a clear cell adenocarcinoma. Endometrial clear cell adenocarcinomas are not graded.

Serous endometrial intraepithelial carcinoma may also be seen in association with clear cell adenocarcinoma, and the associated benign endometrium is generally atrophic rather than hyperplastic.

Prognosis and predictive factors
Patients with clear cell adenocarcinoma are frequently diagnosed in advanced clinical stages, and, thus, have a poor prognosis [24,400,1595,3003]. On the other hand, clear cell adenocarcinoma limited to the uterine corpus has a considerably better prognosis than serous adenocarcinoma of the same stage.

Mixed adenocarcinoma
Definition
Mixed adenocarcinoma is a tumour composed of an admixture of a type I (endometrioid carcinoma, including its variants, or mucinous carcinoma) and a type II carcinoma (serous or clear cell) in which the minor type must comprise at least 10% of the total volume of the tumour. The percentage of the minor component should be stated in the pathology report. It is generally accepted that 25% or more of a type II tumour implies a poor prognosis, although the significance of lesser proportions is not well understood [2648,2691].

Squamous cell carcinoma
Definition
A primary carcinoma of the endometrium composed of squamous cells of varying degrees of differentiation.

Epidemiology
Squamous cell carcinoma of the endometrium is uncommon; only about seventy cases have been reported [2397]. Among patients with known racial origin, 50% are non-White (African, Hispanic, or Asian). The median age is 61.6 years (range 41-83 years).

Clinical features
The main complaint at presentation is uterine bleeding.

Macroscopy
The tumours are often polypoid or papillary with a mean size of 3.5 cm. Infiltration of the myometrium is apparent in some cases.

Histopathology
Squamous cell carcinoma of the endometrium usually occurs in postmenopausal women and is often associated with cervical stenosis and pyometra. Only the transitional cell component invades the myometrium deeply [1669]. All endometrial transitional cell carcinomas are negative for cytokeratin 20 (CK20), but half are positive for cytokeratin 7 (CK7) [1554,1669].

Differential diagnosis
The much more common situation of a cervical squamous cell carcinoma extending into the endometrium must be excluded. Predominantly squamous differentiation of an endometrioid adenocarcinoma must also be excluded before making the diagnosis of primary pure squamous cell carcinoma of the endometrium.

Prognosis and predictive factors
The prognosis of most squamous cell carcinomas of the endometrium is rather poor, although the verrucous variant may be more favourable.

Transitional cell carcinoma
Definition
A carcinoma in which 90% or more is composed of cells resembling urothelial transitional cells. Lesser quantities of transitional cell differentiation would qualify the tumour as a mixed carcinoma with transitional cell differentiation.

Epidemiology
Transitional cell differentiation in endometrial carcinomas is extremely uncommon with fewer than 15 cases reported [1554,1669]. Among patients with known racial origin, 50% are non-White (African, Hispanic, or Asian). The median age is 61.6 years (range 41-83 years).

Clinical features
The main complaint at presentation is uterine bleeding.

Macroscopy
The tumours are often polypoid or papillary with a mean size of 3.5 cm. Infiltration of the myometrium is apparent in some cases.

Histopathology
The transitional cell component is often grade 2 or 3 and assumes a papillary configuration. It is always admixed with another type of carcinoma, most often endometrioid, but it may be clear cell or serous. HPV-associated koilocytic changes occur rarely. Only the transitional cell component invades the myometrium deeply [1669]. All endometrial transitional cell carcinomas are negative for cytokeratin 20 (CK20), but half are positive for cytokeratin 7 (CK7) [1554,1669].

Differential diagnosis
The differential diagnosis includes metastatic transitional cell carcinoma from
the ovary and bladder. Unlike primary endometrial tumours, those metastatic to the endometrium are pure transitional cell tumours. The CK7 positive, CK20 negative immunoprofile also supports müllerian rather than urothelial differentiation.

**Somatic genetics**

Human papillomavirus (HPV) type 16 has been detected in 22% of cases studied; however, the results were negative for types 6, 11, 18, 31 and 33 in all cases assessed (1554,1672). These findings suggest that HPV may play an aetiologic role in at least some cases.

**Prognostic and predictive factors**

Although information on prognostic factors is limited on these rare tumours, several women who have survived have had low stage (stage I) disease. At least two cases with extraterine extension of the disease to either the adnexa or ovarian hilus have survived over 5 years following radiation therapy suggesting that these tumours may have a more favourable response to radiation therapy than other stage II endometrial carcinomas.

**Small cell carcinoma**

**Definition**

An endometrial carcinoma resembling small cell carcinoma of the lung.

**Epidemiology**

Small cell carcinoma of neuroendocrine type is an uncommon tumour of the endometrium that comprises less than 1% of all carcinomas.

**Histopathology**

The histological appearance is similar to that of small cell carcinoma in other organs. Small cell carcinomas are positive for cytokeratin and mostly positive for neuroendocrine markers, whereas one-half are positive for vimentin.

**Prognosis and predictive factors**

In contrast to small cell carcinoma elsewhere in the female genital tract, the prognosis is far better in stage I disease with a 5-year survival of about 60% (23, 1271).

**Undifferentiated carcinoma**

Undifferentiated carcinomas are those lacking any evidence of differentiation.
Rare types of endometrial carcinoma

Almost every type of carcinoma reported elsewhere has been described in at least a single case report as primary in the endometrium.

Histopathology

These tumours are histologically (and usually clinically, if enough cases are available for analysis) identical to their more common counterparts in other organs. They include adenoid cystic carcinoma (985), glassy cell carcinoma (1103), and mesonephric carcinoma (2110). Oncocytic/oxyphilic carcinoma is thought by some to be a variant of clear cell carcinoma, whereas others consider it to be a separate tumour.

Endometrial hyperplasia

Definition

A spectrum of morphologic alterations ranging from benign changes, caused by an abnormal hormonal environment, to premalignant disease.

Criteria for histological typing

The endometrial hyperplasias are classified by their degree of architectural complexity as simple or complex (adenomatous) and by their cytological (nuclear) features as hyperplasia or atypical hyperplasia. The endometrium is uniquely endowed throughout the female reproductive lifespan with a complex regular cycle of periodic proliferation, differentiation, breakdown and regeneration. This high cellular turnover, conditioned by ovarian hormones and growth factors, has many opportunities for losing its regulatory controls. Endometrial hyperplasia encompasses conditions that range from benign estrogen-dependent proliferations of glands and stroma to monoclonal outgrowths of genetically altered glands.

WHO classification

Many classifications had been proposed prior to 1994 when the World Health Organization (WHO) adopted its current Table 4.02 World Health Organization classification of endometrial hyperplasia (2002).

<table>
<thead>
<tr>
<th>Hyperplasias (typical)</th>
<th>Atypical hyperplasias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple hyperplasia without atypia</td>
<td>Simple atypical hyperplasia</td>
</tr>
<tr>
<td>Complex hyperplasia without atypia (adenomatous without atypia)</td>
<td>Complex atypical hyperplasia (adenomatous with atypia)</td>
</tr>
</tbody>
</table>

The high degree of morphological variability of endometrial proliferations even within the same sample is responsible for the difficulty in defining consistent and clinically meaningful diagnostic criteria (240,3135). A further complication is fragmentation and scantiness of many aspiration biopsies. Nevertheless, histological interpretation remains the most accessible, albeit somewhat subjective, method of evaluating endometrial hyperplasias.
Although this classification has been widely applied, its reproducibility is somewhat disappointing, and molecular data with direct implications for histological diagnosis were unavailable at the time of the 1994 classification. Nevertheless, it remains the best available classification and has been adopted in this new edition.

Endometrial hyperplasias are assumed to evolve as a progressive spectrum of endometrial glandular alterations divided into four separate categories by architecture and cytology. The vast majority of endometrial hyperplasias mimic proliferative endometria, but rare examples demonstrate secretory features. The entire spectrum of metaplastic changes may be observed in hyperplastic endometria.

**Hyperplasias without atypia**

Hyperplasias without atypia represent the exaggerated proliferative response to an unopposed estrogenic stimulus; the endometrium responds in a diffuse manner with a balanced increase of both glands and stroma. In simple hyperplasia the glands are tubular although frequently cystic or angular, and some even show minor epithelial budding. The lining is pseudostratified with cells displaying regular, elongated nuclei lacking atypia. In complex (adenomatous) hyperplasia the glands display extensive architectural changes represented by irregular epithelial budding into both lumina and stroma and a typical cytology with pseudostratified but uniform, elongated and polarized glandular nuclei; squamous epithelial morules can be present. There is most often a shift in the gland to stroma ratio in favour of the glands.

**Atypical hyperplasias**

The main feature which differentiates this category from the previous one is the atypical cytology of the glandular lining as represented by loss of axial polarity, unusual nuclear shapes that are often rounded, irregularity in the nuclear membranes, prominent nucleoli and cleared or dense chromatin. Atypia occurs nearly always focally.

Simple atypical hyperplasia features atypical glandular cytology superimposed on the architecture of simple hyperplasia. This pattern is extremely unusual. The frequently found complex atypical (adenomatous with atypia) hyperplasia is a lesion characterized by an increased glandular complexity with irregular outgrowths and cytological atypia. There may be associated foci of non-endometrioid differentiation such as squamous morules. Due to the expansion and crowding of glands, the interglandular stroma is diminished but remains present. Characteristic features of adenocarcinoma are absent.

The assessment of cytological atypia is the key problem in assigning individual cases to one of the four different WHO categories. Definitions of cytological atypia are difficult to apply in the endometrium because nuclear cytological changes occur frequently in hormonal imbalance, benign regeneration and metaplasia. Paradoxically, atypical hyperplasia may exhibit more atypical features than adenocarcinoma, and some grade 1 invasive endometrioid carcinomas have an extremely bland cytology. Perhaps, it would be more appropriate to consider cytological changes in the context of overall glandular architecture. Indeed, architectural fociality of the lesion is so closely linked with atypia that possibly they are inseparable. In this way, atypia is best observed by comparison with adjoining normal glands.

**Caveat: sampling problems**

The focal nature of atypical endometrial hyperplasias may allow young women to maintain fertility, but has the disadvantage of possible underdiagnosis due to incomplete sampling. The problem is greatest in scanty fragmented specimens, something commonly encountered in routine office biopsies. Clearly, this situation is responsible for the false negative biopsies during follow up. Hysteroscopic direction may assist in targeting a macroscopically apparent localized lesion but is not a common practice in most settings.

**Contemporary approach to endometrial hyperplasia**

Poor reproducibility of the 1994 WHO hyperplasia schema has led to a proposal to reduce the number of diagnostic classes. New concepts of pathogenesis have been incorporated into an integrated genetic, histomorphometric and clinical outcome model of
Tumours of the uterine corpus

Premalignant disease [1956,1958] (see section on genetics of endometrial carcinoma and precursor lesions). The clinical relevance of the model, however, has yet to be established.

**Endometrial polyp**

**Definition**
A benign nodular protrusion above the endometrial surface consisting of endometrial glands and stroma that is typically at least focally fibrous and contains thick-walled blood vessels.

**Histopathology**
Histologically, they are pedunculated or sessile lesions with a fibrous stroma in which characteristic thick-walled, tortuous, dilated blood vessels are found. The glandular component is patchily distributed and shows dilated, occasionally crowded glands lined with an atrophic epithelium, although rarely cyclic activity may be observed. Rare cases of atypical stromal cells have been documented in endometrial polyps [2834], similar to those seen in polyps of the lower female genital system. Polyps can be differentiated from polypoid hyperplasias due to the distinctive stromal and vascular features of the former. Atypical hyperplasias and malignant tumours including adenocarcinomas of endometrioid and other types such as serous, as well as sarcomas and mixed tumours [2675] can be found arising in polyps.

**Somatic genetics**
Endometrial polyps constitute benign monoclonal proliferations of mesenchyme [891] and frequently show karyotypic abnormalities of chromosomal regions 6p21 and 12q15 [2854], sites in which the **HMGIC** and **HMG1Y** genes are located.

**Genetics of endometrial carcinoma and precancer**

**Genotype and histotype**
Endometrial adenocarcinoma is characterized by the abrogation of **PTEN** or **TP53** tumour suppressor pathways, respectively, for the endometrioid (type I) and non-endometrioid (type II, including serous and clear cell types) clinicopathological subgroups [2647]. Deletion and/or mutation of the **PTEN** and **TP53** genes themselves are early events with widespread distribution in advanced tumours and a presence in the earliest stages of disease.

**Somatic genetics**
Despite these histological differences, the cytogenetic profile of tamoxifen-related polyps is identical to non-iatrogenic polyps [609].

**Tamoxifen-related lesions**

**Definition**
Lesions that develop in the endometrium in patients undergoing long term tamoxifen therapy.

**Epidemiology**
Patients undergoing long term tamoxifen treatment often have enlarged uterus and frequently show endometrial cysts; up to 25% have endometrial polyps [531].

**Macroscopy**
Tamoxifen-related polyps differ from non-iatrogenic endometrial polyps in that they are larger, sessile with a wide implantation base in the fundus and frequently show a honeycomb appearance.

**Histopathology**
Histologically, the differential features with normal endometrial polyps include the bizarre stellate shape of glands and the frequent epithelial (mucinous, ciliated, eosinophilic, microglandular) and stromal (smooth muscle) metaplasias [665,1437,2558]. There is often a periglandular stromal condensation (cambium layer). Malignant transformation occurs in up to 3% of cases, and endometrioid adenocarcinoma is the most frequent type. However, other types of malignant neoplasm such as serous carcinoma and carcinosarcoma may develop in this setting.

**Somatic genetics**
Despite these histological differences, the cytogenetic profile of tamoxifen-related polyps is identical to non-iatrogenic polyps [609].

---

Fig. 4.19 Endometrial polyp. The glands are cystic and contain mucoid material, the stroma is fibrous, and the vessels are prominent.

Fig. 4.20 Endometrial polyp with complex hyperplasia. Note the foci of crowded, convoluted glands in an atrophic endometrial polyp.

Fig. 4.21 Uterine tamoxifen-related lesion. Thickened myometrium in a 69 year old patient with subendometrial cysts and a polyp (arrow).

Fig. 4.22 TP53 mutations in endometrial carcinoma. Left: Wild type sequence in an endometrioid carcinoma: Exon 8 mutations in two serous carcinomas (arrows). Middle: GTT > TTT; Val > Phe (codon 274). Right: CGT > CAT; Arg > His (codon 273).
detectable premalignant (type I) [1959] or non-invasive malignant (type II) phases of tumourigenesis [2647,2863]. A comprehensive model of sequential genetic damage has not been formulated for endometrial cancer despite a growing number of candidate genes. PTEN checks cell division and enables apoptosis through an Akt-dependent mechanism. Functional consequences of PTEN mutation may be modulated in part by the hormonal environment, as PTEN is expressed only during the estrogen-driven proliferative phase of the endometrium [1957]. The use of PTEN immunohistochemistry as a tool for diagnosis of clinically relevant neoplastic endometrial disease is limited by the fact that one-third to one-half of type I cancers continue to express PTEN protein, and loss of PTEN function occurs as an early event that may precede cytological and architectural changes [1959].

**Molecular delineation of premalignant disease**

Type I cancers begin as monoclonal outgrowths of genetically altered premalignant cells, and many bear genetic stig mata of microsatellite instability, KRAS mutation and loss of PTEN function that are conserved in subsequent cancer [1642,1956]. The earliest molecular changes, including PTEN, are detectable at a stage before glands have undergone any change in morphology [1959]. The accumulation of genetic damage is thought to cause emergence of histologically evident monoclonal lesions. Further elaboration of the histopathology of endometrial precancers has been accomplished through correlative histomorphometric analysis of genetically ascertained premalignant lesions [1958]. Because these lesions were initially defined by molecular methods, their diagnostic criteria differ from those of atypical endometrial hyperplasia. They have been designated endometrial intraepithelial neoplasia (‘EIN’) [1955].

### Table 4.03

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Type I</th>
<th>Type II</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Immunoreactivity (mutant)</td>
<td>5-10%</td>
<td>80-90%</td>
<td>(228,2647)</td>
</tr>
<tr>
<td>PTEN</td>
<td>No immunoreactivity</td>
<td>55%</td>
<td>11%</td>
<td>(1957)</td>
</tr>
<tr>
<td>KRAS</td>
<td>Activation by mutation</td>
<td>13-26</td>
<td>0-10%</td>
<td>(228,1512,1594,1787)</td>
</tr>
<tr>
<td>Beta-catenin</td>
<td>Immunoreactivity (mutant)</td>
<td>25-38%</td>
<td>rare</td>
<td>(1787)</td>
</tr>
<tr>
<td>MLH1</td>
<td>Microsatellite instability / epigenetic silencing</td>
<td>17%</td>
<td>5%</td>
<td>(799,828,1594)</td>
</tr>
<tr>
<td>P27</td>
<td>Low immunoreactivity</td>
<td>68-81%</td>
<td>76%</td>
<td>(2562)</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>High immunoreactivity</td>
<td>41-56%</td>
<td>19%</td>
<td>(2562)</td>
</tr>
<tr>
<td>P16</td>
<td>Low immunoreactivity</td>
<td>20-34%</td>
<td>10%</td>
<td>(2562)</td>
</tr>
<tr>
<td>Rb</td>
<td>Low immunoreactivity</td>
<td>3-4%</td>
<td>10%</td>
<td>(2562)</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Low immunoreactivity</td>
<td>65%</td>
<td>87%</td>
<td>(1512)</td>
</tr>
<tr>
<td>Bax</td>
<td>Low immunoreactivity</td>
<td>48%</td>
<td>43%</td>
<td>(1512)</td>
</tr>
</tbody>
</table>

**Receptors**

| ER and PR     | Positive immunoreactivity           | 70-73% | 19-24%  | (1512)     |

ER = Estrogen receptor  
PR = Progesterone receptor

### Table 4.04

Essential diagnostic criteria of endometrial intraepithelial neoplasia (EIN).

<table>
<thead>
<tr>
<th>EIN Criterion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Architecture</td>
<td>Gland area exceeds that of stroma, usually in a localized region.</td>
</tr>
<tr>
<td>2. Cytological alterations</td>
<td>Cytology differs between architecturally crowded focus and background.</td>
</tr>
<tr>
<td>3. Size &gt;1 mm</td>
<td>Maximum linear dimension should exceed 1 mm. Smaller lesions have unknown natural history.</td>
</tr>
<tr>
<td>4. Exclude benign mimics and cancer</td>
<td></td>
</tr>
</tbody>
</table>

---

**Fig. 4.23** Endometrioid adenocarcinoma (type I). Note the focal accumulation of mutant TP53 protein within a TP53 wild-type carcinoma.

**Fig. 4.24** Serous intraepithelial carcinoma (type II) expresses TP53 mutant protein.

---

**Epithelial tumours and related lesions** 231
Endometrial intraepithelial neoplasia (EIN)

This lesion is defined as the histopathological presentation of premalignant endometrial disease as identified by integrated molecular genetic, histomorphometric and clinical outcome data. Tissue morphometry (D-Score [153] predictive of cancer outcome) and genetic studies are cross validating in that these methodologically independent techniques provide concordant identification of EIN lesions when applied to a common pool of study material [1958]. The EIN scheme partitions endometrial proliferations into different therapeutic groups. Distinctive diagnostic categories include:

1. Benign architectural changes of unopposed estrogens (endometrial hyperplasia).
2. EIN.
3. Well differentiated adenocarcinoma.

The histological changes produced by unopposed estrogens (non-atypical hyperplasias) are quite unlike localizing EIN lesions. The latter originate focally through monoclonal outgrowth of a mutant epithelial clone with altered cytol-ogy and architecture. Computerized morphometric analysis, which quantifies specific architectural patterns associated with increased clinical cancer risk [154], objectively defined the morphol-ogy of monoclonal EIN lesions. Because of differing diagnostic criteria, only 79% of atypical endometrial hyperplasias translate to EIN, and approximately a third of all EIN diagnoses are garnered from non-atypical hyperplasia catego-ries.

Genetic susceptibility

The overwhelming majority of endometri-al cancers are sporadic, but they may rarely present as a manifestation of mul-ticancer familial syndromes. Examples include hereditary nonpolyposis colon cancer (HNPCC), caused by mutation of DNA mismatch repair genes that produce constitutive microsatellite instability [799] and Cowden syndrome in patients with germline PTEN inactivation [1957].

Prognosis and predictive factors

In addition to tumour type and, for type I adenocarcinomas, tumour grade, other histological and non-histological determinations influence the prognosis of endometrial carcinoma. The most important of these is the surgical stage, which in 1988 replaced the clinical staging sys-tem that had been in use for many years [2642]. The extent of surgical staging performed is based in part on the med-ical condition of the patient and in part on the preoperative or intraoperative assessment of tumour risk factors such as type and grade, depth of myometrial invasion and extension to involve the cervix [2692,2714].

Myometrial invasion is thus an important issue, both as a prognostic factor in its own right and as a determinant of the extent of staging and of subsequent therapy in cases treated by hysterectomy. FIGO divides stage I tumours into IA (lim-it ed to the endometrium), IB (invasion of less than half of the myometrium), and IC (invasion of more than half of the myometrium), [51,2976]. Some oncolo-gists, however, make treatment decisions based on thirds (inner, mid, outer) of myometrial invasion or distance in mil-limetres (mm) from the serosal surface. Thus, the pathologist can best satisfy the desires for all of this information by reporting the maximal depth of tumour invasion from the endometromyal junction and the thickness of the myometrium at that point (e.g. 7 mm tumour invasion into a 15 mm thick myometrium) [2686]. True myometrial invasion must be distin-guished from carcinomatous extension (not invasion) into pre-existing "tongues" of endometrium penetrating the myometrium or into foci (sometimes deep-seated) of adenomyosis [2652, 2688]. It should also be noted that tumour extension to the uterine serosa raises the stage to IIIA. Vascular or lymphatic space invasion is an unfavourable prognostic factor that should be reported [78]. Perivascular lymphocytic infiltrates may be the first clue to vascular invasion and, thus, should prompt deeper levels within the suspect block and/or the submission of more tissue sections for histo-

logical examination.

It is also important to evaluate cervical involvement in the hysterectomy speci-men since extension to the cervix raises the stage to II. The distinction between stage IIA and IIB is based on whether the extension involves the endocervical sur-face and/or underlying glands only or invades the cervical stroma. One should be aware that an adenocarcinoma involv-ing glands only might be an entirely separ-ate adenocarcinoma in situ primary in the endocervix. Non-histological factors may also play a role in determining the prognosis of endometrial carcinoma. It is unclear at the present time, however, what the cost/benefit ratio of performing addition-al studies might be since the prognosis and treatment are currently based on the combination of tumour type, grade, where appropriate, and extent, as dis-cussed above. Nevertheless, patients with carcinomas of intermediate progno-sis, such as stage I well differentiated endometrioid adenocarcinoma with focal deep myometrial invasion might benefit from additional information including such factors as tumour ploidy [1349,1441], hormone receptor status [575,1441], tumour suppressor genes [1309,1449], oncogenes [1205,1449], proliferation markers [966,1449,2012] and morphometry [2751]. Which, if any, of these or other studies will prove to be most useful is problematic at this time.
Mesenchymal tumours and related lesions

Definition
Uterine mesenchymal tumours are derived from the mesenchyme of the corpus consisting of endometrial stroma, smooth muscle and blood vessels or admixtures of these. Rarely, these tumours may show mesenchymal differentiation that is foreign to the uterus.

Epidemiology
The most common malignant mesenchymal tumours of the uterine corpus are leiomyosarcoma and endometrial stromal tumours, and both are more frequent in Black than in White women (1139, 1729).

Clinical features

Signs and symptoms
The most common presentation for mesenchymal tumours is uterine enlargement, abnormal uterine bleeding or pelvic pain.

Imaging
Non-invasive imaging, usually by ultrasound, but occasionally by magnetic resonance imaging (MRI), can be utilized in selected cases to distinguish between a solid ovarian tumour and a pedunculated leiomyoma or to distinguish leiomyomas from adenomyosis. On MRI leiomyomas present as well delineated lesions of low signal intensity on T1 and T2-weighted images. They may, however, undergo degenerative changes resulting in various, non-specific MRI appearances [1947,2971]. On MRI the presence of a large, heterogeneous mass with irregular contours should raise concern for sarcoma.

Endometrial stromal and related tumours

Definition and historical annotation
Endometrial mesenchymal tumours in their better-differentiated forms are composed of cells resembling those of proliferative phase endometrial stroma. Numerous thin-walled small arteriolar type (plexiform) vessels are characteristically present. Endometrial stromal sarcomas (ESS) have been traditionally divided into low and high grade types based on mitotic count. However, since high grade endometrial sarcomas lack specific differentiation and bear no histological resemblance to endometrial stroma, it has been proposed that they be designated undifferentiated endometrial or uterine sarcoma (811). In this classification the distinction between low grade ESS and undifferentiated endometrial sarcoma is not made on the basis of mitotic count but on features such as nuclear pleomorphism and necrosis.

ICD-O codes
Endometrial stromal sarcoma, low grade 8931/3
Endometrial stromal nodule 8930/0
Undifferentiated endometrial sarcoma 8930/3

Histopathology
Endometrial stromal tumours are composed of cells resembling those of proliferative endometrial stroma and are far less frequent than smooth muscle tumours. Endometrial stromal tumours are subdivided into benign and malignant groups based on the type of tumour margin [1432,2054,2097,2883]. Those with pushing margins are benign stromal nodules, whereas those with infiltrating margins qualify as stromal sarcomas. There is general agreement on the morphologic definition of typical cases of both low grade ESS and undifferentiated endometrial sarcoma. Characteristically, low grade ESS, a clinically indolent neoplasm, features a plexiform vasculature, minimal cytological atypia and infrequent mitotic figures. The usual undifferentiated sarcoma, a highly aggressive neoplasm, lacks a plexiform vasculature, features substantial cytological atypia and has frequent and often atypical mitotic figures. However, there is no valid evidence that the isolated finding of a mitotic index of 10 or more per 10 high power fields is an adverse prognostic finding in a neoplasm that is otherwise a typical low grade ESS. A small minority of cases share features of low grade ESS and undifferentiated sarcoma, and their classification is controversial.

Immunoprofile
The neoplastic cells of both the stromal nodule and low grade ESS are immunoreactive for vimentin, CD10

Fig. 4.25 Low grade endometrial stromal sarcoma (ESS). A Worm-like, soft, yellow masses focally replace the myometrium. B The myometrium is extensively infiltrated by basophilic islands of low grade ESS. C A tongue of low grade ESS protrudes into a vascular space.
Tumours of the uterine corpus

[486,1821] and at least focally for actin [914]. They are usually, but not always [914], negative for desmin and h-caldesmon [2065,2101,2488]. Low grade ESS is almost always positive for both estrogen and progesterone receptors. (1411,2350,2502). Rarely, low grade endometrial stromal tumours, particularly those with areas displaying a sex cord pattern, may be positive for alpha-inhibin (1521), CD99 (167) and cytokeratin (29). The sex cord areas may also be immunoreactive for desmin, whereas the surrounding endometrial stromal cells are not (678,1661).

Somatic genetics
Fusion of two zinc finger genes (JAZF1 and JJAZ1) by translocation t(7;17) is present in most low grade endometrial stromal tumours (1189,1252,1503). Endometrial stromal nodules and low grade ESSs are typically diploid with a low S-phase fraction (292,1220).

Prognosis and predictive factors
The histological distinction between undifferentiated endometrial sarcoma and low grade ESS has important implications regarding prognosis (2601) Low grade ESSs are indolent tumours with a propensity for local recurrence, usually many years after hysterectomy. Distant metastases are less common. In contrast, undifferentiated endometrial sarcomas are highly aggressive tumours with the majority of patients presenting with extraterine disease at the time of diagnosis and dying within two years of diagnosis (232,811).

Endometrial stromal sarcoma, low grade
Definition
This tumour fits the definition of endometrial stromal tumour presented above and is distinguished from the stromal nodule on the basis of myometrial infiltration and/or vascular space invasion.

Epidemiology
Low grade ESS is a rare tumour of the uterus accounting for only 0.2% of all genital tract malignant neoplasms (645,1509,1745). In general low grade ESSs affect younger women than other uterine malignancies; studies have demonstrated that the mean age ranges from 42-58 years, and 10-25% of patients are premenopausal (437,645).

Clinical features
The clinical features have been discussed above.

Macroscopy
Low grade ESS may present as a solitary, well delineated and predominantly intra-mural mass, but extensive permeation of the myometrium is more common, with extension to the serosa in approximately half of the cases. The sectioned surface appears yellow to tan, and the tumour has a softer consistency than the usual leiomyoma. Cystic and myxoid degeneration as well as necrosis and haemorrhage are seen occasionally.

Localization
Metastases are rarely detected prior to the diagnosis of the primary lesion (29,684,3222). Extraterine extension is present in up to a third of the women with low grade ESS at the time of hysterectomy. The extension may appear as worm-like plugs of tumour within the vessels of the broad ligament and adnexa.

Histopathology
Low grade ESS is usually a densely cellular tumour composed of uniform, oval to spindle-shaped cells of endometrial stromal-type; by definition significant atypia and pleomorphism are absent. Although most tumours are paucimotic, mitotic rates of 10 or more per 10 high power fields can be encountered, and a high mitotic index does not in itself alter the diagnosis. A rich network of delicate small arterioles resembling the spiral arterioles of the late secretory endometrium supports the proliferating cells. Cells with foamy cytoplasm (tumour cells, foamy histiocytes, or both) are prominent in some cases. Endometrial type glands occur in 11-40% of endometrial stromal tumours (516,1343,2054). Sex cord-like structures may also be found (511). Myxoid and fibrous change may occur focally or diffusely (2054,2102). Perivascular hyalinization and a stellate pattern of hyalinization occur in some cases. Reticulin stains usually reveal a dense network of fibrils surrounding individual cells or small groups of cells. Necrosis is typically absent or inconspicuous.

Focal smooth muscle differentiation (spindle or epithelioid) or cells with differentiation that is ambiguous between stromal and smooth muscle cells may develop in endometrial stromal tumours; these
areas are limited to less than 30% of the tumour. When the smooth muscle component comprises 30% or more of the tumour, the lesion is designated as a mixed endometrial stromal and smooth muscle tumour. Focal rhabdoid differentiation has been described in one case [1813]. The differential diagnosis includes stromal nodule, intravenous leiomyomatosis, adenomyosis with sparse glands and adenosarcoma. In a biopsy or curettage specimen it is often impossible to distinguish low grade ESS from a stromal nodule, a non-neoplastic stromal proliferation or a highly cellular leiomyoma.

**Histogenesis**

Extraterine primary endometrioid stromal sarcomas occur and often arise from endometriosis [280].

**Prognosis and predictive factors**

Low grade ESS is characterized by indolent growth and late recurrences; up to one-half of patients develop one or more pelvic or abdominal recurrences. The median interval to recurrence is 3-5 years but may exceed 20 years. Pulmonary metastases occur in 10% of stage I tumours [1311]. The 5-year survival rate for low grade ESS ranges from 67% [2048] to nearly 100% with late metastases and a relatively long-term survival despite tumour dissemination [427,811,2263]. The surgical stage is the best predictor of recurrence and survival for ESSs [300,437]. Both recurrent and metastatic ESSs may remain localized for long periods and are amenable to successful treatment by resection, radiation therapy, progestin therapy or a combination thereof [300,1750,3080]. Conservative management has been advocated for some patients with low grade ESS [1677]. In some studies that have utilized progestin therapy, 100% survival rates have been achieved even for patients with stage III tumours [2263].

**Endometrial stromal nodule**

**Definition**

A benign endometrial stromal tumour characterized by a well delineated, expansile margin and composed of neoplastic cells that resemble proliferative phase endometrial stromal cells supported by a large number of small, thin-walled arteriolar-type vessels.

**Clinical features**

Women with a stromal nodule range in age from 23-75 years with a median of 47 years [292,437,2097,2098,2101,2098,2883]. About one-third of the women are postmenopausal. Two-thirds of the women present with abnormal uterine bleeding and menorrhagia. Pelvic and abdominal pain occur less frequently.

**Macroscopy**

The tumour is characteristically a solitary, well delineated, round or oval, fleshy nodule with a yellow to tan sectioned surface. The median tumour diameter is 4.0 cm (range 0.8-15 cm) [2883]. About two-thirds are purely intramural without any apparent connections to the endometrium, 18% of the lesions are polypoid, and others involve both the endometrium and myometrium.

**Histopathology**

The histological appearance is identical to that described above for low grade ESS except for the absence of infiltrative margins [292,437,2097,2098,2101,2102,2883]. Rare, focal marginal irregularity in the form of finger-like projections that do not exceed 3 mm is acceptable. Smooth and skeletal muscle along with sex cord differentiation may be present focally [1685]. The differential diagnosis includes low grade ESS and highly cellular leiomyoma. The presence of at least focal neoplastic smooth muscle bundles, large, thick walled vessels and strong immunoreactivity with desmin and h-caldesmon and the absence of reactivity with CD10 help distinguish a highly cellular leiomyoma from a stromal nodule.
Prognosis and predictive factors
Endometrial stromal nodules are benign (437,2101,2883). A hysterectomy may be required if the lesion has not been completely excised.

Undifferentiated endometrial sarcoma

Definition
A high grade endometrial sarcoma that lacks specific differentiation and bears no histological resemblance to endometrial stroma.

Synonym
Undifferentiated uterine sarcoma.

Macroscopy
Macroscopically, undifferentiated uterine sarcomas are characterized by one or more polypoid, fleshy, grey to yellow endometrial masses and often show prominent haemorrhage and necrosis.

Histopathology
Histologically, undifferentiated endometrial sarcomas show marked cellular atypia and abundant mitotic activity, often including atypical forms. They lack the typical growth pattern and vascularity of low grade ESS (651,811) and displace the myometrium in contrast to the infiltrative pattern of low grade ESS. They resemble the sarcomatous component of a carcinosarcoma, and the possibility of carcinosarcoma and other specific sarcomas should be excluded with adequate sampling.

These sarcomas are most often aneuploid with an S-phase fraction greater than 10% (292) and negative for estrogen and progesterone receptors.

Prognosis and predictive factors
These tumours are aggressive, and death occurs from tumour dissemination within three years after hysterectomy in most cases.

Smooth muscle tumours

Definition
Benign or malignant neoplasms composed of cells demonstrating smooth muscle differentiation.

ICD-O codes
Leiomyosarcoma, NOS 8890/3
Epithelioid variant 8891/3
Myxoid variant 8896/3
Smooth muscle tumour of uncertain malignant potential 8897/1
Leiomyoma, NOS 8890/0
Leiomyoma, histological variants
Cellular leiomyoma 8892/0
Epithelioid leiomyoma 8891/0
Myxoid leiomyoma 8896/0
Atypical leiomyoma 8893/0

Table 4.05
Diagnostic criteria for leiomyosarcoma.

<table>
<thead>
<tr>
<th>Standard smooth muscle differentiation</th>
<th>Epithelioid differentiation</th>
<th>Myxoid differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Fascicles of cigar-shaped spindled cells with scanty to abundant eosinophilic cytoplasm</td>
<td>Rounded cells with central nuclei and clear to eosinophilic cytoplasm</td>
</tr>
<tr>
<td>Criteria for leiomyosarcoma</td>
<td>Any coagulative tumour cell necrosis</td>
<td>Any coagulative tumour cell necrosis</td>
</tr>
<tr>
<td>In the absence of tumour cell necrosis the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ≥ 10mf/10hpf. When the mitotic index is less than 10mf/10hpf, the chance of recurrence is low (less than a 2-3%) and the tempo of recurrence is slow. This group is labelled 'atypical leiomyoma with low risk of recurrence'.</td>
<td>In the absence of tumour cell necrosis the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ≥ 5mf/10hpf</td>
<td>In the absence of tumour cell necrosis, the diagnosis requires diffuse, moderate to severe cytological atypia and a mitotic index of ≥ 5mf/10hpf</td>
</tr>
<tr>
<td>Comments</td>
<td>In the absence of coagulative tumour cell necrosis and significant atypia a high mitotic index is compatible with a benign clinical course. When the mitotic index exceeds 15 mf/10hpf the term 'mitotically active leiomyoma with limited experience' can be used</td>
<td>Focal epithelioid differentiation may be mimicked by cross-sectioned fascicles of standard smooth muscle</td>
</tr>
</tbody>
</table>

mf/10hpf = mitotic figure(s) per 10 high power fields. See ref. (211) for discussion of mitosis counting techniques.
Lipoleiomyoma 8890/0
Leiomyoma, growth pattern variants
Diffuse leiomyomatosis 8890/1
Intravenous leiomyomatosis 8890/1
Benign metastasizing leiomyoma 8898/1

Leiomyosarcoma

Definition
A malignant neoplasm composed of cells demonstrating smooth muscle differentiation.

Epidemiology
Leiomyosarcoma represents the most common pure uterine sarcoma and comprises slightly over 1% of all uterine malignancies [1139]. The incidence of leiomyosarcoma is reported to be 0.3-0.4/100,000 women per year [1139]. Leiomyosarcoma arises nearly exclusively in adults. The median age of patients with leiomyosarcoma was 50-55 years in larger studies [947,1745], and 15% of the patients were younger than 40 years. The risk factors for endometrial carcinomas such as nulliparity, obesity, diabetes mellitus and hypertension are not known to relate to leiomyosarcoma.

Clinical features
Leiomyosarcomas localized to the uterus and leiomyomas produce similar symptoms. Although a rapid increase in the size of the uterus after menopause may raise the possibility of leiomyosarcoma, in fact sarcoma is not more prevalent (less than 0.5%) in women with “rapidly growing” leiomyomas [1622,2187]. Leiomyosarcoma may spread locally, regionally or by haematogenous dissemination. This fact of natural history has implications for both diagnosis and management. Local and regional extension may produce an abdominal or pelvic mass and gastrointestinal or urinary tract symptoms. Haematogenous dissemination is most often to the lungs. Leiomyosarcoma is only infrequently diagnosed on endometrial samplings [1622].

Macroscopy
Leiomyosarcomas are characteristically solitary intramural masses and are usually not associated with leiomyomas. Leiomyosarcomas average 8.0 cm in diameter and are fleshy with poorly defined margins. Zones of haemorrhage and necrosis characteristically interrupt their grey-yellow or pink sectioned surface.
Histopathology

The usual leiomyosarcoma is a cellular tumour composed of fascicles of spindle-shaped cells that possess abundant eosinophilic cytoplasm. Typically, the nuclei are fusiform, usually have rounded ends and are hyperchromatic with coarse chromatin and prominent nucleoli. Tumour cell necrosis is typically prominent but need not be present. The mitotic index usually exceeds 15 figures per 10 high power fields. Vascular invasion is identified in up to 25% of leiomyosarcomas. Giant cells resembling osteoclasts occasionally are present in otherwise typical leiomyosarcomas, and, rarely, xanthoma cells may be prominent (1058,1776).

A diagnosis of leiomyosarcoma should be made with great caution in women less than 30 years of age and only after exclusion of exposure to Leuprolide, which sometimes induces a pattern of necrosis identical to coagulative tumour cell necrosis (664).

Epithelioid variant

Epithelioid leiomyosarcomas combine an “epithelioid” phenotype with the usual features of malignancy, i.e. high cellularity, cytological atypia, tumour cell necrosis and a high mitotic rate (130,1538, 2292). Specifically, epithelioid differentiation denotes tumour cells that have a rounded configuration with eosinophilic to clear cytoplasm. When the cytoplasm is totally clear the label "clear cell" is used. Most malignant epithelioid smooth muscle tumours are of the leiomyoblastoma type, although clear cell leiomyosarcoma has been reported.

Myxoid variant

Myxoid leiomyosarcoma is a large, gelatinous neoplasm that often appears to be circumscribed on macroscopic examination (131,1465). The smooth muscle cells are widely separated by myxoid material. The characteristic low cellularity largely accounts for the presence of only a few mitotic figures per 10 high power fields in most myxoid leiomyosarcomas. In almost all instances myxoid leiomyosarcomas show cellular pleomorphism and nuclear enlargement. They commonly show myometrial and, sometimes, vascular invasion.

Prognosis and predictive factors

Leiomyosarcoma is a highly malignant neoplasm (1745,2096). The variation in survival rates reported historically is largely the result of the use of different criteria for its diagnosis. Overall 5-year survival rates range from 15-25% (185,231,377,1585,3109). The 5-year survival rate is 40-70% in stage I and II tumours (291,947,1381,1585, 1765, 1797, 2045, 2049, 2200,3139). Premenopausal women have a more favourable outcome in some series (947, 1381, 1585, 1797,3005,3139) but not in others (185,1148). Most recurrences are detected within 2 years (231,377,1148, 1381). The prognosis of leiomyosarcoma depends chiefly upon the extent of spread. For tumours confined to the uterine corpus, some investigators have found that the size of the neoplasm is an important prognostic factor (812,1364, 2049) with the best demarcation occurring at 5 cm. Several recent series, including the large Gynecologic Oncology Group study of early stage leiomyosarcoma, have found the mitotic index to be of prognostic significance (811,947,1585,1745), whereas others have not (812). The utility of grading leiomyosarcomas is controversial, and no universally accepted grading system exists. Pathologists should comment on the presence or absence of extratumour extension and/or vascular space involvement, the maximum tumour diameter and the mitotic index.

Smooth muscle tumour of uncertain malignant potential

Definition

A smooth muscle tumour that cannot be diagnosed reliably as benign or malignant on the basis of generally applied criteria.

Histopathology

This category of smooth muscle tumour of uncertain malignant potential should
be used sparingly and is reserved for smooth muscle neoplasms whose appearance is ambiguous for some reason, and the relevant diagnostic possibilities differ in their clinical implications (211). Examples include cases in which the subtype of smooth muscle differentiation is in doubt, i.e. standard smooth muscle, epithelioid or myxoid, and application of the competing classification rules would lead to different clinical predictions. On other occasions the assessment of a diagnostic feature, e.g. the type of necrosis or the interpretation of mitotic figures, is ambiguous, and the competing alternative interpretations would lead to different clinical predictions.

**Leiomyoma**

**Definition**
A benign neoplasm composed of smooth muscle cells with a variable amount of fibrous stroma.

**Macroscopy**
Leiomyomas are typically multiple, spherical and firm. The sectioned surface is white to tan and has a whorled trabecular texture. Leiomyomas bulge above the surrounding myometrium from which they are easily shelled out. Submucosal leiomyomas distort the overlying endometrium, and, as they enlarge, they may bulge into the endometrial cavity and produce bleeding. Rare examples become pedunculated and prolapse through the cervix. Intramural leiomyomas are the most common. Subserosal leiomyomas can become pedunculated, and on torsion with necrosis of the pedicle the leiomyoma may lose its connection with the uterus. Very rarely, some become attached to another pelvic structure (parasitic leiomyoma). The appearance of a leiomyoma often is altered by degenerative changes. Submucosal leiomyomas frequently are ulcerated and haemorrhagic. Haemorrhage and necrosis are observed in some leiomyomas, particularly in large ones in women who are pregnant or who are undergoing high-dose progestin therapy. Dark red areas represent haemorrhage and sharply demarcated yellow areas reflect necrosis. The damaged smooth muscle is replaced eventually by firm white or translucent collagenous tissue. Cystic degeneration also occurs, and some leiomyomas become extensively calcified.

**Histopathology**
Most leiomyomas are composed of easily recognized smooth muscle featuring whorled, anastomosing fascicles of uniform, fusiform cells. Characteristically, the spindle-shaped cells have indistinct borders and abundant, often fibrillar, eosinophilic cytoplasm. Sometimes, particularly in cellular leiomyomas, the cytoplasm is sparse, and the fascicular arrangement of the cells may be muted. Nuclei are elongated with blunt or tapered ends and have finely dispersed chromatin and small nucleoli. Mitotic figures usually are infrequent. Most leiomyomas are more cellular than the surrounding myometrium. Leiomyomas lacking increased cellularity are identified by their nodular circumscripted and by the disorderly arrangement of the smooth muscle fascicles within them, out of alignment with the surrounding myometrium. Degenerative changes are common in leiomyomas. Hyaline fibrosis, oedema and, on occasion, marked hydropic change can be present (525). Haemorrhage, necrosis, oedema, myxoid change, hypercellular foci and cellular hypertrophy occur in leiomyomas in women who are pregnant or taking progesterins. Not infrequently, there is increased mitotic activity near the areas of necrosis. On the other hand, the coagulative tumour cell necrosis common in leiomyosarcoma is not associated very often with acute inflammation and haemorrhage. Progestational agents are associated with a slight increase in mitotic activity, but not to the level observed in a leiomyosarcoma. In addition, the mitotic figures seen in conjunction with inflammatory necrosis have a normal histologi-

---

**Table 4.06**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition or comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis</td>
<td>Death of a portion of tissue</td>
</tr>
<tr>
<td>Coagulative tumour cell necrosis</td>
<td>Abrupt transition from viable tumour to necrotic tumour, ghost outlines of cells usual, haemorrhage and inflammation uncommon.</td>
</tr>
<tr>
<td>Hyaline necrosis</td>
<td>Intervening zone of collagen or granulation tissue between nonviable and viable tumour, haemorrhage common, cellular outlines often not visible.</td>
</tr>
<tr>
<td>Atypia</td>
<td>Assessed at scanning power</td>
</tr>
<tr>
<td>Diffuse vs. focal</td>
<td>Cells diffusely present in most fields examined vs. scattered widely spaced aggregates of cells</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>Expressed in mitotic figures per 10 high power fields in the mitotically most active areas</td>
</tr>
<tr>
<td>Only unequivocal mitotic figures are counted (211)</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 4.33** MRI showing an enlarged uterus with multiple leiomyomas.
cal appearance. The margins of most leiomyomas are histologically circumscribed, but occasional benign tumours demonstrate interdigitation with the surrounding myometrium, which may rarely be extensive.

**Immunoprofile**
Smooth muscle neoplasms react with antibodies to muscle-specific actin, alpha-smooth muscle actin, desmin and h-caldesmon. Anomalous expression of cytokeratin immunoreactivity is observed frequently both in the myometrium and in smooth muscle tumours, the extent and intensity of reactivity depending on the antibodies used and the fixation of the specimen. Epithelial membrane antigen is negative in smooth muscle tumours. CD10 reactivity may focally be present.

**Histological variants**
Most subtypes of leiomyoma are chiefly of interest in that they mimic malignancy in one or more aspects.

**Mitotically active leiomyoma**
Mitotically active leiomyomas occur most often in premenopausal women. They have the typical macroscopic and histological appearances of a leiomyoma with the exception that they usually have 5 or more mitotic figures per 10 high power fields [211,2293]. Occasionally, these smooth muscle tumours contain >15 mitotic figures per 10 high power fields, in which case the term mitotically active leiomyoma with limited experience is used. The clinical evolution is benign, even if the neoplasm is treated by myomectomy. It is imperative that this diagnosis not be used for neoplasms that exhibit moderate to severe nuclear atypia, contain abnormal mitotic figures or demonstrate zones of coagulative tumour cell necrosis.

**Cellular leiomyoma**
Cellular leiomyoma accounts for less than 5% of leiomyomas, and by definition their cellularity is "significantly" greater than that of the surrounding myometrium [211,2101]. The isolated occurrence of hypercellularity may suggest a diagnosis of leiomyosarcoma, but cellular leiomyomas lack tumour cell necrosis and moderate to severe atypia and have infrequent mitotic figures. A cellular leiomyoma comprised of small cells with scanty cytoplasm can be confused with an endometrial stromal or pure sex cord-like tumour.

**Haemorrhagic cellular leiomyoma and hormone induced changes**
A haemorrhagic cellular or "apoplectic" leiomyoma is a form of cellular leiomyoma that is found mainly in women who are taking oral contraceptives or who either are pregnant or are postpartum [1960,2050]. Macroscopic examination reveals multiple stellate haemorrhagic areas. Coagulative tumour cell necrosis is generally absent. Normal mitotic figures are present and are usually confined to a narrow zone of granulation and in which the term mitotically active leiomyoma with limited experience is used. The clinical evolution is benign, even if the neoplasm is treated by myomectomy. It is imperative that this diagnosis not be used for neoplasms that exhibit moderate to severe nuclear atypia, contain abnormal mitotic figures or demonstrate zones of coagulative tumour cell necrosis.

**Cellular leiomyoma**
Cellular leiomyoma accounts for less than 5% of leiomyomas, and by definition their cellularity is "significantly" greater than that of the surrounding myometrium [211,2101]. The isolated occurrence of hypercellularity may suggest a diagnosis of leiomyosarcoma, but cellular leiomyomas lack tumour cell necrosis and moderate to severe atypia and have infrequent mitotic figures. A cellular leiomyoma comprised of small cells with scanty cytoplasm can be confused with an endometrial stromal or pure sex cord-like tumour.

**Haemorrhagic cellular leiomyoma and hormone induced changes**
A haemorrhagic cellular or "apoplectic" leiomyoma is a form of cellular leiomyoma that is found mainly in women who are taking oral contraceptives or who either are pregnant or are postpartum [1960,2050]. Macroscopic examination reveals multiple stellate haemorrhagic areas. Coagulative tumour cell necrosis is generally absent. Normal mitotic figures are present and are usually confined to a narrow zone of granulation and in which the term mitotically active leiomyoma with limited experience is used. The clinical evolution is benign, even if the neoplasm is treated by myomectomy. It is imperative that this diagnosis not be used for neoplasms that exhibit moderate to severe nuclear atypia, contain abnormal mitotic figures or demonstrate zones of coagulative tumour cell necrosis.

**Cellular leiomyoma**
Cellular leiomyoma accounts for less than 5% of leiomyomas, and by definition their cellularity is "significantly" greater than that of the surrounding myometrium [211,2101]. The isolated occurrence of hypercellularity may suggest a diagnosis of leiomyosarcoma, but cellular leiomyomas lack tumour cell necrosis and moderate to severe atypia and have infrequent mitotic figures. A cellular leiomyoma comprised of small cells with scanty cytoplasm can be confused with an endometrial stromal or pure sex cord-like tumour.

**Haemorrhagic cellular leiomyoma and hormone induced changes**
A haemorrhagic cellular or "apoplectic" leiomyoma is a form of cellular leiomyoma that is found mainly in women who are taking oral contraceptives or who either are pregnant or are postpartum [1960,2050]. Macroscopic examination reveals multiple stellate haemorrhagic areas. Coagulative tumour cell necrosis is generally absent. Normal mitotic figures are present and are usually confined to a narrow zone of granulation.
Epithelioid leiomyoma

Epithelioid leiomyomas are composed of epithelial-like cells [130, 1538, 2292]. They are yellow or grey and may contain leiomyoma. Mixtures of the various patterns can be safely regarded as benign. Histologically, the epithelioid cells are round or polygonal, they are arranged in sheets or clusters or cords, and their nuclei are round, relatively large and centrally positioned. There are three basic subtypes of epithelioid leiomyoma: leiomyoblastoma, clear cell leiomyoma and plexiform leiomyoma. Mixtures of the various patterns are common, hence the designation "epithelioid" for all of them.

Small tumours without cytological atypia, tumour cell necrosis or an elevated mitotic index can be safely considered benign. Plexiform tumours invariably are benign. Epithelioid leiomyomas with circumscribed margins, extensive hyalinization and a predominance of clear cells generally are benign. The behaviour of epithelioid leiomyomas with two or more of the following features is not well established: (1) Large size (greater than 6 cm), (2) Moderate mitotic activity (2-4 mitotic figures per 10 high power fields), (3) Moderate to severe cytological atypia

Myxoid leiomyoma

Myxoid leiomyomas are benign smooth muscle tumours in which myxoid material separates the tumour cells [131, 1465]. They are soft and translucent. Histologically, abundant amorphous myxoid material is present between the smooth muscle cells. The margins of a myxoid leiomyoma are circumscribed, and neither cytological atypia nor mitotic figures are present. When unassociated with either coagulative tumour cell necrosis or a mitotic index in excess of 10 mitotic figures per 10 high power fields, cytological atypia, when severe, is an unreliable criterion for identifying clinically malignant myxoid leiomyomas. Such lesions have been completely sampled, such tumours are designated "atypical leiomyoma with minimal, if any, recurrence potential." Such lesions have behaved benignly except for a single reported case.

Lipoleiomyoma

Scattered adipocytes in an otherwise typical leiomyoma are a relatively common finding; a leiomyoma that contains a striking number of these cells is called a lipoleiomyoma [2357, 2671].

Growth pattern variants

Growth pattern variants may produce unusual clinical, macroscopic and histological features.

Diffuse leiomyomatosis

Diffuse leiomyomatosis is an unusual condition in which numerous small smooth muscle nodules produce symmetrical, sometimes substantial, enlargement of the uterus [518]. The hyperplastic smooth muscle nodules range from histological to 3 cm in size, but most are less than 1 cm in diameter. They are composed of uniform, bland, spindle-shaped smooth muscle cells and are less circumscribed than leiomyomas. The clinical course may be complicated by haemorrhage, but the condition is benign.

Dissecting leiomyoma

Dissecting leiomyoma refers to a benign smooth muscle proliferation with a border marked by the dissection of compressive tongues of smooth muscle into the surrounding myometrium and, occasionally, into the broad ligament and pelvis [2469]. This pattern of infiltration may also be seen in intravenous leiomyomatosis. When oedema and congestion are prominent, a uterine dissecting leiomyoma with extraterine extension may resemble placental tissue; hence the name cotyledonoid dissecting leiomyoma [2470].
Intravenous leiomyomatosis

Intravenous leiomyomatosis is a very rare smooth muscle tumour featuring nodular masses and cords of histologically benign smooth muscle growing within venous channels outside the confines of a leiomyoma (1928,2051). Intravenous leiomyomatosis should be distinguished from the common vascular intrusion within the confines of a leiomyoma. Macroscopically, Intravenous leiomyomatosis consists of a complex, coiled or nodular myometrial growth often with convoluted, worm-like extensions into the uterine veins in the broad ligament or into other pelvic veins. On occasion, the growth extends into the vena cava, and sometimes it extends into the right heart. Histologically, tumour is found within venous channels that are lined by endothelium. The histological appearance is highly variable, even within the same tumour. The cellular composition of some examples of intravenous leiomyomatosis is similar to a leiomyoma, but most contain prominent zones of fibrosis or hyalinization. Smooth muscle cells may be inconspicuous and difficult to identify. Any variant smooth muscle histology, i.e. cellular, atypical, epithelioid or lipoleiomyomatous, may be encountered in intravenous leiomyomatosis.

Benign metastasizing leiomyoma

Benign metastasizing leiomyoma is an ill-defined clinicopathological condition which features “metastatic” histologically benign smooth muscle tumour deposits in the lung, lymph nodes or abdomen that appear to be derived from a benign uterine leiomyoma (798,2923). Reports of this condition often are difficult to evaluate. Almost all cases of benign metastasizing leiomyoma occur in women who have a history of pelvic surgery. The primary neoplasm, typically removed years before the extraterine deposits are detected, often has been inadequately studied. Most examples of “benign metastasizing leiomyoma,” however, appear to be either a primary benign smooth muscle lesion of the lung in a woman with a history of uterine leiomyoma or pulmonary metastases from a histologically non-informative smooth muscle neoplasm of the uterus. The findings of a recent cytogenetic study were most consistent with a monoclonal origin of both uterine and pulmonary tumours and the interpretation that the pulmonary tumours were metastatic (2923). The hormone dependence of this proliferation is suggested by the finding of estrogen and progesterone receptors in metastatic deposits and the regression of tumour during pregnancy, after the menopause and after oophorectomy.

Somatic genetics

Uterine leiomyomas often have chromosomal abnormalities detectable by cytogenetic analysis, most frequently involving the HMGIC (12q15) and HMGIIY (6p21) genes (2204a).

Miscellaneous mesenchymal tumours

Definition

A diverse group of mesenchymal tumours of the uterus that do not show predominantly smooth muscle or stromal differentiation.

Mixed endometrial stromal and smooth muscle tumour

Definition and historical annotation

These neoplasms, previously designated stromomyoma, are composed of an admixture of endometrial stromal and smooth muscle elements (1448,2098,2550,2860). Small areas of smooth muscle differentiation are commonly seen in otherwise typical endometrial stromal neoplasms and vice versa, but a minimum of 30% of the minor component is recommended for the designation of mixed endometrial stromal-smooth muscle neoplasm (2098).

Macroscopy

These neoplasms may have a predominant intramural, submucosal or subserosal location. Some have been described as well circumscribed, whereas others have been multinodular or have had infiltrating margins. Some neoplasms contain areas with a whorled appearance admixed with tan foci that are softer than typical leiomyomas (2098).

Histopathology

A population of small cells with round to ovoid nuclei and inconspicuous cytoplasm characterizes the endometrial stromal component. Numerous small arterioles are a characteristic feature. The endometrial stromal component usually exhibits minimal cytological atypia, and the mitotic rate is variable. Areas exhibiting sex cord-like differentiation and perivascular hyalinization may be present in the endometrial stromal component (2098). A case has been described with an associated glandular component consisting of benign endometrial glands surrounded by endometrial stroma (1812).

The smooth muscle component is usually benign in appearance and is often arranged in nodules with a prominent central area of hyalinization creating a starburst appearance. However, in some cases the smooth muscle component may exhibit any one or a combination of

Fig. 4.40 Perivascular epithelioid cell tumour. A Low power image shows a “tongue-like” growth pattern, similar to low grade endometrial stromal sarcoma. B High power image shows epithelioid cells with clear to pale granular cytoplasm without significant atypia or mitotic figures. C HMB-45 stain is positive.
cytological atypia, tumour cell necrosis and conspicuous mitotic activity. The smooth muscle component is positive for desmin and alpha-smooth muscle actin. However, there may be positivity of the endometrial stromal component with these antibodies, and they cannot be used to reliably distinguish between endometrial stroma and smooth muscle. Studies have shown that markers such as CD10 that stain endometrial stroma but are focally positive in many smooth muscle neoplasms and h-caldesmon and calponin that stain smooth muscle may be of value in distinguishing the two components {44,486,1821,2065}. Sex cord-like areas may exhibit immunohistochemical staining with alpha-inhibin and other sex cord-stromal markers [1521, 1808].

**Prognosis and predictive factors**
The limited literature on these rare neoplasms suggests that they should be evaluated and reported in the same way as endometrial stromal neoplasms; i.e. malignant if there is vascular or myometrial invasion, benign otherwise (2098, 2311).

**Perivascular epithelioid cell tumour**

**Definition**
A tumour composed predominantly or exclusively of HMB-45-positive perivascular epithelioid cells with eosinophilic granular cytoplasm. It is a member of a family of lesions thought to be composed, at least in part, of perivascular epithelioid cells. Other members of this group include some forms of angiomyolipoma and lymphangioleiomyomatosis, as well as clear cell 'sugar' tumour.

**Synonym**
PEComa.

**Epidemiology**
The age of patients ranged from 40-75 years with a mean of 54 (2998).

**Clinical features**
Most patients present with abnormal uterine bleeding.

**Macroscopy**
A mass is present in the uterine corpus.

**Histopathology**
The tumours are divided into two groups (2998). The first demonstrates a tongue-like growth pattern similar to that seen in low grade ESS. These tumours are composed of cells that have abundant clear to eosinophilic pale granular cytoplasm and stain diffusely for HMB-45 and also variably express muscle markers. The second group is composed of epithelioid cells with less prominent clear cell features and a smaller number of cells that are HMB-45 positive. These tumours exhibit more extensive muscle marker expression and a lesser degree of tongue-like growth than the first group.

**Genetic susceptibility**
One-half of the patients in the second group had pelvic lymph nodes involved by lymphangioleiomyomatosis, and one-fourth had tuberous sclerosis.

**Prognosis and predictive factors**
Hysterectomy is the usual treatment. Some uterine cases have exhibited aggressive behaviour. Uterine perivascular epithelioid cell tumour should be considered of uncertain malignant potential until long-term outcome data for a larger number of patients become available (2998).

**Adenomatoid tumour**

**Definition**
A benign tumour of the uterine serosa and myometrium originating from mesothelium and forming gland-like structures.
cause obvious diagnostic problems. Sometimes a papillary pattern may be apparent. Ultrastructural examination shows the long slender microvilli characteristic of mesothelial cells.

**Immunoprofile**
Immunohistochemical positivity with anti-cytokeratin antibodies and anti-mesothelial antibodies, such as HBME-1 and calretinin, is usual. This finding may be useful in the distinction between adenomatoid tumour and lymphangioma. There is no reactivity with Ber-EP4, helping to exclude a carcinoma in those cases that have signet-ring cell morphology (211, 2101, 2123).

**Histogenesis**
The histogenesis has been debated in the past, but immunohistochemical and ultrastructural studies have shown these neoplasms to be of mesothelial origin. When located within the uterus (654, 2041, 2311, 2768, 2924), they are probably derived from the serosal mesothelium.

**Prognosis and predictive factors**
Adenomatoid tumours are invariably benign with no risk of recurrence or metastasis.

**Rare mesenchymal tumours**
Definition
A variety of mesenchymal tumours, both malignant and benign, occurring within the uterus that are not endometrial stromal, smooth muscle or mesothelial in type. These are rare and are identical histologically to their counterparts arising in more usual sites.

**Malignant tumours**
In cases of malignancy the neoplasm should be extensively sampled in order to exclude sarcomatous overgrowth in a MMMT or an adenosarcoma. The most common of these neoplasms to arise in the uterus is rhabdomyosarcoma (716, 1149, 1814, 2112). The latter is usually of embryonal type in young females and of pleomorphic type in the middle aged or elderly. Occasional cases of uterine alveolar rhabdomyosarcoma have also been described (475). Occasional residual entrapped benign endometrial glands may be present, especially towards the surface of these neoplasms. That finding should not be taken as evidence of an adenosarcoma. Other malignant mesenchymal neoplasms described in the uterus include malignant fibrous histiocytoma (1404), angiosarcoma (including the epithelioid variant) (2551, 2853), liposarcoma (180), osteosarcoma (784, 1137, 1844), chondrosarcoma (1489), alveolar soft part sarcoma (2219). Ewing tumour, malignant peripheral nerve sheath tumour, malignant pigmented neuroectodermal tumour of infancy (2580) and peripheral primitive neuroectodermal tumour (638, 1894, 2017). In general, these are all bulky neoplasms, frequently high stage at presentation, and the histology is similar to their counterparts elsewhere. Immunohistochemical studies may assist in establishing a definitive diagnosis.

Haemangiopericytoma has also been described in the uterus, but it is likely that most of the reported cases represent vascular endometrial stromal neoplasms (2693). Malignant rhabdoid tumours have also been described (948, 1255). Since a rhabdoid component may rarely be found in an otherwise typical endometrial stromal neoplasm (1813), it is possible that some rhabdoid tumours represent an unusual histological variant of an endometrial stromal or some other neoplasm. As with other extrarenal rhabdoid tumours, the uterine neoplasm may represent a peculiar histological growth pattern that may be found in a variety of neoplasms; therefore, extensive sampling should be undertaken to exclude a diagnosis of rhabdoid differentiation in another more common neoplasm. Only when other elements are not identified should a diagnosis of uterine malignant rhabdoid tumour be considered.

**Benign tumours**
Benign tumours include lipoma, haemangioma, lymphangioma and rhabdomyoma (466, 686). Occasional uterine myxomas have been described in Carney syndrome (2654). Before diagnosing these entities, a lipoleiomyoma should be excluded in the case of lipoma, a vascular leiomyoma in the case of haemangioma, an adenomatoid tumour in the case of lymphangioma and a myxoid smooth muscle neoplasm in the case of myxoma. A single case of postoperative spindle cell nodule of the endometrium that occurred following a uterine curettage has been described (504).
Mixed epithelial and mesenchymal tumours

**Definition**
Tumours of the uterine corpus composed of an epithelial and a mesenchymal component.

**ICD-O codes**
- Carcinosarcoma: 8980/3
- Adenosarcoma: 8933/3
- Carcinofibroma: 8934/3
- Adenofibroma: 9013/0
- Adenomyoma: 8932/0
- Atypical polypoid variant: 8932/0

**Carcinosarcoma**

**Definition**
A neoplasm composed of an admixture of malignant epithelial and mesenchymal components.

**Synonyms**
Malignant müllerian mixed tumour, malignant mesodermal mixed tumour, metaplastic carcinoma.

These tumours are still classified as "mixed" by convention, although there is increasing evidence that they are monoclonal and should be considered subsets of endometrial carcinoma.

**Epidemiology**
Carcinosarcoma is the most common neoplasm of this group (703). Carcinosarcomas usually occur in elderly postmenopausal women, although occasional cases may occur in younger women and rarely even in young girls. The median age of patients presenting with carcinosarcoma is 65 years, higher than that of patients with leiomyosarcoma (813,1745). Less than 5% of patients are younger than 50 years.

**Aetiology**
An occasional case is secondary to prior pelvic irradiation. In recent years an association between long term tamoxifen therapy and the development of uterine carcinosarcoma has been suggested (813,1811,2947).

**Clinical features**

**Signs and symptoms**
Vaginal bleeding is the most frequent presenting symptom of patients with carcinosarcoma, followed by an abdominal mass and pelvic pain (703). Carcinosarcomas may be polypoid and may prolapse through the cervix to present as an upper vaginal mass. The most important diagnostic method is uterine curettage, but in 25% of cases the diagnosis is made following hysterectomy (2965).

**Imaging**
Magnetic resonance imaging (MRI) of women with a typical carcinosarcoma usually shows an enlarged uterus with a widened endometrial cavity and evidence of deep myometrial invasion. Whereas a carcinosarcoma cannot be distinguished from endometrial carcinoma by means of MRI, the presence of a large tumour with extensive myometrial invasion as well as the presence of ovarian or intraperitoneal metastases should raise suspicion (1060,2838).

**Macroscopy**
At the time of presentation uterine carcinosarcomas are usually polypoid, bulky, necrotic and haemorrhagic neoplasms that fill the endometrial cavity and deeply invade the myometrium, often extending beyond the uterus. If cartilage or bone forms a significant portion of the neoplasm, the neoplasm may have a hard consistency. Occasionally, these neoplasms may arise within a benign endometrial polyp.

**Tumour spread and staging**
Intra-abdominal and retroperitoneal nodal metastases are frequent (1745).

**Histopathology**
The malignant epithelial element is usually glandular, although rarely it may be non-glandular, most commonly consisting of squamous or undifferentiated carcinoma. The glandular component may be either endometrioid or non-endometrioid, such as serous or clear cell in type. The sarcomatous elements may be either homologous or heterologous. In homologous neoplasms the mesenchymal component usually consists of undifferentiated sarcoma, leiomyosarcoma or endometrial stromal sarcoma and is usually, although not always, high grade. Heterologous mesenchymal elements most commonly consist of malignant cartilage or malignant skeletal muscle in the

<table>
<thead>
<tr>
<th>Table 4.07</th>
<th>Nomenclature of mixed epithelial and mesenchymal tumours defined by phenotypes of epithelial and mesenchymal components.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign mesenchyme</strong></td>
<td><strong>Malignant mesenchyme</strong></td>
</tr>
<tr>
<td>Adenofibroma</td>
<td>Carcinofibroma</td>
</tr>
<tr>
<td>Adenomyoma (including atypical)</td>
<td></td>
</tr>
<tr>
<td>Malignant mesenchyme</td>
<td>Adenosarcoma</td>
</tr>
</tbody>
</table>

**Fig. 4.42** Carcinosarcoma. Sagittal section of the uterus shows a solid, polypoid tumour within the fundus.
Tumours of the uterine corpus

form of rhabdomyoblasts, although other elements such as osteosarcoma and liposarcoma may rarely occur.

In general, both carcinomatous and sarcomatous elements are easily identifiable, although in some cases one or other element may form a minor component that may be only identified following extensive sampling of the neoplasm. Any uterine neoplasm composed of high grade sarcoma, especially when heterologous elements are present, should be extensively sampled in order to rule out a carcinosarcoma or sarcomatous overgrowth in an adenosarcoma. Any uterine carcinosarcoma with a component of yolk sac tumour has been described in a patient with an elevated serum alpha-fetoprotein level [2665]. Occasional tumours with a rhabdoid phenotype [190] or a malignant neuroectodermal component [931] have also been described. Occasional uterine carcinosarcomas of mesonephric origin have been reported [3171]. Other unusual histological features include melanocytic [77] and neuroendocrine differentiation [537].

Immunoprofile

In general, the epithelial elements are immunoreactive with anti-cytokeratin antibodies and the mesenchymal elements with vimentin. The mesenchymal elements often show focal staining with anti-cytokeratin antibodies supporting an epithelial origin of this component. The usual concordance of TP53 stains between the epithelial and mesenchymal components supports a common monoclonal origin for both elements [1796, 2827]. Desmin, myoD1, myoglobin and sarcomeric actin staining may highlight a rhabdomyosarcomatous mesenchymal component. Cartilaginous elements usually stain with S-100 protein.

Histogenesis

It should be noted that clinical, immunohistochemical, ultrastructural and molecular studies have all suggested that carcinosarcomas are really metaplastic carcinomas in which the mesenchymal component retains at least some epithelial features in the vast majority of cases [1809]. Though still classified as “mixed” by convention, these tumours are perhaps better considered subsets of endometrial carcinoma and certainly should not be grouped histogenetically or clinically with uterine sarcomas [1810]. On the other hand, the tumours other than carcinosarcoma in this group are considered to be true mixed tumours.
Prognosis and predictive factors

The clinical course of uterine carcinosarcoma is generally aggressive with a poor overall prognosis, considerably worse than that of a poorly differentiated endometrial carcinoma. The pattern of spread is generally similar to that of high grade endometrial carcinoma, and deep myometrial invasion and extratumoral spread are often observed at the time of presentation. The clinical staging is the same as that for endometrial carcinoma. Some studies have found no independent prognostic factors other than tumour stage, whereas others have found that the characteristics of the epithelial component such as high grade carcinoma, including serous or clear cell components, are associated with a worse prognosis (2692). Previously, it was thought that the presence of heterologous mesenchymal components indicated a worse outcome; however, recent larger studies have suggested that the histological features of the mesenchymal component bear no relationship to the overall prognosis (2692).

The biological behaviour of uterine carcinosarcomas is more akin to high grade endometrial carcinomas than to uterine sarcomas (282,2692). Carcinosarcomas primanarily spread via lymphatics, whereas pure uterine sarcomas commonly spread haematogenously. Detailed studies of uterine carcinosarcoma have shown that metastatic foci and foci within lymphatic or vascular spaces are commonly carcinomatous with pure sarcomatous elements being rare (282,2692,2767). Although the tumour stage is the most important prognostic factor, recurrences may be encountered even in those rare cases lacking myometrial infiltration. However, tumours confined to an otherwise benign polyp appear to have a somewhat better outcome (188,1382).

Adenosarcoma

Definition

Adenosarcoma is a biphasic neoplasm containing a benign epithelial component and a sarcomatous mesenchymal component.

Epidemiology

Adenosarcoma occurs in women of all ages, ranging from 15-90 years with a median age at diagnosis of 58. Adenosarcomas have been reported in women undergoing tamoxifen therapy for breast cancer (509) and occasionally after prior pelvic radiation (515). There is no association of adenosarcoma with obesity or hypertension.

Clinical features

Typical symptoms of patients with adenosarcoma are abnormal vaginal bleeding, an enlarged uterus and tissue protruding from the external os. The tumour may not be correctly diagnosed as adenosarcoma until re-excision of a recurrent polypoid lesion (515).

Macroscopy

Adenosarcomas typically grow as exophytic polypoid masses that extend into the uterine cavity. Rarely, they may arise in the myometrium, presumably from adenomyosis. Although the tumour is usually a single polypoid mass, it sometimes may present as multiple papillary masses. On sectioning, the surface is tan brown with focci of haemorrhage and necrosis. Small cysts are frequently present. Most adenosarcomas do not invade the myometrium.

Histopathology

Under low magnification a leaf-like pattern closely resembling phylloides tumour of the breast is observed. Isolated glands, often dilated and compressed into thin slits, are dispersed throughout the mesenchymal component. Characteristically, there is stromal condensation surrounding the glands and clefts. It is in these areas where the greatest degree of stromal atypia and mitotic activity is present. By definition the epithelium is benign and may show focal metaplastic changes. The mesenchymal component of an adenosarcoma is generally a low grade homologous stromal sarcoma containing varying amounts of fibrous tissue and smooth muscle. Mesenchymal mitotic figures, usually stated to be more than one per 10 high power fields, are required in the hypercellular cuffs. Cytological atypia is typically only mild, but is occasionally moderate. Sex cord-like components resembling those in endometrial stromal sarcomas are found in less than 10% of adenosarcomas. Heterologous components consisting of striated muscle (most commonly), cartilage, fat and other components are present in approximately 10-15% of tumours. The diagnosis of sarcomatous overgrowth is made if the pure

Fig. 4.44 Adenosarcoma. A The tumour is composed of tubular and convoluted, cleft-like glands of endometrioid type surrounded by a cuff of cellular mesenchyme. B A polypoid structure compresses a glandular lumen producing a leaf-like pattern similar to that of a mammary phylloides tumour. The epithelial component is cytologically bland, and the mesenchymal component is cellular and fibromatous without significant nuclear atypia but contained abundant mitoses.
sarcomatous component, usually of high grade, occupies 25% or more of the total tumour volume.

**Immunoprofile**
As might be expected, the epithelial component reacts with a broad spectrum of antibodies to cytokeratins. The mesenchymal component usually reacts focally with antibodies to CD10. Variable degrees of staining for smooth muscle markers, desmin and caldesmon, can also be observed.

**Differential diagnosis**
The differential diagnosis includes adenofibroma and in children sarcoma botryoides (embryonal rhabdomyosarcoma).

**Prognosis and predictive factors**
Adenosarcoma is considered a low grade neoplasm but recurs in approximately 25-40% of cases, typically in the pelvis or vagina, and distant metastasis has been reported in 5% of cases [515]. The metastases almost always are composed of a sarcomatous element only, but rarely epithelium has been reported. Factors in the primary tumour that are predictive of a poor outcome are extrauterine spread, deep myometrial invasion into the outer half of the myometrium and sarcomatous overgrowth. Vascular invasion is usually not identified but, if present, is a poor risk factor. Rhabdomyosarcomatous differentiation was an adverse prognostic factor in one series [1388]. There appears to be no correlation between the prognosis and the level of mitotic activity. Long-term follow-up is necessary because recurrences may manifest after many years. Most tumour deaths occur more than five years after the diagnosis.

**Carcinofibroma**

**Definition**
A neoplasm composed of an admixture of a malignant epithelial element and a benign mesenchymal component.

**Epidemiology**
These are extremely uncommon neoplasms with few cases reported in the literature [1286,2228,2916].

**Histopathology**
Adenosarcomas have a papillary or club-like growth pattern. They are composed of benign epithelial and mesenchymal components, the epithelial component forming a lining on the underlying mesenchymal core. Clift-like spaces are often present. The epithelial component may be endometrioid or ciliated in type but often is non-descript cuboidal or columnar. Rarely, there are foci of squamous metaplasia. The mesenchyme is usually of a non-specific fibroblastic type, although rarely it may contain endometrial stromal or smooth muscle components. Stromal atypia, mitotic activity and periglandular cuffing are absent or inconspicuous. Rarely, adipose tissue or skeletal muscle components are present, and such lesions have been designated lipoadenofibroma or adenomyofibroma [1239,2711].

**Differential diagnosis**
If there is a stromal mitotic count of >1 mitosis per 10 high power fields, marked stromal hypercellularity with periglandular cuffing and/or more than mild stromal atypia, a diagnosis of low grade adenosarcoma should be made.

**Prognosis and predictive factors**
Adenosarcomas are benign lesions, although they may recur following “polypectomy” [2625]. Occasional
Mixed epithelial and mesenchymal tumours

249

Adenomyoma including atypical polypoid adenomyoma

**Definition**
A lesion composed of benign epithelial (usually endometrial glands) and mesenchymal components in which the mesenchymal component is fibromyomatous. Atypical polypoid adenomyoma is a variant of adenomyoma in which the glandular component exhibits architectural complexity with or without cytological atypia.

**Epidemiology**
Adenomyoma may occur at any age, whereas atypical polypoid adenomyoma characteristically occurs in premenopausal women [1690, 1801, 3228].

**Macroscopy**
Adenomyomas and atypical polypoid adenomyomas usually are polypoid submucosal lesions but may rarely be intramural or subserosal [1002]. They have a firm sectioned surface. Atypical polypoid adenomyoma usually involves the lower uterine segment or upper endocervix.

**Histopathology**
Adenomyoma is composed of an admixture of benign endometrial glands (there may be minor foci of tubal, mucinous or squamous epithelium) with minimal cytological atypia and architectural complexity embedded in a benign fibromyomatous mesenchyme. Often endometrial type stroma surrounds the endometrial glandular component, and the former is in turn surrounded by smooth muscle [1002].

Atypical polypoid adenomyoma
In atypical polypoid adenomyoma the glands characteristically show marked architectural complexity; there is no endometrial type stroma around the distorted glands. There is often also cytological atypia that varies from mild to marked. Foci may be present that architecturally resemble well differentiated adenocarcinoma, and such tumours have been designated "atypical polypoid adenomyoma of low malignant potential" [1690]. Extensive squamous or morular metaplasia of the glandular elements, with or without central necrosis, is a common finding. The mesenchymal component is composed of swirling and interlacing fascicles of benign smooth muscle.

**Differential diagnosis**
It should be noted that many simple endometrial polyps contain a minor component of smooth muscle within the stroma; however, this finding alone is not sufficient for the diagnosis of adenomyoma. The designation adenomyoma has also been used for a localized adenomyosis that forms a discrete mass, but such usage is confusing and not recommended. Differentiation from a well differentiated endometrioid adenocarcinoma invading the myometrium may be difficult, especially on a curettage or biopsy specimen. However, the usual lack of pronounced cellular atypia and the absence of a stromal desmoplastic response would be against a diagnosis of adenocarcinoma. Additional features against a diagnosis of carcinoma are the usual youth of the patient and the presence of normal endometrial fragments in the sample.

**Genetic susceptibility**
Atypical polypoid adenomyomas may occur in women with Turner syndrome [517].

**Prognosis and predictive factors**
Adenomyoma is generally cured by simple polypectomy, but if associated with myometrial adenomyosis, symptoms may persist. Atypical polypoid adenomyoma may recur, especially following incomplete removal. In addition, superficial myometrial infiltration is often identified in hysterectomy specimens, a finding that may be more common in those cases with marked glandular architectural complexity [1690]. A small number of cases are associated with an underlying endometrioid adenocarcinoma with a transition zone between the two components [1882, 2813].
Gestational trophoblastic disease

Definition
A heterogeneous group of gestational and neoplastic conditions arising from trophoblast, including molar gestations and trophoblastic tumours.

Epidemiology
Gestational trophoblastic disease (GTD) varies widely among various populations with figures as high as 1 in 120 pregnancies in some areas of Asia and South America compared to 0.6−1.1 per 1000 in the United States (1162). The incidence of hydatidiform moles is greater in women older than 40 years (161) and is also increased in those younger than 20 years. Patients who have had prior GTD are more at risk of having a second GTD after subsequent pregnancies. Other risk factors include: a diet low in vitamin A, lower socioeconomic status and blood group A women married to group 0 men (161,162,244,363).

Aetiology
Hydatiform moles arise from abnormal conceptions. Partial moles result from diandric triploidy, whereas complete moles result from diandry (fertilization of an empty ovum). Up to 50% of choriocarcinomas and 15% of placental site trophoblastic tumours follow complete moles.

Clinical features
Signs and symptoms
A complete molar pregnancy usually presents with first trimester bleeding, a uterus larger than expected for gestational age and the absence of fetal parts on ultrasound in association with a markedly elevated beta-human chorionic gonadotropin (β-hCG) level (568). Other signs include hyperemesis, toxemia during the first or second trimester, theca lutein cysts and hyperthyroidism. Patients with partial molar gestations usually present as spontaneous abortions, sometimes with increased β-hCG levels. GTD should always be considered when a patient has continued vaginal bleeding following delivery or abortion.

Imaging
A characteristic pattern of multiple vesicles (snowstorm pattern) is commonly seen with complete molar pregnancy. The diagnosis of partial molar pregnancy by ultrasonography is more difficult.

Tumour spread and staging
Choriocarcinoma spreads haematogenously and may involve the lung (57–80%), vagina (30%), pelvis (20%), brain (17%), and liver (10%) (168,243). Since β-hCG titres accurately reflect the clinical disease, histological verification is not required for diagnosis. Staging should be based on history, clinical examination and appropriate laboratory and radiological studies.

Metastatic GTD is also categorized by the WHO scoring system as low, medium, and high risk (51,2976). Since β-hCG titres accurately reflect the clinical disease, histological verification is not required for diagnosis. Staging should be based on history, clinical examination and appropriate laboratory and radiological studies.

Metastatic GTD is also categorized by the WHO scoring system as low, medium, and high risk (51,2976). The individual scores for each prognostic factor are added together to obtain a total score. A total prognostic score less than or equal to 4 is considered low risk, a total score of 5−7 is considered middle risk, and a total score of 8 or greater is considered high risk. (See TNM and FIGO classification of gestational trophoblastic tumours at the beginning of the chapter).

Somatic genetics
Overexpression of TP53 protein may be associated with more aggressive behaviour in gestational trophoblastic disease since it is more commonly observed in complete moles and choriocarcinoma (937,1616,2307), but TP53 mutations are uncommon (471). Overexpression of the p21 gene has also been detected in complete moles and choriocarcinoma (469). No correlation between p21 and TP53 expression has been detected in gestational trophoblastic disease.

Both complete mole and choriocarcinoma exhibit overexpression of several growth factors including c-Myc, epidermal growth factors receptor (EGFR), c-erbB-2, Rb, mdm2, and bcl-2 as compared to normal placenta and partial mole (938,2966). Expression of c-fms protein does not differ between normal placenta and gestational trophoblastic diseases (938). In one study strong immunostaining of c-erbB-3 and epidermal growth factor receptor in extravillous trophoblast of complete mole was significantly correlated with the development of persistent gestational trophoblastic tumour (2966). The molecular pathogenesis of gestational trophoblastic diseases may involve these and potentially other growth-regulatory factors.

Prognosis and predictive factors
Major adverse prognostic variables for GTD are:

(1) Age >39
(2) Prior term pregnancy
(3) Interval from antecedent pregnancy of >12 months
(4) β-hCG >105 IU/litre
(5) Tumour mass >5cm
(6) Disease in liver and brain
(7) Failure of 2 or more prior chemotherapies

The above factors are included in a prognostic score (see the TNM and FIGO classification of gestational trophoblastic tumours at the beginning of the chapter). The patients are separated into low risk and high risk groups for different treatments (1123,3111).

The prognosis of patients with low risk disease is very close to 100% survival, whilst patients with high risk disease have a survival of 85–95%, depending on the number of patients with ultra high risk disease in the patient population.
**Trophoblastic tumours**

**Definition**
Neoplasms derived from trophoblast.

**ICD-O codes**
- Choriocarcinoma 9100/3
- Placental site trophoblastic tumour 9104/1
- Epithelioid trophoblastic tumour 9105/3

**Gestational choriocarcinoma**

**Definition**
A malignant neoplasm composed of large sheets of biphasic, markedly atypical trophoblast without chorionic villi.

**Clinical features**
Gestational choriocarcinoma may occur subsequent to a molar pregnancy (50% of instances), an abortion (25%), a normal gestation (22.5%) or an ectopic pregnancy (2.5%) (1203). In rare cases an intraplacental choriocarcinoma is diagnosed immediately following pregnancy from placental pathological examination (343,722,907,1923).

**Histopathology**
Choriocarcinoma consists of an admixture of syncytiotrophoblast, cytotrophoblast and intermediate trophoblast as single cells and clusters of cells with prominent haemorrhage, necrosis and vascular invasion (775a,1593,1801a,1802a,2011,2024a,2077a). Choriocarcinoma does not possess tumour stroma or vessels; correspondingly, the diagnostic viable tumour is located at the periphery of haemorrhagic foci. Extraordinarily, choriocarcinomas have developed and been diagnosed as intraplacental tumours [112,343,722,907,1562,1923,2103].

**Immunoprofile**
All trophoblastic cell types are strongly immunoreactive for cytokeratins (640). In addition, the syncytiotrophoblast is strongly immunoreactive for β-hCG and weakly immunoreactive for human placental lactogen (hPL); intermediate trophoblast shows the opposite immunoprofile (935).

**Differential diagnosis**
The differential diagnosis of choriocarcinoma in endometrial curettings includes previllous trophoblast from an early gestation, persistent molar tissue following hydatidiform mole, placental site trophoblastic tumour, epithelioid tro-

---

**Fig. 4.46** A Gestational choriocarcinoma. Note the plexiform pattern with triphasic differentiation into cytotrophoblast, syncytiotrophoblast and intermediate trophoblast and marked cytological atypia. B Intraplacental choriocarcinoma. There is a distinct interface between malignant biphasic trophoblast in the maternal intervillous space seen on the lower right and mature chorionic villi on the left.

**Fig. 4.47** A Placental site trophoblastic tumour. Coronal section shows the neoplasm diffusely infiltrating the uterine wall. B Tumour cells show marked cytological atypia and numerous mitotic figures.
phoblastic tumour and undifferentiated carcinoma.

**Somatic genetics**
Recent studies using cDNA microarray analysis have demonstrated decreased expression of heat shock protein-27 in choriocarcinoma, a finding which has been associated with chemotherapy responsiveness in other cancers [3014].

**Placental site trophoblastic tumour**

**Definition**
A monophasic neoplasm composed of intermediate trophoblast and cytotrophoblast without a significant component of syncytiotrophoblast.

**Histopathology**
The tumour cells are medium to large sized and mononuclear or multinucleated with mild to marked nuclear atypia, prominent nucleoli, eosinophilic to clear cytoplasm, scattered mitoses and occasional intranuclear inclusions [746,747, 842, 861, 933, 1018, 1019, 1177, 1237, 1511, 1540, 1543, 1589, 2967, 3202, 3227]. They permeate the myometrium and vessels in a manner reminiscent of the implantation site trophoblast.

**Differential diagnosis**
The differential diagnosis of placental site trophoblastic tumour includes placental site nodule, exaggerated implantation site, epithelioid leiomyosarcoma, epithelioid trophoblastic tumour and poorly differentiated carcinoma. Extensive sampling and immunohistochemistry for keratin, β-hCG and hPL are helpful in distinguishing among the above lesions [2658,2659].

**Epithelioid trophoblastic tumour**

**Definition**
A tumour composed of a monomorphic population of intermediate trophoblastic cells closely resembling those of the chorion laeve (membranous chorion).

**Histopathology**
The epithelioid trophoblastic tumour is a relatively uncommon, recently described neoplasm that differs from the placental site trophoblastic tumour in that the tumour cells of the epithelioid trophoblastic tumour are smaller and less pleomorphic and grow in a nodular as opposed to a diffusely infiltrative pattern. Because they are frequently found in the cervix, they may be confused with hyalinizing squamous cell carcinomas. Epithelioid trophoblastic tumours are focally immunoreactive for placental-like alkaline phosphatase (PLAP) and hPL but strongly and diffusely immunoreactive for E-cadherin and epidermal growth factor receptor [2658].

**Hydatidiform mole**

**Definition**
An abnormal placenta with villous hydrops and variable degrees of trophoblastic proliferation.

**ICD-O codes**

- Hydatidiform mole, NOS 9100/0
- Complete 9100/0
- Partial 9103/0
- Invasive 9100/1

**Complete hydatidiform mole**

**Definition**
A hydatidiform mole involving most of the
chorionic villi and typically having a diploid karyotype.

**Histopathology**

The villous hydrops of a complete mole is characterized by extensive cavitation. The trophoblastic proliferation differs from normal villi by its circumferential distribution, hyperplasia and cytological atypia (978,1203). Intermediate trophoblast of the molar implantation site characteristically displays marked cytologic atypia (1901). A gestational sac, amnion, umbilical cord and fetal tissue are not found (481). It has recently been suggested that villous stromal nuclear negative staining for the paternally imprinted gene product p57 may be diagnostically useful for confirming the diagnosis of a complete mole (425). The extent of trophoblastic atypia and hyperplasia do not correlate with the behaviour in complete mole (776,978).

In the past most complete hydatidiform moles were diagnosed early in the second trimester at an average gestational age of 14 weeks (1924). Currently, with the widespread use of routine ultrasonography in pregnancy, complete moles are diagnosed between 8 and 12 weeks of gestational age (1924). Moles diagnosed at this "early" stage differ histologically from moles diagnosed in the second trimester (1426,1924). Although villous cavitation may be minimal in an "early" mole, other characteristic villous stromal features are present, including hypercellularity and a myxoid basophilic stroma (resembling that of a myxoid fibroadenoma). In addition, unusual villous shapes with complex bulbous protrusions ("cauliflower-like" villi) and trophoblastic atypia are present.

**Somatic genetics**

Complete and partial molar pregnancies have distinctly different cytogenetic origins. Complete moles generally have a 46,XX karyotype, and the molar chromosomes are completely of paternal origin (1385). Most complete moles appear to arise from an anuclear empty ovum fertilized by a (23X) haploid sperm that then replicates its own chromosomes (3172). Whereas most complete moles have a 46,XX chromosomal pattern, about 10% of complete moles have a 46,XY karyotype (2197). The 46,XY complete mole arises from fertilization of an anuclear empty egg by two sperm. While all chromosomes in a complete mole are entirely of paternal origin, incomplete or partial moles have an admixture of paternal and maternal chromosomes and display a spectrum of mosaicism.

**Gestational trophoblastic disease**

253
origin, the mitochondrial DNA is of maternal origin [146].

**Partial hydatidiform mole**

**Definition**
A hydatidiform mole having two populations of chorionic villi, one of normal size and the other hydropic, with focal trophoblastic proliferation. The lesion typically has a triploid karyotype.

**Histopathology**
Histologically, partial moles are characterized by the concurrence of four features (977, 1319, 1593, 2170, 2348, 2365, 2828, 2829):
1. Two populations of villi, one hydropic and one "normal";
2. Minimal trophoblastic hyperplasia involving syncytiotrophoblast;
3. Enlarged cavitated villi;
4. Other villi with scalloped borders, often containing trophoblastic inclusions.

Stromal blood vessels often contain nucleated fetal red blood cells; other evidence suggesting fetal development is common, including portions of the chorionic sac wall, amnion, umbilical cord and embryonic/fetal tissue.

The differential diagnosis of partial hydatidiform mole includes:
1. Complete mole.
2. Hydropic abortus.
3. Several rare sporadic genetic syndromes with focal placental hydrops and a fetus, such as the Beckwith-Weidemann syndrome [1558] and placental angiomatous malformation [2522], which collectively have been termed "placental mesenchymal dysplasia" [1337].

In instances in which the histological diagnosis is uncertain, cytogenetic analysis or flow cytometry may be of assistance [549, 682, 933, 1485, 1557-1563, 2170].

**Somatic genetics**
In contrast to complete moles, partial moles generally have a triploid karyotype that results from fertilization of an apparently normal ovum by two sperm [2828]. The reported incidence of triploidy in partial moles varies from 90-93% respectively [1560, 1593]. When fetuses are identified with partial moles, they usually have stigmata of triploidy including multiple congenital anomalies and growth retardation.

**Invasive hydatidiform mole**

**Definition**
Invasive hydatidiform mole is defined as villi of hydatidiform mole within the myometrium or its vascular spaces.

**Histopathology**
Most invasive moles follow complete hydatidiform mole and have the characteristic histological appearance of that lesion. Rare examples of invasive partial mole have also been described [33, 942, 1065, 2841, 3131]. A hysterectomy is usually required for the histological diagnosis.

**Metastatic hydatidiform mole**

**Definition**
Metastatic hydatidiform mole is defined as extrauterine molar villi within blood vessels or tissues, most commonly the vagina or the lung.

**Non-neoplastic, non-molar trophoblastic lesions**

**Placental site nodule or plaque**

The placental site nodule or plaque (1260, 3203) is a well circumscribed lesion with abundant hyalinized stroma infiltrated by scattered, degenerated-appearing intermediate trophoblastic cells; these cells show no significant cytological atypia, but rare mitoses may be present.

**Exaggerated placental site**

The exaggerated implantation site represents a non-neoplastic exaggeration of the normal implantation process, usually found concurrently with immature villi.
Sex cord-like, neuroectodermal and neuroendocrine tumours, lymphomas and leukaemias

Sex cord-like tumours

Definition
Tumours of the uterine corpus that closely resemble some true ovarian sex cord tumours.

Epidemiology
Among these rare tumours the most numerous are the sex cord-like tumours [511], which closely resemble some true ovarian sex cord tumours.

Histopathology
These are diagnosed only when they are not found within otherwise classical endometrial stromal or smooth muscle tumours. Histologically, sex cord elements are represented by trabecular ribbons and nodules or isolated cells with luteinized or foamy cytoplasm that are histologically and immunohistochemically identical to ovarian steroid-producing cells, being strongly positive for alpha-inhibin, calretinin and CD99 [167, 1521, 1808]. They may be capable of hormone-secreting activity [2034]. They have a prominent epithelial component that can be tubular, retiform [3247] or glomeruloid. They also show frequent positivity for cytokeratins, vimentin, smooth muscle actin and, occasionally, epithelial membrane antigen (EMA) [930].

Neuroectodermal tumours

Definition
A variety of tumours of the uterine corpus that show neuroectodermal differentiation.

Epidemiology
Different types of neuroectodermal tumours are found in the uterus. When pure, they usually present in young patients [1188]; however, when mixed with carcinoma or carcinosarcoma they are usually found in older women [638, 931, 2710]. Recently, peripheral primitive neuroectodermal tumour/Ewing tumour has been reported in both young [1597] and postmenopausal patients [2710].

Histopathology
Well differentiated variants with an appearance similar to low grade astrocytoma [3201] should be differentiated from non-neoplastic fetal parts implanted in the endometrium following abortion. Most often, the tumour cells differentiate into neuroblastic, neuroepithelial, glial and neuronal elements [1188]. Peripheral primitive neuroectodermal tumour/Ewing tumour shows a characteristic immunophenotype positive for neuron-specific enolase, vimentin and CD99 as well as the presence of EWS/FLI-1 fusion transcripts.

Melanotic paraganglioma

Definition
A tumour morphologically identical to paraganglioma, but functionally producing mainly melanin pigment instead of neuroendocrine granules.

Epidemiology
Only two examples of melanotic paraganglioma have been described in the uterus in women 31 and 46 years of age [2866].

Macroscopy
Both were incidental findings in uteri removed for unrelated benign lesions. The larger lesion was 1.5 cm and appeared as a black pigmented lesion on macroscopic examination; the other was a histological finding.

Histopathology
Both lesions were well circumscribed and composed of large nests of round or angulated polygonal cells with abundant clear or granular pale eosinophilic cytoplasm. Both cases had psammoma bodies, and large amounts of coarse melanin pigment.
granules were present in many cells. The large cells do not stain with S-100 protein. At the ultrastructural level intracellular melanosomes and premelanosomes abound, and a few neuroendocrine granules are present; the cells lack microvilli or dendritic processes.

**Prognosis and predictive factors**

Both women were free of any recurrences at 2.2 and 3.2 years after the discovery of the tumour [2866].

**Lymphomas and leukaemias**

**Definition**

A malignant lymphoproliferative or haematopoietic neoplasm that may be primary or secondary.

**Clinical findings**

The patients typically present with vaginal bleeding [2354].

**Tumour spread and staging**

Most lymphomas and leukaemias that involve the uterine corpus are a manifestation of disseminated disease. On rare occasions the corpus is the first known site of a malignant lymphoma.

**Histopathology**

The majority of cases are of the large B cell type [114]. Lymphomas of the uterine corpus must be distinguished from an atypical lymphoma-like inflammatory lesion of the endometrium. The latter is characterized by a massive infiltrate of lymphoid cells, some of which are immature. The presence of other inflammatory cells including plasma cells and neutrophils within the infiltrate and the typical absence of myometrial invasion or a macroscopic mass are helpful in the differential diagnosis [851]. Cases of uterine leiomyoma massively infiltrated by lymphocytes may also mimic a lymphoma [488].

**Rare tumours**

**Definition**

A variety of benign or malignant tumours of the uterine corpus that are not otherwise categorized.

**Histopathology**

Germ cell tumours such as teratomas and yolk sac tumours can develop in the endometrium, either in a pure form [398, 2196, 2763, 2836] or associated with endometrioid tumours [103, 2665]. Extrarenal Wilms tumours (nephroblastosomas) have also been reported in the uterus [1783, 1934]. Their histological appearance is similar to that of the tumours occurring in other sites.
Secondary tumours of the uterine corpus

**Definition**
Tumours of the uterine corpus that originate from, but are discontinuous with, a primary extraterine tumour or a tumour in the cervix or elsewhere in the uterus.

**Clinical features**
**Signs and symptoms**
The mean age of patients with extragenital tumour metastasis to the uterus is 60 years. Patients have abnormal uterine bleeding since most neoplasms metastatic to the uterus infiltrate the endometrium diffusely.

**Imaging**
Imaging studies are non-specific [1240, 1282, 1576, 3184].

**Macroscopy**
Metastases may appear as solitary or multiple tumours or be diffusely infiltrating.

**Histopathology**
The majority of metastases to the uterus are confined to the myometrium. However, approximately one-third involve the endometrium and thus can be detected in biopsy specimens [1529]. Metastatic carcinoma within the endometrium and/or myometrium characteristically infiltrates as single cells, cord or glands. The appearance is particularly striking in lobular carcinoma of the breast, which usually retains its single-file pattern, and with metastatic signet-ring cell carcinoma of the stomach or colon. Metastatic colon carcinoma of the usual type may form large tumour masses and can mimic an endometrial carcinoma of mucinous or endometrioid type.

Metastatic carcinoma in the endometrium should be suspected if one or more of the following features are present [1539].

1. A tumour with an unusual macroscopic or histological pattern for primary endometrial carcinoma.
2. Diffuse replacement by tumour of endometrial stroma with sparing of occasional normal endometrial glands.
3. Lack of premalignant changes in endometrial glands.
4. Lack of tumour necrosis

For specific identification of certain primary tumours immunohistochemical studies are frequently required.

**Origin and histogenesis**
In most instances the primary tumour is well known, or disseminated disease is clinical evident. Occasionally, a tumour diagnosed by curettage or hysterectomy represents the first sign of an extraterine primary tumour.

Secondary tumours of the uterine corpus can be divided into two major groups: tumours of the genital and extragenital organs. Neoplasms of neighbouring organs such as cervix, fallopian tubes, ovaries, bladder and rectum can metastasize to the uterus corpus via lymphatics or blood vessels but mostly represent local direct extension. Haematogenous or lymphatic uterine metastases from any extragenital primary tumour may occur but are extremely rare. Reported primary tumours include carcinomas of the breast, stomach, colon, pancreas, gallbladder, lung, urinary bladder and thyroid and melanoma [192, 1452, 1455, 1529, 1531, 1620, 1720]. Mammary lobular carcinoma, gastric signet-ring cell carcinoma and colonic carcinoma are the most frequently reported extragenital primary tumours [1529, 1531].

**Prognosis and predictive factors**
When uterine metastases are present, the patient usually has widely disseminated disease. However, in one series the average survival was 20 months after the diagnosis of uterine metastases. The reason for this relatively favourable outcome might be the predominance of cases of metastatic breast carcinoma [1529].

---

Fig. 4.59 Metastatic colon carcinoma to the myometrium. A Note the tumour cells in lymphatic vessels in the right upper portion of the field with a plexiform pattern on the left. B The neoplastic glands are positive for cytokeratin 20.

Fig. 4.60 Metastatic melanoma to the endometrium. Tumour cells containing melanin pigment surround an atrophic endometrial gland.
Cervical carcinoma is the second most common cancer in women worldwide. Chronic infection with human papilloma-virus (HPV) is a necessary event in the evolution of cervical carcinomas. The incidence of cervical cancer, which is predominantly of the squamous cell type, has markedly declined in many developed countries, mainly due to cytological screening programmes. Today, more than 80% of women dying from cervical cancer live in developing countries. It is anticipated that preventive HPV vaccination will become available in the near future.
### WHO histological classification of tumours of the uterine cervix

#### Epithelial tumours

<table>
<thead>
<tr>
<th>Squamous tumours and precursors</th>
<th>Neuroendocrine tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma, not otherwise specified 8070/3</td>
<td>Carcinoïd 8240/3</td>
</tr>
<tr>
<td>Keratinizing 8071/3</td>
<td>Atypical carcinoid 8249/3</td>
</tr>
<tr>
<td>Non-keratinizing 8072/3</td>
<td>Small cell carcinoma 8041/3</td>
</tr>
<tr>
<td>Basaloid 8083/3</td>
<td>Large cell neuroendocrine carcinoma 8013/3</td>
</tr>
<tr>
<td>Verrucous 8051/3</td>
<td>Undifferentiated carcinoma 8020/3</td>
</tr>
<tr>
<td>Warty 8051/3</td>
<td></td>
</tr>
<tr>
<td>Papillary 8052/3</td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelioma-like 8082/3</td>
<td></td>
</tr>
<tr>
<td>Squamotransitional 8120/3</td>
<td></td>
</tr>
<tr>
<td>Early invasive (microinvasive) squamous cell carcinoma 8076/3</td>
<td></td>
</tr>
<tr>
<td>Squamous intraepithelial neoplasia (CIN) 3 / squamous cell carcinoma in situ 8070/2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign squamous cell lesions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Condyloma acuminatum</td>
<td></td>
</tr>
<tr>
<td>Squamous papilloma 8052/0</td>
<td></td>
</tr>
<tr>
<td>Fibroepithelial polyp</td>
<td></td>
</tr>
</tbody>
</table>

#### Glandular tumours and precursors

| Adenocarcinoma 8140/3 | Carcinoïd (malignant müllerian mixed tumour; meta-plastic carcinoma) 8890/3 |
| Mucinous adenocarcinoma 8480/3 | Adenocarcinoma 8333/3 |
| Endocervical 8482/3 | Wilms tumour 8960/3 |
| Intestinal 8144/3 | Adenofibroma 9013/0 |
| Signet-ring cell 8490/3 | Adenomyoma 8932/0 |
| Minimal deviation 8480/3 | |
| Villoglandular 8262/3 | |
| Endometrioid adenocarcinoma 8380/3 | |
| Clear cell adenocarcinoma 8310/3 | Malignant melanoma 8720/3 |
| Serous adenocarcinoma 8440/3 | Blue naevus 8760/0 |
| Mesonephric adenocarcinoma 9110/3 | |
| Early invasive adenocarcinoma 8140/3 | |
| Adenocarcinoma in situ 8140/2 | Tumours of germ cell type |
| Glandular dysplasia | Yolk sac tumour 9071/3 |
| Benign glandular lesions | Dermoid cyst 9064/0 |
| Müllerian papilloma | Mature cystic teratoma 9038/0 |
| Endocervical polyp | |

#### Other epithelial tumours

| Adenosquamous carcinoma 8560/3 | Malignant lymphoma (specify type) |
| Glassy cell carcinoma variant 8075/3 | Leukaemia (specify type) |
| Adenoid cystic carcinoma 8200/3 | |
| Adenoid basal carcinoma 8098/3 | |

#### Neuroendocrine tumours

| Carcinoïd 8240/3 | |
| Atypical carcinoid 8249/3 | |
| Small cell carcinoma 8041/3 | |
| Large cell neuroendocrine carcinoma 8013/3 | |
| Undifferentiated carcinoma 8020/3 | |

#### Mesenchymal tumours and tumour-like conditions

| Leiomyosarcoma 8890/3 | |
| Endometrioid stromal sarcoma, low grade 8831/3 | |
| Endometrioid stromal sarcoma, grade 3 8831/3 | |
| Undifferentiated endocervical sarcoma 8805/3 | |
| Sarcoma botryoides 8910/3 | |
| Alveolar soft part sarcoma 9581/0 | |
| Angiosarcoma 9120/3 | |
| Malignant peripheral nerve sheath tumour 9540/0 | |
| Leiomyoma 8890/0 | |
| Genital rhabdomyoma 8905/0 | |
| Postoperative spindle cell nodule | |

#### Mixed epithelial and mesenchymal tumours

| Carcinoïd (malignant müllerian mixed tumour; meta-plastic carcinoma) 8890/3 | |
| Adenocarcinoma 8333/3 | |
| Wilms tumour 8960/3 | |
| Adenofibroma 9013/0 | |
| Adenomyoma 8932/0 | |

#### Melanocytic tumours

| Malignant melanoma 8720/3 | |
| Blue naevus 8760/0 | |

#### Miscellaneous tumours

<table>
<thead>
<tr>
<th>Tumours of germ cell type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yolk sac tumour 9071/3</td>
<td></td>
</tr>
<tr>
<td>Dermoid cyst 9064/0</td>
<td></td>
</tr>
<tr>
<td>Mature cystic teratoma 9038/0</td>
<td></td>
</tr>
</tbody>
</table>

#### Lymphoid and haematopoietic tumours

| Malignant lymphoma (specify type) | |
| Leukaemia (specify type) | |

#### Secondary tumours

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org).
2. Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
3. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are only available for lesions categorized as squamous intraepithelial neoplasia grade 3 (e.g., cervical intraepithelial neoplasia 3) = 8076/3, squamous cell carcinoma in situ = 8070/2, glandular intraepithelial neoplasia grade 3 = 8148/3 and adenocarcinoma in situ = 8140/2.
# TNM and FIGO classification of carcinomas of the uterine cervix

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>FIGO Categories</th>
<th>FIGO Stages</th>
<th>FIGO Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong> – Primary Tumour</td>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td>Stage 0</td>
</tr>
<tr>
<td></td>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td>Tis, IA, I1</td>
</tr>
<tr>
<td></td>
<td>Tis</td>
<td>Carcinoma in situ (preinvasive carcinoma)</td>
<td>Tis, IA, I1</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>Cervical carcinoma confined to uterus (extension to corpus should be disregarded)</td>
<td>T1a, IA, I1</td>
</tr>
<tr>
<td></td>
<td>T1a</td>
<td>Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions - even with superficial invasion - are T1b/Stage IB</td>
<td>T1a1, IA1, I1A</td>
</tr>
<tr>
<td></td>
<td>T1a1</td>
<td>Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread</td>
<td>T1a1, IA1, I1A</td>
</tr>
<tr>
<td></td>
<td>T1a2</td>
<td>Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less</td>
<td>T1a2, IA2, I1A</td>
</tr>
<tr>
<td><strong>N</strong> – Regional Lymph Nodes</td>
<td>NX Regional nodes cannot be assessed</td>
<td>Stage 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N0 No regional lymph node metastasis</td>
<td>T0, Tis, IA, I1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N1 Regional lymph node metastasis</td>
<td>T1a, IA, I1</td>
<td></td>
</tr>
<tr>
<td><strong>M</strong> – Distant Metastasis</td>
<td>MX Distant metastasis cannot be assessed</td>
<td>Stage 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M0 No distant metastasis</td>
<td>T0, Tis, IA, I1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M1 Distant metastasis</td>
<td>T1a, IA, I1</td>
<td></td>
</tr>
</tbody>
</table>

Note: The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>FIGO Categories</th>
<th>FIGO Stages</th>
<th>FIGO Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis, IA, I1</td>
<td>N0, M0</td>
<td>T3a, IIIA</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1a</td>
<td>N0, M0</td>
<td>T3b, IIIB, IVB</td>
</tr>
<tr>
<td>Stage IA1</td>
<td>T1a1</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage IA2</td>
<td>T1a2</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1b</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage IB1</td>
<td>T1b1</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>T1b2</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2a</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage II1</td>
<td>T2b</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3a</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1, T2, T3a</td>
<td>N1, M0</td>
<td>T4, IVA</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>N0, M0</td>
<td>T4, IVA</td>
</tr>
</tbody>
</table>

1 [31,296].
2 A help desk for specific questions about the TNM classification is available at http://tnm.uicc.org.
3 The regional lymph nodes are the paracervical, parametrial, hypogastric (internal iliac, obturator), common and external iliac, presacral, and lateral sacral nodes.
Epithelial tumours

This section covers the entire spectrum of invasive squamous and glandular carcinomas and their intraepithelial precursor lesions that originate for the most part from the transformation zone of the cervix. In addition, benign epithelial tumours are described which are not considered precursors of invasive cancer.

Epidemiology

In 1990 cervical cancer comprised 10% of cancers in women for a total of approximately 470,000 cancer cases worldwide (846), representing the third most common cancer in females and the most common cancer in Sub-Saharan Africa, Central America, South Central Asia and Melanesia. Approximately 230,000 women die annually from cervical cancer, and over 190,000 of those are from developing countries. Zimbabwe and India stand out not only for their high incidence but also for an unfavourable incidence to mortality ratio. Some relatively high-incidence countries can also be found in Eastern and Central Europe (1638).

The incidence of cervical cancer has been declining in the last three or four decades in most developed countries predominantly due to the introduction of cervical screening programmes. Other reasons include a decrease in parity (1943) and improved living conditions (226). In women under 45 years of age, however, mortality rates are levelling off or increasing in several countries (226). Stable or, in some instances, upward mortality trends in high-risk populations in Latin America (2395) and Eastern Europe (1638) are especially disturbing. Finally, adenocarcinoma of the cervix, which accounts for 10-15% of all cervical cancers, has shown an increased incidence in the last three decades (3028).

Aetiology

Sexually transmitted virus, human papillomavirus (HPV), is the major aetiologic factor, as shown by:

1. The identification of HPV DNA in most cervical cancer biopsy specimens worldwide (3044);
2. Relative risks (RRs) for cervical squamous cell and adenocarcinoma of greater than 70 for several high-risk HPV types in case-control studies (1199, 1293);
3. RRs of approximately 10 for women with HPV infection in cohort studies (3143).

Several host and environmental factors contribute, however, to enhance the probability of HPV persistence and progression to cervical neoplasia. Immune impairment, whether due to immunosuppressive treatments (274) or human immunodeficiency (HIV) infection (913, 920), increases the risk of cervical intraepithelial neoplasia (CIN) and invasive cancer of the cervix 5 to 10-fold. Among HPV-DNA positive women long-term use of oral contraceptives (1911), high parity (1943), tobacco smoking (3164) and certain sexually transmitted infections, such as Chlamydia trachomatis (2733), are associated with a RR between 2 and 4.

HPV-induced carcinogenesis

The products of two early genes, E6 and E7, have been shown to play a major role in HPV-mediated cervical carcinogenesis. This has been established by three different lines of evidence:

1. The first indication came from the analysis of HPV-infected cells, which showed that viral DNA is randomly integrated in the genome of the majority of cervical carcinomas. Integration leads to disruption of several viral genes with preservation of only the E6 and E7 genes, which are actively transcribed.
2. The discovery that E6 and E7 proteins are able to induce cellular transformation in vitro confirmed their oncogenic role. Immortalized rodent fibroblasts can be fully transformed by expression of HPV 16 E6 or E7 protein. These rodent cells acquire the ability to grow in an anchorage-independent manner and are tumorigenic when injected in nude mice. In addition, HPV 16 E6 and E7 are able to immortalize primary human keratinocytes, the natural host cell of the virus. In agreement with the in vitro assays, transgenic mice co-expressing both viral genes exhibit epidermal hyperplasia and various tumours.
3. Finally, biochemical studies have clarified the mechanism of action of E6
and E7. The viral oncoproteins are able to form stable complexes with cellular proteins and alter, or completely neutralize, their normal functions.

The best understood interactions of E6 and E7 with cellular proteins are those involving the tumor suppressor proteins TP53 and pRb, respectively. Both interactions lead to a rapid degradation of the cellular proteins via the ubiquitin pathway. The major role of TP53 is to safeguard the integrity of the genome by inducing cell cycle arrest or apoptosis, while pRb plays a key role in controlling the correct G1/S transition acting at the restriction point (R) of the cell cycle. Therefore, loss of TP53 and pRb functions results in abrogation of apoptosis and in unscheduled proliferation. Both events greatly increase the probability of HPV-infected cells evolving towards malignancy.

**Clinical features**

**Signs and symptoms**

Early invasive cancers can be asymptomatic. As the tumour grows and becomes exophytic, vaginal bleeding and discharge are the two most common symptoms. With lateral growth into the parametrium, the ureters become obstructed. If both ureters are obstructed, the patient presents with anuria and uremia. Pelvic sidewall involvement can cause sciatic pain and, less commonly, lymphoedema of the lower extremities. Anterior tumour growth in advanced

---

**Table 5.01**

Risk factors for cervical cancer: HPV infection vs. persistence and malignant transformation.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HPV infection</th>
<th>HPV persistence and transformation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sex partners</td>
<td>+</td>
<td>n.e.</td>
<td>(320)</td>
</tr>
<tr>
<td>Partner’s multiple partners</td>
<td>+</td>
<td>n.e.</td>
<td>(320)</td>
</tr>
<tr>
<td>Poor hygiene</td>
<td>+</td>
<td>n.e.</td>
<td>(193)</td>
</tr>
<tr>
<td>Absence of male circumcision</td>
<td>+</td>
<td>+</td>
<td>(423)</td>
</tr>
<tr>
<td>Immunodeficiency, HIV</td>
<td>+</td>
<td>+</td>
<td>(820)</td>
</tr>
<tr>
<td>High parity</td>
<td>n.e.</td>
<td>+</td>
<td>(1944)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>n.e.</td>
<td>+</td>
<td>(1911)</td>
</tr>
<tr>
<td>Smoking</td>
<td>n.e.</td>
<td>+</td>
<td>(2826)</td>
</tr>
<tr>
<td>STDs other than HPV</td>
<td>n.e.</td>
<td>+</td>
<td>(108,2734)</td>
</tr>
<tr>
<td>Poor nutritional status</td>
<td>n.e.</td>
<td>+</td>
<td>(2324)</td>
</tr>
</tbody>
</table>

STDs = Sexually transmitted diseases (especially C. trachomatis).  

n.e. = No evidence for being a risk factor at this time.
stage disease causes urinary frequency, bladder pain and haematuria. Direct extension into the bladder may cause urinary retention from bladder outlet obstruction and eventually a vesicovaginal fistula. Posterior extension leads to low back pain, tenesmus and rectovaginal fistula.

On examination cervical cancer may appear as a red, friable, exophytic or ulcerated lesion. Rectovaginal palpation can detect induration or nodularity of the parametria in advanced lesions.

Colposcopy

The colposcope is a noninvasive binocular instrument with a magnification of 6 to 40-fold designed to examine the cervix. The area of the cervix where the transformation of columnar to metaplastic squamous epithelium occurs is known as the transformation zone. Since most cervical neoplasia arises in the transformation zone, the relevant colposcopic signs are observed within its limits. Whenever the transformation zone is not seen in its entirety, the colposcopy is termed “unsatisfactory.”

Colposcopy involves the application of 4-5% acetic acid on the cervix and is based on the colour and margin of the aceto-white epithelium, the surface contour, the arrangement of the blood vessels and iodine staining. Abnormal colposcopic findings include leukoplakia, aceto-white epithelium, punctuation and mosaic and atypical vessels [372,417, 2705]. White keratotic lesions apparent before the application of acetic acid are termed “leukoplakia”.

Aceto-white epithelium, which appears only after contact with acetic acid, is most marked with cervical intraepithelial neoplasia (CIN) and early invasive cancer. Significant lesions are sharply delineated, densely opaque and persist for several minutes. Glandular lesions produce more subtle changes [3159]. Fine or coarse stippling within aceto-white epithelium produced by the end-on view of finger-like intraepithelial capillaries is called punctuation. A mosaic pattern arises when the stromal ridges containing the blood vessels subdivide the aceto-white epithelium into blocks of varying size and shape. Atypical tortuous vessels with bizarre irregular branches showing gross variation in calibre are suggestive of early invasive disease. Cervical neoplasia fails to stain deeply with iodine due to the lack of glycogen. Variations in quality and quantity of the above atypical appearances help in differentiating cervical neoplasia from physiological, benign, infective, inflammatory and reactive changes in the cervix. Colposcopy and histopathology are complementary to the diagnosis and management of CIN.

Tumour spread and staging

Cervical cancer is the only gynaecological cancer that is clinically staged by physical examination, chest X-ray, intravenous pyelogram, cystoscopy and proctoscopy. The staging of cervical tumours is by the TNM/FIGO classification [51,2976]. One-half of early invasive foci originate from the surface epithelium [2349]. The uterine corpus is commonly involved as the tumour expands. Ovarian metastasis is rare, occurring more frequently in bulky cancers and in adenocarcinomas as compared to squamous cell cancers [1914,1966]. Clinically undetected parametrial spread is identified by histological examination in 31-63% of stage IB cervical cancer.
and 58% of stage IIA patients [221]. Cervical cancers spread along fascial planes. As the parametria are invaded, the incidence of pelvic node involvement increases to 36% [221]. All para-aortic nodal metastases are associated with pelvic node metastasis; 11.5% of stage IB, 26.7% of stage IIA and 40% of stage IIB cancers had pelvic node involvement and in 90% of cases of low grade CIN and in 90% of cases of high grade CIN [447].

**Somatic genetics**

**TP53**

Inactivation of TP53 appears to play a key role in the development of cervical carcinoma [1178,2911] either because binding with the E6 protein of oncogenic HPV types inactivates it or because it undergoes mutation. Patterns of TP53 immunoreactivity suggest also that TP53 inactivation is important in the progression from intraepithelial to invasive neoplasia [1659,2004,2954]. TP53 reactivity has been demonstrated in both in situ and invasive adenocarcinoma [495,1807]. TP53 gene alterations are rare in minimal deviation adenocarcinoma [2937] and are not found in villoglandular adenocarcinomas [1363].

**Loss of heterozygosity**

Loss of heterozygosity (LOH) has been detected in multiple chromosomal regions in CIN (3p, 5p, 5q, 6p, 6q, 11q, 13q, 17q), invasive carcinoma (3p, 6p, 6q, 11q, 17p, 18q) and lymph node metastases from cervical carcinomas (3p, 6p, 11q, 17p, 18q, X) [263,666,1119,1444,1445,1584,1706,1712]. These changes accumulate in a fashion that parallels the progression of cervical carcinoma and indicate the stepwise nature of cervical carcinogenesis. Chromosomal instability is probably an early event. At least two tumour suppressor genes on 6p related to invasive cervical carcinoma have been demonstrated in 50% of cases of low grade CIN and in 90% of cases of high grade CIN [447].

**FHIT gene**

Recent studies have found that abnormalities of the FHIT (fragile histidine triad) gene, including loss of heterozygosity, homozygous deletions and aberrant transcripts, are common in cervical carcinomas, implicating this gene in cervical carcinogenesis [1938,2807,3187]. FHIT abnormalities have been observed in various histological types of cervical carcinomas [2616]. FHIT gene abnormalities have been found in both CIN and invasive carcinoma, but the incidence did not increase with progression to invasion or with advancing clinical stage [1964]. By contrast, another group [3188] found aberrations of FHIT to be more common in invasive carcinomas than in CIN suggesting that FHIT gene inactivation occurred as a late event in cervical carcinogenesis, after the tumour had acquired an invasive character.

**Monoclonality**

The finding that early invasive carcinoma is monoclonal supports the view that monoclonality is not a late event due to clonal competition or selection [1086]. Nearly all cases of high grade CIN have been found to be monoclonal, whilst only a small proportion of low grade CIN are monoclonal [489,789,2184]. Recurrent chromosome aberrations have been demonstrated in both invasive cervical squamous carcinoma and high grade CIN, there being a consistent chromosome gain at 3q and deletions at 3p [1208,1469].

**Genetic susceptibility**

Few studies have addressed familial clustering in cervical carcinoma [743,2230], the largest report being based on

---

**Epithelial tumours**

6.5% and 58% of stage IIA patients [221]. Cervical cancers spread along fascial planes. As the parametria are invaded, the incidence of pelvic node involvement increases to 36% [221]. All para-aortic nodal metastases are associated with pelvic node metastasis; 11.5% of stage IB, 26.7% of stage IIA and 40% of stage IIB cancers had pelvic node involvement and 2.1%, 0% and 7.2% of these had para-aortic node involvement respectively [2514]. In contrast to the orderly lymphatic spread of cervical cancers, lung and brain metastases reflect haematogenous spread and are an aberrant behaviour that cannot be predicted by stage of disease [1737].

**Precursor lesions**

Precursor lesions of squamous cell carcinoma and adenocarcinoma are well defined with the exception of low grade cervical glandular intraepithelial neoplasia, i.e. glandular dysplasia or glandular atypia.

**FHIT**

Recent studies have found that abnormalities of the FHIT (fragile histidine triad) gene, including loss of heterozygosity, homozygous deletions and aberrant transcripts, are common in cervical carcinomas, implicating this gene in cervical carcinogenesis [1938,2807,3187]. FHIT abnormalities have been observed in various histological types of cervical carcinomas [2616]. FHIT gene abnormalities have been found in both CIN and invasive carcinoma, but the incidence did not increase with progression to invasion or with advancing clinical stage [1964]. By contrast, another group [3188] found aberrations of FHIT to be more common in invasive carcinomas than in CIN suggesting that FHIT gene inactivation occurred as a late event in cervical carcinogenesis, after the tumour had acquired an invasive character.

**Monoclonality**

The finding that early invasive carcinoma is monoclonal supports the view that monoclonality is not a late event due to clonal competition or selection [1086]. Nearly all cases of high grade CIN have been found to be monoclonal, whilst only a small proportion of low grade CIN are monoclonal [489,789,2184]. Recurrent chromosome aberrations have been demonstrated in both invasive cervical squamous carcinoma and high grade CIN, there being a consistent chromosome gain at 3q and deletions at 3p [1208,1469].

**Genetic susceptibility**

Few studies have addressed familial clustering in cervical carcinoma [743,2230], the largest report being based on

---

**Epithelial tumours**

6.5% and 58% of stage IIA patients [221]. Cervical cancers spread along fascial planes. As the parametria are invaded, the incidence of pelvic node involvement increases to 36% [221]. All para-aortic nodal metastases are associated with pelvic node metastasis; 11.5% of stage IB, 26.7% of stage IIA and 40% of stage IIB cancers had pelvic node involvement and 2.1%, 0% and 7.2% of these had para-aortic node involvement respectively [2514]. In contrast to the orderly lymphatic spread of cervical cancers, lung and brain metastases reflect haematogenous spread and are an aberrant behaviour that cannot be predicted by stage of disease [1737].

**Precursor lesions**

Precursor lesions of squamous cell carcinoma and adenocarcinoma are well defined with the exception of low grade cervical glandular intraepithelial neoplasia, i.e. glandular dysplasia or glandular atypia.

**Somatic genetics**

**TP53**

Inactivation of TP53 appears to play a key role in the development of cervical carcinoma [1178,2911] either because binding with the E6 protein of oncogenic HPV types inactivates it or because it undergoes mutation. Patterns of TP53 immunoreactivity suggest also that TP53 inactivation is important in the progression from intraepithelial to invasive neoplasia [1659,2004,2954]. TP53 reactivity has been demonstrated in both in situ and invasive adenocarcinoma [495,1807]. TP53 gene alterations are rare in minimal deviation adenocarcinoma [2937] and are not found in villoglandular adenocarcinomas [1363].

**Loss of heterozygosity**

Loss of heterozygosity (LOH) has been detected in multiple chromosomal regions in CIN (3p, 5p, 5q, 6p, 6q, 11q, 13q, 17q), invasive carcinoma (3p, 6p, 6q, 11q, 17p, 18q) and lymph node metastases from cervical carcinomas (3p, 6p, 11q, 17p, 18q, X) [263,666,1119,1444,1445,1584,1706,1712]. These changes accumulate in a fashion that parallels the progression of cervical carcinoma and indicate the stepwise nature of cervical carcinogenesis. Chromosomal instability is probably an early event. At least two tumour suppressor genes on 6p related to invasive cervical carcinoma have been demonstrated in 50% of cases of low grade CIN and in 90% of cases of high grade CIN [447].

**FHIT gene**

Recent studies have found that abnormalities of the FHIT (fragile histidine triad) gene, including loss of heterozygosity, homozygous deletions and aberrant transcripts, are common in cervical carcinomas, implicating this gene in cervical carcinogenesis [1938,2807,3187]. FHIT abnormalities have been observed in various histological types of cervical carcinomas [2616]. FHIT gene abnormalities have been found in both CIN and invasive carcinoma, but the incidence did not increase with progression to invasion or with advancing clinical stage [1964]. By contrast, another group [3188] found aberrations of FHIT to be more common in invasive carcinomas than in CIN suggesting that FHIT gene inactivation occurred as a late event in cervical carcinogenesis, after the tumour had acquired an invasive character.

**Monoclonality**

The finding that early invasive carcinoma is monoclonal supports the view that monoclonality is not a late event due to clonal competition or selection [1086]. Nearly all cases of high grade CIN have been found to be monoclonal, whilst only a small proportion of low grade CIN are monoclonal [489,789,2184]. Recurrent chromosome aberrations have been demonstrated in both invasive cervical squamous carcinoma and high grade CIN, there being a consistent chromosome gain at 3q and deletions at 3p [1208,1469].

**Genetic susceptibility**

Few studies have addressed familial clustering in cervical carcinoma [743,2230], the largest report being based on
the Swedish Family-Cancer Database (1184). The relative risk when the mother or a daughter was affected by cervical cancer was 2. An aggregation of tobacco-related cancers and cancers linked with HPV and immunosuppression was found in such families. Thus, familial predisposition for cervical cancer is likely to imply genes which modulate immune response, e.g. human leukocyte antigen (HLA) haplotypes (2524) and/or shared sexual or lifestyle factors in family members.

Prognosis and predictive factors

Clinical criteria

The clinical factors that influence prognosis in invasive cervical cancer are age, stage of disease, volume, lymphatic spread and vascular invasion (370,663, 673,818,970,1506,2525,2672,2782). In a large series of cervical cancer patients treated by radiation therapy, the frequency of distant metastases (most frequently to the lung, abdominal cavity, liver and gastrointestinal tract) was shown to increase with increasing stage of disease from 3% in stage IA to 75% in stage IVA (818). Radiotherapy and surgery produce similar results for early invasive cancer (stages IB and IIA). More advanced lesions (IIB to IV) containing has been found to be significant - with a poor prognosis (2969).

Histopathological criteria

Among histopathological variables based on histological findings and not included in the staging system for cervical cancer (1532), the grading of tumours does not seem to be a strong predictive factor (3233). In non-squamous cell carcinomas the only histological type of cervical cancer of prognostic significance is small cell carcinoma (68). There is some evidence that women with adenocarcinoma and adenosquamous carcinoma have a poorer prognosis than those with squamous cell carcinoma after adjustment for stage (2314).

Genetic predictive factors

TP53. The prognostic value of TP53 immunoreactivity in cervical carcinoma is controversial. Some have found no association between p53 overexpression and the presence of mutant p53 protein and clinical outcome (1267,2251), whilst others have reported that TP53 expression identifies a subset of cervical carcinomas with a poor prognosis (2369).

c-myc. c-myc amplification has been demonstrated in CIN and invasive cervical carcinoma (110,666,2004) suggesting that it is important in early cervical carcinogenesis. Moreover, c-myc overexpression correlates with high risk HPV-positive neoplasia and with cellular proliferation (666). It has been claimed that an increased level of c-myc transcripts is strongly indicative of a poor prognosis in early stage cervical carcinoma (1314) but not in late stage disease (2823).

Squamous tumours and precursors

Definition

Primary squamous epithelial tumours of the uterine cervix, either benign or malignant.

ICD-O codes

Squamous cell carcinoma 8070/3
Keratinizing 8071/3
Non-keratinizing 8072/3
Basaloid 8083/3
Verrucous 8051/3
Warty 8051/3
Papillary 8052/3
Lymphoepithelioma-like 8082/3
Squamotransitional cell 8120/3
Microinvasive squamous 8076/3
Cell carcinoma
Cervical intraepithelial neoplasia 3 8077/2
Squamous cell carcinoma in situ 8070/2
Squamous papilloma 8052/0

Squamous cell carcinoma

Definition

An invasive carcinoma composed of squamous cells of varying degrees of differentiation.

Macroscopy

Macroscopically, squamous cell carcinoma may be either predominantly exophytic, in which case it grows out from the surface, often as a papillary or polypoid excrescence, or else it may be mainly endophytic, such that it infiltrates into the surrounding structures without much surface growth.
Histopathology

There have been few recent developments in the histological diagnosis of frankly invasive squamous cell carcinoma of the cervix \[362,1201\]. They vary in their pattern of growth, cell type and degree of differentiation. Most carcinomas infiltrate as networks of anastomosing bands with intervening stroma and appear as irregular islands, sometimes rounded, but more usually angular and spiked. Often, particularly in small tumours, CIN may be found on the surface and at the edge of the invasive tumour, and, occasionally, difficulty may be encountered in distinguishing between invasive islands and CIN involving crypts. Similarly, invasion cannot be excluded when neoplastic squamous epithelium shows features of CIN 2 or 3 but underlying stroma is not present. A number of histological grading systems have been proposed that depend upon the type and degree of differentiation of the predominant cell \[2794\]. A simpler classification is a modification of the four grades of Broders \[350\] and subdivides the tumours into well differentiated (keratinizing), moderately differentiated and poorly differentiated types. Approximately 60% are moderately differentiated, and the remaining tumours are evenly distributed between the well and poorly differentiated groups. A simple two-tiered classification is recommended, keratinizing and non-keratinizing, to avoid nosological confusion with small cell carcinoma, a term that should be reserved for tumours of neuroendocrine type.

The cervical stroma separating the islands of invasive carcinoma is usually infiltrated by a variety of cell types, mainly lymphocytes and plasma cells. A markedly eosinophilic stromal response \[262\] or a foreign body type giant cell reaction is occasionally seen. A variety of histological types of squamous cell carcinoma have been described.

Keratinizing

These tumours contain keratin pearls composed of circular whorls of squamous cells with central nests of keratin. Intercellular bridges, keratohyaline granules and cytoplasmic keratinization are usually observed. The nuclei are usually large and hyperchromatic with coarse chromatin. Mitotic figures are not frequent and are usually seen in the less well-differentiated cells at the periphery of the invasive masses. In cytological preparations the cells usually have bizarre shapes with mostly eosinophilic cytoplasm and large, irregular, hyperchromatic nuclei. Necrotic debris is present.

Non-keratinizing

These tumours are composed of generally recognizable polygonal squamous cells that may have individual cell keratinization and intercellular bridges, but keratin pearls are absent. Cellular and nuclear pleomorphism is more obvious than in the well differentiated tumours, and mitotic figures are usually numerous. In cytological preparations the cells are solitary or arranged in syncytia and show anisokaryosis. The nuclei are relatively large with unevenly distributed, coarsely granular chromatin and may have irregular nuclei.

Basaloid

Basaloid squamous cell carcinoma is composed of nests of immature, basal type squamous cells with scanty cytoplasm that resemble closely the cells of squamous carcinoma in situ of the cervix. Some keratinization may be evident in the centres of the nests, but keratin pearls are rarely present. In the vulva this tumour has been associated with HPV infections, predominantly type 16 \[1541,2936\]. This underrecognized variant of squamous cell carcinoma is an aggressive tumour with basaloid features \[1057\]. This tumour along with adenoid cystic carcinoma is at one end of the spectrum of basaloid tumours of the cervix. The opposite end are low grade lesions such as adenoid basal carcinoma. To avoid confusion in the diagnosis of a cervical tumour with basaloid features, the term "basaloid carcinoma" should be avoided \[1057\].

Verrucous

Verrucous carcinoma is a highly differentiated squamous cell carcinoma that has a hyperkeratotic, undulating, warty surface and invades the underlying stroma in the form of bulbous pegs with a pushing border. The tumour cells have abundant cytoplasm, and their nuclei show minimal atypia. Features of HPV infection are not evident. Verrucous carcinomas have a tendency to recur locally after excision but do not metastasize. They are distinguished from condyloma by their broad papillae that lack fibrovascular cores and the absence of koilocytosis. Verrucous carcinoma is distinguished from the more common types of squamous cell carcinoma in that it shows no more than minimal nuclear atypia.

Warty

This lesion is defined as a squamous cell carcinoma with a warty surface and cellular features of HPV infection \[720,1541,2936\]. High risk HPV-DNA is typically detected \[2936\]. It is also referred to as condylomatus squamous cell carcinoma.

Papillary

This is a tumour in which thin or broad papillae with connective tissue stroma are covered by epithelium showing the features of CIN. Whilst a superficial biopsy may not reveal evidence of invasion, the underlying tumour is usually a typical squamous cell carcinoma \[345,2333\]. Such tumours are positive for HPV type 16. Papillary squamous cell carcinoma differs from warty squamous carcinoma by the inconspicuous keratinization and lack of cellular features of HPV infection and from transitional cell carcinoma by its squamous cell differentiation \[345\].

Lymphoepithelioma-like

Histologically, lymphoepithelioma-like carcinoma is strikingly similar to the nasopharyngeal tumour of the same name. It is composed of poorly defined islands of undifferentiated cells in a background intensely infiltrated by lym-
The tumour cells have uniform, vesicular nuclei with prominent nucleoli and moderate amounts of slightly eosinophilic cytoplasm. The cell borders are indistinct, often imparting a syncytial-like appearance to the groups. Immunohistochemistry identifies cytokeratins within the tumour cells and T-cell markers in the majority of the lymphocytes. The presence of an intense chronic inflammatory reaction in a tumour indicates a cell-mediated immune reaction, and some evidence suggests that lymphoepithelioma-like carcinoma of the cervix may have a favourable prognosis. Using the polymerase chain reaction to examine frozen tissue from a lymphoepithelioma-like carcinoma of the cervix, Epstein-Barr virus (EBV) genomic material was not identified in a case from Spain (1696). Thus, if EBV plays a role in the genesis of this tumour, it exhibits geographical variation.

**Squamous cell carcinoma**

A squamous cell carcinoma with early stromal invasion, the extent of which has not been precisely defined, and a low risk of local lymph node metastasis.

**Synonym**

Microinvasive squamous cell carcinoma.

**Histopathology**

Certain features of high grade CIN increase the likelihood of identifying early invasion. These include:

1. Extensive CIN 3,
2. Widespread, expansile and deep extension into endocervical crypts.
3. Luminal necrosis and intraepithelial squamous maturation (57).

The first sign of invasion is referred to as early stromal invasion; this is an unmeasurable lesion less than 1 mm in depth that can be managed in the same way as high grade CIN. The focus of early invasion in their Asian population (2957). It is of note that EBV was not identified in a case analysed from Spain (1696). Thus, if EBV plays a role in the genesis of this tumour, it exhibits geographical variation.
stromal invasion often appears to be better differentiated than the overlying CIN. Early stromal invasion is encompassed in the term microinvasive carcinoma.

The criteria for the diagnosis of microinvasive carcinoma were historically based on the depth of invasion, and the ascribed upper limit has varied in the literature from 3 to 5 mm. Microinvasive carcinoma now equates most closely to FIGO stage IA, the definition of which includes both the depth and horizontal dimension of the tumour. The current FIGO staging is controversial because it does not recognize early stromal invasion as a separate entity [371]. Whether microinvasive carcinoma should include FIGO Stage IA2 because there is a significantly increased risk of local lymph node metastasis of 2% and a recurrence rate of 0.9%. On the other hand, invasion of 3.1-5.0 mm is associated with an overall risk of lymph node metastasis of <1% and a risk of an invasive recurrence of 0.9%. On the other hand, invasion of 3.1-5.0 mm is associated with an overall risk of lymph node metastasis of 2% and a recurrence rate of 4% [2138]. Microinvasive squamous cell carcinoma is usually associated with stromal oedema and a stromal desmoplastic and lymphocytic response, features that aid in its distinction from crypt involvement by CIN. Immunohistochemical stains for CD31 and CD34 may aid in the recognition of lymphatic vascular space involvement. Preclinical invasive carcinomas of the cervix with dimensions greater than those acceptable as stage IA carcinoma should be designated by the histopathologist simply as stage IB carcinomas.

Table 5.02
Classification of HPV-associated intraepithelial lesions of the cervix.

<table>
<thead>
<tr>
<th>Term</th>
<th>HPV risk category</th>
<th>Comparison of classification systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exophytic condyloma</td>
<td>Low risk</td>
<td>—</td>
</tr>
<tr>
<td>Squamous papilloma</td>
<td>Low risk</td>
<td>—</td>
</tr>
<tr>
<td>Flat condyloma</td>
<td>Low and high risk</td>
<td>—</td>
</tr>
<tr>
<td>CIN 1</td>
<td>Low and high risk</td>
<td>Low grade CIN Mild dysplasia</td>
</tr>
<tr>
<td>CIN 2</td>
<td>High risk</td>
<td>High grade CIN Moderate dysplasia</td>
</tr>
<tr>
<td>CIN 3</td>
<td>High risk</td>
<td>High grade CIN Severe dysplasia/CIS</td>
</tr>
</tbody>
</table>

CIN = Cervical intraepithelial neoplasia
SIL = Squamous intraepithelial lesion
CIS = Carcinoma in situ
LG = Low grade
HG = High grade

"Finger-like" or "confluent" patterns of stromal invasion are of questionable clinical significance and probably are a reflection of a greater depth of stromal invasion.

Cervical intraepithelial neoplasia

Definition

The spectrum of CIN representing the precursor lesions of cervical squamous cell carcinoma [2368].

Synonyms

Dysplasia/carcinoma-in-situ, squamous intraepithelial lesion.

Epidemiology

The risk of CIN is closely linked to the number of sexual partners and to HPV exposure. It is highest in early reproductive life [1160]. HPV is detected in as many as 39% of adolescents in a single screening visit [2451], and 20% of women under age 19 in a sexually transmitted disease clinic developed CIN 2 or 3 [1513]. The strong association between HPV 16 and high grade CIN coupled with follow-up studies suggests that infections by this virus induce a high grade lesion over a relatively short period of time [586,1513,1699]. The risk of CIN drops substantially in the fourth and fifth decades, coinciding with a sharp reduction in frequency of HPV attributed to the development of immunity to HPV and elimination of the virus from the genital tract in most women. Other factors influencing risk include immunological, such as HIV infection, and other host factors, including coincident cervical infections and HLA status.

Aetiology

At puberty there is a change in the anatomical relationships of the lower part of the cervix composed of squamous epithelium, an original squamocolumnar junction and endocervical columnar epithelium. There is eversion of the columnar epithelium, which undergoes squamous metaplasia through a sequence of reserve cell hyperplasia, immature squamous metaplasia and mature squamous metaplasia with the formation of a new squamocolumnar junction. These histological changes are entirely physiological. However, it is this epithelium of the cervical transformation zone that is particularly susceptible to oncogenic stimuli.

In the last 25 years “flat” and exophytic condylomata of the cervix and CIN have been linked by an association with HPVs, many of them weakly or strongly associated with cancer (intermediate and high risk HPVs) [586,737,1014,1841,2305]. Although some HPVs are not associated with cervical cancer (low risk HPVs), the majority are associated with high risk HPVs [1699]. High risk HPV infection may present histologically as CIN 1, although certain infections, such as HPV type 16,

Fig. 5.13 Early squamous cell carcinoma of the cervix. Early stromal invasion is indicated by a bed of more mature squamous cells extending from a focus of in situ carcinoma.

Epithelial tumours 269
have a strong association with high grade CIN lesions [587,1068,1639, 1878,3127]. CIN represents the preinvasive counterpart of invasive cervical squamous cell carcinoma, and there is now abundant evidence for its malignant potential. However, there is no inevitability about neoplastic progression; such lesions may regress, remain phenotypically stable or progress [2137].

**Histopathology**

Conventionally, these are subjectively divided into three grades: CIN 1, 2 and 3, though the histological features represent a diagnostic continuum. Increasingly, there is a tendency to use a two-tiered classification of low and high grade CIN that equates to CIN 1 and CIN 2 and 3 respectively. These precursors may also be referred to as low and high grade squamous intraepithelial lesion (SIL) (2177). Because of the inherent difficulty in distinguishing pure HPV infection from unequivocal CIN 1 in flat, non-condylomatous epithelium (sometimes confusingly referred to as flat condyloma), HPV infection alone is included in the low grade SIL category, a terminology that has been more widely accepted by cytopathologists [1612]. The relationship of the varying terminology is shown in Table 5.1.

**Cervical intraepithelial neoplasia 1**

Maturation is present in the upper two-thirds of the epithelium, and the superficial cells contain variable but usually mild atypia, which may include viral cytopathic effect (koilocytosis). Nuclear abnormalities are present throughout but are slight. Mitotic figures are present in the basal third and are not numerous. Abnormal forms are rare.

**Cervical intraepithelial neoplasia 2**

Maturation is present in the upper half of the epithelium, and nuclear atypia is conspicuous in both the upper and lower epithelial layers. Mitotic figures are generally confined to the basal two-thirds of the epithelium. Abnormal forms may be seen.

**Cervical intraepithelial neoplasia 3**

Maturation (including surface keratinization) may be absent or confined to the superficial third of the epithelium. Nuclear abnormalities are marked throughout most or all of the thickness of the epithelium. Mitotic figures may be numerous and are found at all levels of the epithelium. Abnormal mitoses are frequent.

**Growth fraction**

HPVs, particularly high risk HPVs, are associated with alterations in the cell cycle. Therefore, cell cycle biomarkers may be useful in distinguishing non-diagnostic atypia from CIN. Expression of a generic cell cycle proliferation marker (Ki-67) is typically confined to the suprabasal cells of the lower third of the normal epithelium. The presence of Ki-67 positive cells in the upper epithelial layers occurs in HPV infection, which induces cell cycle activity in these cells [1881,2356]. P16<sup>INK4a</sup>, a cyclin-dependent kinase inhibitor, is a promising marker of CIN [1422,2527].

**Differential diagnosis**

Transitional cell metaplasia is a benign condition that may be mistaken for high grade CIN. After the menopause immature squamous mucosa may exhibit histological features resembling transitional epithelium [1140,3085].

**Related lesions**

CIN is usually associated with the cytopathic effects of HPV infection, which include koilocytosis, dyskeratosis and multinucleation. Koilocytosis is characterized by karyomegaly, nuclear enlargement with binucleation, irregularities in the nuclear membrane and hyperchromasia (1508). Atypical reserve cell hyperplasia and atypical immature squamous metaplasia may be regarded as variants of CIN, though grading of such lesions may be difficult [979,2179].

**Cytopathology**

In cytology the grading of CIN is largely based on nuclear characteristics. The number of abnormal cells and the relative nuclear area increase with the severity of the lesion.

In CIN 1 the cells show a slightly enlarged nucleus (less than one-third of the total area of the cell), some anisokaryosis, finely granular and evenly distributed chromatin and mild hyperchromasia. The cytoplasmic borders are well defined.

In CIN 2 the cells and nuclei vary in size and shape. The nuclear to cytoplasmic ratio is increased (nucleus less than half of cell area). Nuclear chromatin is moderately hyperchromatic and shows some irregular distribution.

In CIN 3 the nuclear to cytoplasmic ratio is high (nucleus at least two-thirds of cell area). Nuclei are hyperchromatic with coarsely granular and irregularly distributed chromatin.
Cells typical of carcinoma in situ are arranged singly or in syncytial aggregations (indistinct cell borders and overlapping nuclei). Cytoplasm is scarce or absent; nuclei are round to oval.

**Prognosis and predictive factors**

Systematic reviews of randomized controlled trials in subjects who underwent cryotherapy, laser ablation, loop electrosurgical excision procedure (LEEP) or surgical conization for the treatment of CIN of any grade reveal no substantial differences in outcome (1777, 2068, 2299).

**Benign squamous cell lesions**

**Condyloma acuminatum**

**Definition**

A benign tumour characterized by papillary fronds containing fibrovascular cores and lined by stratified squamous epithelium with evidence of HPV infection, usually in the form of koilocytosis.

**Aetiology**

The exophytic condyloma is strongly associated with HPV types 6 and 11 (3057).

**Histopathology**

These lesions exhibit acanthosis, papillomatosis and koilocytosis. The latter is characterized by karyomegaly, nuclear enlargement with binucleation, irregularities in the nuclear membrane and hyperchromasia. These lesions closely resemble vulvar condylomas (585).

**Squamous papilloma**

**Definition**

A benign tumour composed of a single papillary frond in which mature squamous epithelium without atypia or koilocytosis lines a fibrovascular stalk.

**Epidemiology**

Lesions with a histological appearance similar to squamous papillomas of the vagina and vulva are rare in the cervix.

**Aetiology**

There is no evidence that squamous papilloma as defined above is or is not related to human papillomavirus.

**Macroscopy**

The squamous papilloma is usually solitary, arising on the ectocervix or at the squamocolumnar junction.

**Histopathology**

Histological examination shows a single papillary frond composed of mature squamous epithelium without atypia or koilocytosis lining a fibrovascular stalk.

**Differential diagnosis**

Squamous papilloma is distinguished from condyloma by the absence of complex branching papillae and koilocytes. However, it is important to note that there may be a time during the evolution of condyloma when koilocytes are not easily identifiable.

Squamous papilloma also should be distinguished from papillary immature metaplasia of the cervix, which is characterized by slender filiform papillae and also does not have koilocytosis (3057). In the latter condition the squamous epithelium is less mature with higher nuclear to cytoplasmic ratios but lacks nuclear atypia. Papillary immature metaplasia has been associated with HPV types 6 or 11 (3057).

**Fibroepithelial polyp**

**Definition**

A polyp lined by squamous epithelium that contains a central core of fibrous tissue in which stellate cells with tapering cytoplasmic processes and irregularly shaped thin-walled vessels are prominent features.

**Synonym**

Stromal polyp.

**Aetiology**

Unlike condyloma, fibroepithelial polyps rarely contain HPV nucleic acids (1837), and, thus, are not related to HPV infection.

**Clinical features**

This lesion can occur at any age but has a predilection for pregnant women.

**Macroscopy**

These are polypoid lesions and are usually solitary.

**Histopathology**

These polypoid lesions are characterized by a prominent fibrovascular stroma cov-
erased by squamous epithelium \( \{380\} \). Unlike squamous papilloma, they do not show acanthosis or a papillary architecture. Bizarre stromal cells, marked hypercellularity and elevated mitotic counts including atypical forms have been described that can lead to an erroneous diagnosis of sarcoma \( \{2067\} \).

**Glandular tumours and precursors**

ICD-O codes
- Adenocarcinoma, NOS 8140/3
- Mucinous adenocarcinoma 8480/3
- Endocervical 8482/3
- Intestinal 8144/3
- Signet-ring cell 8490/3
- Minimal deviation 8480/3
- Villoglandular 8262/3
- Endometrioid adenocarcinoma 8380/3
- Clear cell adenocarcinoma 8310/3
- Serous adenocarcinoma 8441/3
- Mesonephric adenocarcinoma 9110/3
- Early invasive adenocarcinoma 8140/3
- Adenocarcinoma in situ 8140/2

**Adenocarcinoma**

**Definition**
A carcinoma that shows glandular differentiation.

**Clinical features**
About one-half of all adenocarcinomas are exophytic, polyoid or papillary masses. Others are nodular with diffuse enlargement or ulceration of the cervix. Deep infiltration of the wall produces a barrel-shaped cervix. Approximately 15% of patients have no visible lesion.

**Histopathology**
Immunohistochemistry may be useful to distinguish between benign and malignant conditions of the cervix, to discriminate between the various subtypes and to separate primary endocervical from primary endometrial tumours. The tumour that is estrogen receptor positive, vimentin positive and carcinoembryonic antigen negative is almost certainly of endometrial origin, whilst an endocervical source is very likely for the tumour that is estrogen receptor negative, vimentin negative and carcinoembryonic antigen positive \( \{424,1822\} \). A moderate to high Ki-67 proliferation index also points towards endocervical neoplasia \( \{495\} \). It is equally important to recognize that none of these stains are needed in the majority of cases, where the clinical evidence and history are entirely adequate. Carcinoembryonic antigen is usually negative in benign mimics, such as microglandular hyperplasia \( \{2780\} \). In contrast to normal endocervical epithelium, some of the cells of a minimal deviation adenocarcinoma are reactive for serotonin and gastrointestinal tract-pancreatic peptide hormones and uniformly lack immunoreactivity for estrogen and progesterone receptors and CA125.

**Mucinous adenocarcinoma**

**Definition**
An adenocarcinoma in which at least some of the cells contain a moderate to large amount of intracytoplasmic mucin.

**Endocervical**
The endocervical type accounts for 70% of cervical adenocarcinomas, and the tumour cells resemble those of the endocervix. Most tumours are well to moderately differentiated. The glandular elements are arranged in a complex pattern. Papillae may project into the gland lumens and from the surface. At times a cribriform arrangement is observed. A microglandular pattern resembling microglandular hyperplasia of the cervix \( \{3224\} \) and a microcystic variant are rarely seen \( \{2856\} \). The stroma may be desmoplastic. The cells are typically stratified with basal nuclei and abundant pale granular cytoplasm that stains positively for mucin. They show considerable nuclear atypia with variation in nuclear size, coarsely clumped chromatin and prominent nucleoli. Mitoses are usually numerous. Large amounts of mucin may be found in the stroma forming mucin lakes or pools in the so-called colloid carcinoma \( \{1646,2975\} \). In poorly differentiated tumours the cells contain less cytoplasm but usually still form recognizable glandular structures. Co-existent CIN occurs in up to 40% of cases \( \{1739\} \), and adenocarcinoma in situ is also common. Synchronous mucinous tumours may be found elsewhere in the female genital tract \( \{1392,3219\} \). In cytological preparations the cells are arranged in crowded cell aggregates with overlapping nuclei. Gland openings, rosettes, strips with palisading and pseudodifferentiation and cell balls may be seen. The cytoplasm is vacuolated. The nuclei are round, oval or “cigar” shaped and vary in size. The nuclear chromatin is coarse and unevenly distributed with clearing, and nucleoli are present.

**Intestinal variant**
These tumours resemble adenocarcinoma of the large intestine. Intestinal-type change may be found diffusely or only focally within a mucinous tumour. They frequently contain goblet cells and less commonly contain endocrine and Paneth cells.

---

Fig. 5.20 Adenocarcinoma. A A large, polyoid, exophytic tumour arises from the cervix with focal cystic change and necrosis. B A cribriform pattern along with other features may indicate an invasive, rather than an in situ, neoplastic glandular process. C Endocervical variant. Atypical cells with enlarged nuclei, coarsely granular cleared chromatin and nucleoli form a gland opening.
Signet-ring cell variant
Primary signet-ring cell adenocarcinoma is rare in pure form (1157, 1799, 1893, 3013). Signet-ring cells occur more commonly as a focal finding in poorly differentiated mucinous adenocarcinomas and adenosquamous carcinomas. The differential diagnosis includes metastatic tumours (908, 1434) or rare squamous cell carcinomas with signet-ring-like cells that are mucin negative (1533).

Minimal deviation variant
This is a rare highly differentiated mucinous adenocarcinoma in which most of the glands are impossible to distinguish from normal. Adenoma malignum is a synonym.

Histopathology. Most of the glands are lined by deceptively bland, mucin-rich columnar cells with basal nuclei. In the majority of cases, however, occasional glands display moderate nuclear atypia, are angulated or elicit a desmoplastic stromal reaction. The most reliable criteria are the haphazard arrangement of the glands that extend beyond the depth of those of the normal endocervix and the presence of occasional mitoses, which are uncommon in the normal endocervical epithelium. Vascular and perineural involvement is frequent. Transmural and/or parametrial and/or myometrial spread is seen in 40% of cases (1004, 1391). Because the depth of penetration of the glands is a key histological feature, the diagnosis cannot be made in punch biopsies in most cases. Minimal deviation adenocarcinoma should be differentiated from the benign conditions of diffuse laminar endocervical glandular hyperplasia (1362), lobular endocervical glandular hyperplasia (2061), endocervicitis (3193) and adenomyoma of endocervical type (1005). An endometrioid variant of minimal deviation adenocarcinoma has also been described (1391, 1972, 3225).

Somatic genetics. The genetic locus for the putative tumour suppressor gene is in the region of chromosome 19p 13.3 (1610). Somatic mutations of the STK11 gene, the gene responsible for the Peutz-Jeghers syndrome, are characteristic of minimal deviation adenocarcinoma (1397). They were found in 55% of patients with minimal deviation adenocarcinoma and in only 5% of other types of mucinous adenocarcinoma of the cervix.

Genetic susceptibility. These tumours are more likely than any other type of cervical adenocarcinoma to precede or develop coincidentally with ovarian neoplasia, the most common being mucinous adenocarcinoma and sex cord tumour with annular tubules (2769). The latter is associated with the Peutz-Jeghers syndrome in 17% of cases (453). A germline mutation of STK11 was detected in one patient with Peutz-Jeghers syndrome who had a mucinous adenocarcinoma of the cervix (1397).

Villoglandular variant
These have a frond-like pattern resembling villoglandular adenoma of the colon. The tumours generally occur in young women. A possible link to oral contraceptives has been suggested. The epithelium is generally moderately to well differentiated. One or several layers of columnar cells, some of which contain mucin, usually line the papillae and glands. If intracellular mucin is not demonstrable, the tumour may be regarded as the endometrioid variant. Scattered mitoses are characteristic. Invasion may be absent or minimal at the base; rare neoplasms, however, invade deeply. The invasive portion is typically composed of elongated branching glands separated by fibrous stroma. The non-invasive tumours may, in fact, be examples of papillary adenocarcinoma in situ. Associated CIN and/or adenocarcinoma in situ are common. Lymph node metastases are rare (1366, 1387, 1391).

Endometrioid adenocarcinoma
These adenocarcinomas account for up to 30% of cervical adenocarcinomas and have the histological features of an
endometrioid adenocarcinoma of the endometrium; however, squamous elements are less common. Little or no intracellular mucin is present. A distinction from an endocervical type adenocarcinoma is only possible in well differentiated lesions. This neoplasm must be distinguished from one extending into the cervix from the endometrium.

**Clear cell adenocarcinoma**

An adenocarcinoma that is composed mainly of clear or hobnail cells arranged in solid, tubulocystic or papillary patterns or a combination. This rare tumour is histologically similar to clear cell adenocarcinoma of the ovary, endometrium and vagina, where they are more common. Although well known because of its association with in utero exposure to diethylstilbestrol (DES) in young women, its peak frequency is at present in the postmenopausal group. Genomic instability has been suggested as a mechanism of DES-related carcinogenesis [330].

**Serous adenocarcinoma**

A complex pattern of papillae with cellular budding and the frequent presence of psammoma bodies characterize serous adenocarcinoma. Before a diagnosis of primary serous adenocarcinoma of the cervix can be made, spread from the endometrium, ovaries or peritoneum should be excluded. These rare cervical tumours are histologically identical to their ovarian counterparts [565]. A single case was familial. The patient, identical twin sister and mother all had serous tumours of the genital tract [1398].

**Mesonephric adenocarcinoma**

These adenocarcinomas arise from mesonephric remnants and are most often located in the lateral to posterior wall of the cervix but may involve the cervix circumferentially. Among the 20 reported examples, the patients ranged in age from 33-74 years with a median age of about 52 years. Whereas they often present as exophytic lesions, they may remain completely intramural simply expanding the cervical wall. Histologically, they are commonly characterized by tubular glands lined by mucin-free cuboidal epithelium containing eosino-

[Fig. 5.23 Mesonephric adenocarcinoma. A In some areas of the tumour, the proliferation of tubules resembles the diffuse pattern of mesonephric hyperplasia with intraluminal colloid-like secretions. B Other areas contain a more complex growth pattern with early formation of papillary structures (same case as in A). C The tubules exhibit nuclear atypia and mitotic figures.]
The tubular variant is distinguished from focal, florid and diffuse hyperplasia of mesonephric remnants by the presence of cytologic atypia, mitotic activity and the focal presence of intraluminal nuclear debris instead of the colloid-like secretion typical of mesonephric remnants (2679). Mesonephric adenocarcinomas are immunoreactive for epithelial markers (AE1/3, cytokeratin 1, Cam5.2, cytokeratin 7 and epithelial membrane antigen) in 100% of cases, for calretinin (88%), and vimentin (70%). The absence of immunoreactivity with estrogen and progesterone receptor helps to distinguish the endometrioid variant from endometrioid adenocarcinoma (2679). Positive immunoreactivity for CD10 may be another helpful feature (2110). The behaviour of the lesions and prognosis are stage dependent.

**Early invasive adenocarcinoma**

**Definition**

Early invasive adenocarcinoma refers to a glandular neoplasm in which the extent of stromal invasion is so minimal that the risk of local lymph node metastasis is negligible.

**Synonym**

"Microinvasive" adenocarcinoma.

**Tumour spread and staging**

Adenocarcinomas of the cervix exist in early and frankly invasive forms (1611, 2139). The entity of "early invasive" or "microinvasive" carcinoma is controversial. The current, 1995 FIGO staging, omits specific reference to glandular lesions in stage IA (1500). In addition, there are practical problems in identifying microinvasive adenocarcinoma histologically (see below). Nevertheless, it is recommended that the FIGO classification be adopted.

**Histopathology**

The sine qua non of microinvasive adenocarcinoma is stromal invasion. There may be marked glandular irregularity with effacement of the normal glandular architecture, the tumour extending beyond the deepest normal crypt. Cribriform, papillary or solid patterns may be present.

There may be a stromal response in the form of oedema, chronic inflammatory infiltrate or a desmoplastic reaction. Lymphatic capillary-like space involvement is helpful in confirming invasion. Having established the presence of invasion, the depth of invasion and the width of the tumour must be measured. In most cases the depth is measured from the surface rather than the point of origin, which is hard to establish in some cases. Thus, tumour thickness, rather than "depth of invasion", is measured. The width is the greatest diameter of the neoplasm measured parallel to the surface; the measurement should be done by calibrated optics.

**Prognosis and predictive factors**

The prognosis of microinvasive adenocarcinoma (FIGO Stage 1A), as defined above, is excellent and essentially the same as that of its squamous counterpart (768,2143,2573,2732,3076).

**Adenocarcinoma in situ**

**Definition**

A lesion in which normally situated glands are partly or wholly replaced by cytologically malignant epithelium; in the former case the border is characteristically sharp.

**Histopathology**

The epithelium is usually devoid of intracellular mucin and may resemble endo-
metrial epithelium. In some cases the glands are lined by intestinal epithelium containing goblet, neuroendocrine and Paneth cells. The neoplastic glands conform to the expected location of normal endocervical glands and do not extend beyond the deepest normal crypt. A cribriform pattern is common. The epithelium is usually stratified with the long axes of the cells perpendicular to the base. The elongated, pleomorphic and hyperchromatic nuclei are basal in position. Mitoses are common and are disposed on the luminal side. Apoptosis is prominent. The neoplastic epithelium may affect the surface, where it is often single layered, but more commonly is found in the crypts. These features help to explain the frequent failure of its colposcopic detection. The cell types, in order of frequency, are endocervical, endometrioid and intestinal. A putative tubal variant has also recently been described. Although the stroma may be intensely inflamed, there is no desmoplastic reaction. Adenocarcinoma in situ is associated with CIN in at least 50% of cases and is immunoreactive for carcinoembryonic antigen in 80% of cases.

Prognosis and predictive factors
Evidence supporting the precancerous potential of adenocarcinoma in situ includes its occurrence 10-15 years earlier than its invasive counterparts, its common association with microinvasive or invasive adenocarcinoma, its histological similarity to invasive adenocarcinoma and the frequent occurrence of high-risk HPV types. The transformation of adenocarcinoma in situ into invasive adenocarcinoma over time has also been documented on rare occasions. Although the treatment of adenocarcinoma in situ is controversial, increasing evidence is available that conservative therapy, such as conization only, is safe and effective in selected cases.

Glandular dysplasia
Definition
A glandular lesion characterized by significant nuclear abnormalities that are more striking than those in glandular atypia but fall short of the criteria for adenocarcinoma in situ.

Histopathology
The nuclei are not cytologically malignant, and mitoses are less numerous than in adenocarcinoma in situ. Nuclear hyperchromasia and enlargement identify the involved glands, and pseudostratification of cells is prominent. Cribriform and papillary formations are usually absent. The concept that glandular dysplasia forms a biological spectrum of cervical glandular intraepithelial neoplasia remains unproven. Glandular dysplasia must be distinguished from glandular atypia. The latter is an atypical glandular epithelial alteration which does not fulfill the criteria for glandular dysplasia or adenocarcinoma in situ and which may be associated with inflammation or irradiation.

Benign glandular lesions
Müllerian papilloma
Definition
A rare, benign, papillary tumour composed of a complex arborizing fibrovascular core covered by a mantle of single or double-layered mucinous epithelium that may undergo squamous metaplasia.

Clinical features
Müllerian papilloma occurs almost exclusively in children typically between 2 and 5 years of age (range 1-9 years), who present with bleeding, discharge or a friable, polypoid to papillary, unifocal or multifocal mass, usually less than 2 cm in greatest dimension.

Histopathology
These tumours consist of multiple small polypoid projections composed of fibrous stroma and lined by simple epithelium. Occasional cells may have a hobnail appearance simulating clear cell adenocarcinoma; however, no clear cells, atypia or mitoses are present. The stroma is often inflamed and rarely contains psammoma bodies.

Prognosis and predictive factors
Occasional cases recur. (See chapter on the vagina).

Endocervical polyp
Definition
An intraluminal protrusion composed of bland endocervical glands and a fibrovascular stroma.

Epidemiology
These are very common lesions that rarely are of concern clinically and are easy to diagnose histologically.

Clinical features
In 75% of cases they are asymptomatic. The rest present with bleeding (especially post-coital) and/or discharge.

Macroscopy
The great majority are less than 1 cm and single.

Fig. 5.27 Adenocarcinoma in situ. High power magnification shows pseudostratified nuclei and a marked degree of apoptosis.

Fig. 5.28 High grade cervical glandular dysplasia. The histological features are not of sufficient severity to be regarded as adenocarcinoma in situ.

Fig. 5.29 Glandular dysplasia involving endocervical papillae.

276 Tumours of the uterine cervix
Histopathology
Endocervical polyps are usually covered by cuboidal and/or columnar epithelium that often shows atypical regenerative changes that may be mistaken cytologically for malignancy. Polyps are often composed of large retention cysts distended by mucus and covered by normal metaplastic squamous epithelium. Ulceration is uncommon, but the stroma is often inflamed. The presence of bizarre stromal atypia, atypical mitoses or stromal hypercellularity may lead to an unwarranted diagnosis of sarcoma (2067). Other benign alterations within polyps that may be mistaken for malignancy include florid immature squamous metaplasia, papillary hyperplasia, microglandular hyperplasia and decidual reaction (2930).

Prognosis and predictive factors
Polyps occasionally recur, even after complete excision.

Uncommon carcinomas and neuroendocrine tumours

**Definition**
Epithelial tumours of the uterine cervix other than those of squamous or glandular types.

**ICD-O-codes**
- Adenosquamous carcinoma 8560/3
- Glassy cell variant 8015/3
- Adenoid cystic carcinoma 8200/3
- Adenoid basal carcinoma 8098/3
- Neuroendocrine tumours
  - Carcinoid 8240/3
  - Atypical carcinoid 8249/3
  - Small cell carcinoma 8041/3
  - Large cell neuroendocrine carcinoma 8013/3
- Undifferentiated carcinoma 8020/3

**Adenosquamous carcinoma**

**Definition**
A carcinoma composed of a mixture of malignant glandular and squamous epithelial elements.

**Histopathology**
Both elements show atypical features. Scattered mucin-producing cells in an otherwise ordinary looking squamous cell carcinoma have been referred to as mucoepidermoid carcinoma. As there is no convincing evidence that such tumours behave differently, routine mucin staining of squamous cell carcinomas is not recommended, and the former term should no longer be employed. Poorly differentiated tumours resembling poorly differentiated squamous cell carcinoma but with many mucin-producing cells and lacking keratinization or intercellular bridges should be diagnosed as poorly differentiated adenocarcinoma.

Glassy cell carcinoma variant
Glassy cell carcinoma is a poorly differentiated variant of adenosquamous carcinoma and accounts for 1-2% of all cervical carcinomas. The tumour occurs in young women, grows rapidly, develops frequent distant metastases and responds poorly to radiotherapy; however, chemotherapy may be promising (1863). The tumour cells lack estrogen and progesterone receptors (132). Usually, no preinvasive lesion is seen. The tumour cells are large...
with distinct cell borders and a ground-glass cytoplasm. A prominent eosinophilic infiltration in the stroma helps to separate the tumour from non-keratinizing squamous cell carcinoma (1701).

**Prognosis and predictive factors**
The prognosis of adenosquamous carcinoma remains uncertain (68).

**Adenoid cystic carcinoma**

**Definition**
A carcinoma of the cervix that resembles adenoid cystic carcinoma of salivary gland origin.

**Epidemiology**
Most of the patients are over 60 years of age, and there is a high proportion of Black women (849).

**Clinical features**
The majority of patients present with postmenopausal bleeding and have a mass on pelvic examination (849).

**Histopathology**
This rare tumour of the cervix has a histological appearance similar to its counterpart in salivary glands. The characteristic cystic spaces are filled with a slightly eosinophilic hyaline material or basophilic mucin and are surrounded by palisaded epithelial cells (849). In contrast to adenoid cystic carcinoma of salivary gland, the cervical carcinomas show greater nuclear pleomorphism, a high mitotic rate and necrosis (849). A solid variant has been described (65).

Immunostains for basement membrane components such as collagen type IV and laminin are strongly positive (1918). In contrast to an earlier study (849), the majority of the tumours stained for S-100 protein and HHF35 suggesting myoepithelial differentiation (1059). The differential diagnosis includes small cell carcinoma, adenoid basal carcinoma and non-keratinizing squamous cell carcinoma.

**Histogenesis**
This tumour, basaloid squamous cell carcinoma and adenoid basal carcinoma are part of a morphological and biological spectrum of basaloid cervical neoplasms, and a putative reserve cell origin has been suggested (1059). Circumstantial evidence suggests that adenoid
basal carcinoma may be a precursor of adenoid cystic carcinoma [1059].


**Prognosis and predictive factors**

The tumours frequently recur locally or metastasize to distant organs and have an unfavourable prognosis.

---

**Adenoid basal carcinoma**

**Definition**

A cervical carcinoma in which rounded, generally well differentiated nests of basaloid cells show focal gland formation or sometimes central squamous differentiation.

**Epidemiology**

Adenoid basal carcinoma is a rare tumour. The patients are usually more than 50 years old.

**Clinical findings**

Patients are usually asymptomatic and without a clinically detectable abnormality of the cervix. The tumour is often discovered as an incidental finding.

**Histopathology**

The histological appearance shows small nests of basaloid cells, almost always beneath and often arising from CIN or small invasive squamous cell carcinomas [849]. The cells are small with scanty cytoplasm and are arranged in cords and nests with focal glandular or squamous differentiation. There is frequently associated CIN [332,849]. The differential diagnosis includes other small cell tumours [2280].

**Histogenesis**

This tumour, basaloid squamous cell carcinoma and adenoid cystic carcinoma are part of a morphological and biological spectrum of basaloid cervical neoplasms and a putative reserve cell origin has been suggested [1059].

**Prognosis and predictive factors**

The tumour is low grade and rarely metastasizes.

---

**Neuroendocrine tumours**

The group of neuroendocrine tumours includes carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma [63,2803]. Neuroendocrine differentiation is demonstrated with pan-neuroendocrine markers such as chromogranin A, synaptophysin and neuron specific enolase. A variety of peptides and hormones are also present, such as calcitonin, gastrin, serotonin, substance P, vasoactive intestinal peptide, pancreatic polypeptide, somatostatin and adrenocorticotrophic hormone [22], but their clinical significance is limited [2612].

**Carcinoid**

Generally benign, carcinoids have the same characteristic organoid appearance as observed in other sites. The degree of nuclear atypia and mitotic activity are important in the differential diagnosis between typical and atypical carcinoids.

**Atypical carcinoid**

An atypical carcinoid is a carcinoid with cytologic atypia that exhibits increased mitotic activity (5-10 per high power field) and contains foci of necrosis [63].

**Small cell carcinoma**

Small cell carcinomas account for 1-6% of cervical carcinomas [22]. Squamous or glandular differentiation may be present [22,248,830,1761,2219]. The 5-year survival rate is reported to be 14-39% [22,248,2803].

**Large cell neuroendocrine carcinoma**

Large cell neuroendocrine carcinoma is a rare tumour that often has focal adenocarcinomatous differentiation [592a, 1521a, 2361a]. The tumour cells have abundant cytoplasm, large nuclei and prominent nucleoli. Mitoses are frequent. The differential diagnosis includes non-neuroendocrine undifferentiated carcinoma, adenocarcinoma with neuroendocrine features, metastatic neuroendocrine carcinoma and undifferentiated sarcoma. The tumours are aggressive and appear to have a similar outcome to small cell carcinoma [1006].

**Undifferentiated carcinoma**

Undifferentiated carcinoma is a carcinoma lacking specific differentiation. The differential diagnosis includes poorly differentiated squamous cell carcinoma, adenocarcinoma, glassy cell carcinoma and large cell neuroendocrine carcinoma.
Mesenchymal tumours

Definition
A variety of rare benign and malignant mesenchymal tumours that arise in the uterine cervix and which exhibit smooth muscle, skeletal muscle, vascular, peripheral nerve and other types of mesenchymal tissue differentiation. Smooth muscle tumours are the most common.

Malignant mesenchymal tumours

ICD-O codes
Leiomyosarcoma 8890/3
Endometrioid stromal sarcoma, low grade 8931/3
Undifferentiated endocervical sarcoma 8805/3
Sarcoma botryoides 8910/3
Alveolar soft part sarcoma 9581/3
Angiosarcoma 9120/3
Malignant peripheral nerve sheath tumour 9540/3

Epidemiology
Sarcomas are extremely rare. Of 6,549 malignant tumours arising in the uterine cervix reported in the United States in a 5 year period (1973-1977), only 36 (0.5%) were sarcomas [3191]. Leiomyosarcoma is the most common primary sarcoma, although less than thirty cases have been described in the literature [25,212, 543,912,927,1045,1058,1405,2473]. About 100 cases of sarcoma botryoides of the cervix have been reported [170, 333,642,1041,1898,3250]. Fifteen cases of undifferentiated endocervical sarcoma [20,25,1324], ten cases of alveolar soft part sarcoma and six of malignant peripheral nerve sheath tumour primary in the uterine cervix are on record [21,892, 901,1056,1375,1424,1504,1916,2017, 2507,2721]. All the other types of mesenchymal tumours have been case reports. Cervical mesenchymal tumours affect adult patients with the exception of sarcoma botryoides, which usually occurs in children and young women (mean age 18 years) [642]. The prognosis of cervical sarcomas as a group is poor with the exception of sarcoma botryoides.

Clinical features
Most patients with these cervical tumours present with vaginal bleeding or discharge. Large tumours may compress adjacent organs or, if polypoid, protrude through the cervical os into the vagina. Less frequently, the passing of tissue through the vagina is the presenting symptom. At operation sarcomas may be seen to infiltrate the entire thickness of the cervical wall. Pelvic recurrences or regional lymph node metastases are the most common late events.

Leiomyosarcoma

Definition
A malignant tumour composed of smooth muscle cells.

Clinical features
Leiomyosarcoma presents as a mass replacing and expanding the cervix or as a polypoid growth.

Macroscopy
The tumours have a soft and fleshy consistency and often contain areas of necrosis or haemorrhage. The rare myxoid variant of leiomyosarcoma has a typical gelatinous appearance.

Histopathology
Leiomyosarcomas show hypercellular interlacing fascicles of large spindle-shaped or round cells with diffuse moderate to marked nuclear atypia, a high mitotic rate, atypical mitoses, single or multiple prominent nucleoli and tumour cell necrosis. Infiltrative borders and vascular invasion are also frequently seen. Cervical epithelioid leiomyosarcoma, and one case each of myxoid and xanthomatous cervical leiomyosarcoma

Fig. 5.36 Cervical leiomyosarcoma. A Typical variant. The neoplasm shows marked nuclear atypia and coagulative necrosis. B Epithelioid variant. The tumour cells are round and uniform.
have been reported [543,912,927,1045, 1058].

**Differential diagnosis**
The criteria used in the distinction from leiomyoma are the same as those for smooth muscle tumours of the uterine corpus. At least two of three features (marked nuclear atypia, a mitotic rate higher than 10 mitoses per 10 high power fields and tumour necrosis) are required for the diagnosis of leiomyosarcoma [211]. For epithelioid leiomyosarcoma a mitotic count higher than 10 mitoses per 10 high power fields is considered diagnostic of malignancy. A low mitotic count is typical of the myxoid variant [912]. Antibodies to smooth muscle actin and/or desmin may be used to demonstrate smooth muscle differentiation in these tumours. Leiomyosarcoma should be differentiated from postoperative spindle cell nodule [1420]. The latter is mitotically active and may infiltrate the underlying tissue. The distinction from leiomyosarcoma or other malignant spindle cell tumour depends to a large extent on the history of a recent operation at the same site.

**Endometrioid stromal sarcoma, low grade**

**Definition**
A sarcoma arising outside of the fundus composed of cells resembling endometrial stromal cells.

**Epidemiology**
Very rarely, tumours with the features of low grade endometrial stromal sarcoma arise in the cervix [295,437].

**Histopathology**
This tumour may arise from cervical endometriosis and must be distinguished from stromal endometriosis and primary endometrial stromal sarcoma that has invaded the cervix. The term undifferentiated endocervical sarcoma is preferred for high grade lesions.

**Undifferentiated endocervical sarcoma**

**Definition**
An endocervical sarcoma lacking endometrial stromal or other specific differentiation [20,1324].

**Histopathology**
Tumours described in the literature as undifferentiated endocervical sarcoma are characterized by a polyoid or infiltrative cervical growth similar to that exhibited by malignant peripheral nerve sheath tumours arising in the uterine cervix [25,1424].

The tumour is composed of spindle or stellate-shaped cells with scanty cytoplasm, ill defined cell borders and oval hyperchromatic nuclei arranged in a sheet-like, fasciculated or storiform pattern [25]. The prominent vascular pattern typical of endometrioid stromal sarcoma is not a characteristic of these tumours, and the stromal proliferation tends to encircle the endocervical glands creating a foci resemblance to adenosarcoma. Nuclear atypia and markedly increased mitotic activity are seen in all cases, as well as areas of haemorrhage, necrosis and myxoid degeneration.

**Sarcoma botryoides**

**Definition**
A tumour composed of cells with small, round, oval or spindle-shaped nuclei, some of which show evidence of differentiation towards skeletal muscle cells.

**Synonym**
Embryonal rhabdomyosarcoma.

**Macroscopy**
Embryonal rhabdomyosarcoma usually grows in a polyoid fashion. The grape-like type of growth classically exhibited by vaginal sarcoma botryoides is only rarely seen in cervical tumours. The polyoid masses have a glistening translucent surface and a soft consistency and may be pedunculated or sessile. Their size ranges from 2-10 cm [642]. The sectioned surface of the tumour appears smooth and myxoid with small haemorrhagic areas.

**Histopathology**
The histological features are described in the section on the vagina. Islands of mature neoplastic cartilage are more frequently seen in cervical than in vaginal tumours [642].

**Somatic genetics**
In one case of sarcoma botryoides chromosomal analysis has demonstrated deletion of the short arm of chromosome 1, and trisomies 13 and 18 [2156], and in another a point mutation in exon 6 of TP53 was found, but no KRAS point mutations at codons 12,13 and 61 were detected [2627].

**Genetic susceptibility**
An association between ovarian Sertoli-Leydig tumour and cervical sarcoma botryoides has been described [1026]

**Prognosis and predictive factors**
The use of neoadjuvant chemotherapy allows a more conservative approach for these neoplasms [170,1041,3250].

**Alveolar soft part sarcoma**

**Definition**
A sarcoma characterized by solid and alveolar groups of large epithelial-like cells with granular, eosinophilic cytoplasm.
Tumours of the uterine cervix

Macroscopy
These appear macroscopically as a polyp or an intramural nodule measuring less than 5 cm and have a friable or solid consistency.

Histopathology
They are histologically similar to their counterparts in other sites. Most of the tumours exhibit an alveolar architecture, where nests of tumour cells with central loss of cellular cohesion are supported by thin-walled, sinusoidal vascular spaces. A solid pattern of growth may also be present. The tumour cells have an abundant eosino-philic cytoplasm, large nuclei, prominent nucleoli and contain PAS-positive, diastase-resistant, rod-shaped crystals [1056]. A predominantly clear cytoplasm may characterize some neoplasms, and some cells may exhibit prominent nuclear atypia. Electron microscopy shows characteristic intracytoplasmic crystals, electron-dense secretory granules, numerous mitochondria, prominent endoplasmic reticulum, glycogen and a well developed Golgi apparatus [1937].

Prognosis and predictive factors
Alveolar soft part sarcomas of the female genital tract, including those primary in the uterine cervix, appear to have a better prognosis than their counterpart in other sites [2017].

Angiosarcoma
Definition
A malignant tumour the cells of which variably recapitulate the morphologic features of endothelium.

The macroscopic appearance of angiosarcoma is similar to that in other sites forming a haemorrhagic, partially cystic or necrotic mass [2551], and the neoplastic cells are immunoreactive for CD31, CD34, and factor VIII-related antigen [2551].

Malignant peripheral nerve sheath tumour
Definition
A malignant tumour showing nerve sheath differentiation.

Histopathology
Cervical malignant peripheral nerve sheath tumour (MPNST) is similar to MPNST arising in other sites including the occurrence of less common variants such as epithelioid and melanocytic types [2721]. The tumour is composed of fascicles of atypical spindle cells invading the cervical stroma and surrounding endocervical glands with a pattern reminiscent of adenocarcinoma. Myxoid paucicellular areas are characteristically intermixed with others with a dense cellularity [1375]. Mitoses are common. The tumour cells are positive for S-100 protein and vimentin and negative for HMB-45, smooth muscle actin, desmin and myogenin [1424].

Other malignant tumours
Other malignant mesenchymal tumours include alveolar rhabdomyosarcoma [781], liposarcoma [2840,3016], osteosarcoma [289,588] and malignant fibrous histiocytoma [508].

Benign mesenchymal tumours and tumour-like lesions
Definition
Benign mesenchymal tumours and tumour-like lesions that arise in the uterine cervix.

ICD-O codes
Leiomyoma 8890/0
Genital rhabdomyoma 8905/0

Leiomyoma
Definition
A benign tumour composed of smooth muscle cells.

Epidemiology
Leiomyoma is the most common benign mesenchymal tumour of the cervix. It has been estimated that less than 2% of all uteri contain cervical leiomyomas, and that about 8% of uterine leiomyomas are primary in the cervix [2020,2925].

Histopathology
Cervical leiomyoma is histologically identical to those that occur in the uterine corpus.

Genital rhabdomyoma
Definition
A rare benign tumour of the lower female genital tract composed of mature striated muscle cells separated by varying amounts of fibrous stroma.

Clinical features
Cervical rhabdomyoma presenting as a polyloid lesion has been rarely reported [690].
Mesenchymal tumours

Histopathology
The tumour is composed of rhabdomyoblasts with small, uniform nuclei dispersed in a myxoid and oedematous stroma. The typical cambium layer of sarcoma botryoides is absent (690).

Postoperative spindle cell nodule

Definition
A localized, non-neoplastic reactive lesion composed of closely packed proliferating spindle cells and capillaries simulating a leiomyosarcoma occurring at the site of a recent excision.

Clinical features
The lesion develops at the site of a recent operation several weeks to several months postoperatively [1420,2020].

Histopathology
The lesion is composed of closely packed, mitotically active, spindle-shaped mesenchymal cells and capillaries often with an accompaniment of inflammatory cells, and may infiltrate the underlying tissue.

Differential diagnosis
Postoperative spindle cell sarcoma may closely resemble a leiomyosarcoma or other malignant spindle cell tumours, but the history of a recent operation at the same site facilitates its diagnosis.

Other benign tumours

Rare examples of cervical lipoma (334,1910), haemangioma (47,829), glomus tumour (64), localized neurofibromatosis (381,986), schwannoma (1093), pigmented melanocytic schwannoma (2900), granular cell tumour (553,952, 1101), ganglioneuroma (858) and paraganglioma (3229) have been reported.
Mixed epithelial and mesenchymal tumours

Definition
Tumours composed of an admixture of neoplastic epithelial and mesenchymal elements. Each of these components may be either benign or malignant.

ICD-O codes
- Carcinosarcoma 8980/3
- Adenosarcoma 8933/3
- Wilms tumour 8960/3
- Adenofibroma 9013/0
- Adenomyoma 8932/0

Epidemiology
These neoplasms are much less common than their counterparts in the uterine corpus. They may occur in any age group, but carcinosarcomas most commonly involve elderly postmenopausal women (527, 1060).

Clinical features
The presenting symptom is usually abnormal uterine bleeding. In some cases, especially in cases of carcinosarcoma, a friable mass may extrude from the vaginal introitus. The tumour may be identified following an abnormal cervical smear.

Carcinosarcoma

Definition
A neoplasm composed of an admixture of malignant epithelial and mesenchymal elements.

Synonyms
Malignant müllerian mixed tumour, malignant mesodermal mixed tumour, metaplastic carcinoma.

Epidemiology
Carcinosarcomas most commonly involve elderly postmenopausal women (527, 1060). These neoplasms are much less common than their counterparts in the uterine body.

Aetiology
An occasional case of cervical carcinosarcoma has been associated with prior radiation treatment. HPV infection, especially HPV 16, has been found in the epithelial and mesenchymal components suggesting a role in the evolution of these neoplasms (1060).

Histopathology
The histological features are similar to its counterpart in the uterine corpus. However, the epithelial elements are more commonly non-glandular in type and include squamous (keratinizing, non-keratinizing or basaloïd), adenoid cystic, adenoid basal or undifferentiated carcinoma (527, 1060, 1757, 1785, 3177). Adjacent severe dysplasia of the squamous epithelium has also been described. Mesonephric adenocarcinomas of the cervix with a malignant spindle cell component have been reported, representing an unusual subtype of cervical carcinosarcoma (521). Before diagnosing a cervical carcinosarcoma, extension from a primary uterine corpus neoplasm should be excluded (960, 3245).

Prognosis and predictive factors
Cervical carcinosarcomas are aggressive neoplasms, and treatment is usually radical hysterectomy followed by chemotherapy and/or radiotherapy. The prognosis may be better in small tumours with a polypoid appearance. Although aggressive, these neoplasms appear to be more often confined to the uterus compared to their counterparts in the corpus and may have a better prognosis (527, 1060).

Adenosarcoma

Definition
A neoplasm composed of an admixture of benign epithelial and malignant mesenchymal elements.
Epidemiology
Cervical adenosarcomas are much less common than their counterparts in the uterine corpus.

Histopathology
The histological features are similar to its counterpart in the corpus. However, the epithelium is more likely to be squamous or mucinous. Adenosarcomas may or may not invade the underlying cervical stroma.

Prognosis and predictive factors
Because these neoplasms are rare, management is individualized. The therapy is usually simple hysterectomy, and radiation may be considered for deeply invasive neoplasms. They may recur following conservative therapy by simple excision or polypectomy. The prognostic features are not well established. The prognosis is much better than that of cervical carcinosarcoma (848).

Wilms tumour
Definition
A malignant tumor showing blastema and primitive glomerular and tubular differentiation resembling Wilms tumour of the kidney.

Epidemiology
Occasional cases of Wilms tumour arising within the cervix have been described, usually in adolescents (155, 215, 1302).

Macroscopy
Macroscopically, these neoplasms are composed of polyoid masses that protrude through the vagina.

Histopathology
Histologically, the classic triphasic pattern of epithelial, mesenchymal and blastemal elements may be present.

Prognosis and predictive factors
In two cases prolonged survival has been reported following local excision and chemotherapy (155, 206, 215, 1302).

Adenofibroma
Definition
A mixed neoplasm composed of benign epithelial and mesenchymal components.

Epidemiology
These are uncommon in the cervix and are more commonly found within the uterine body (3245).

Macroscopy
Cervical adenofibromas are polypoid neoplasms that usually protrude into the endocervical canal. On sectioning small cystic spaces may be identified.

Histopathology
Histologically, adenofibroma is a benign papillary neoplasm composed of fronds lined by benign epithelium that is usually glandular in type. The epithelium may be cuboidal, columnar, attenuated, ciliated or mucinous. Occasionally, benign squamous epithelium may be present. The mesenchymal component shows little mitotic activity and is usually composed of non-specific fibrous tissue. The main differential diagnosis is a low grade adenosarcoma; the latter, however, exhibits malignant mesenchymal features including hypercellularity with condensation around glands, nuclear atypia and increased mitotic activity.

Prognosis and predictive factors
The therapy is usually local excision or simple hysterectomy. Local excision is usually curative, although recurrence may follow incomplete removal.

Adenomyoma
Definition
A tumour composed of a benign glandular component and a benign mesenchymal component composed exclusively or predominantly of smooth muscle. These tumours are rare within the cervix. A variant is the atypical polypoid adenomyoma.

Macroscopy
Cervical adenomyomas are usually polyoid lesions with a firm sectioned surface. In some cases small cystic areas may be seen that may contain abundant mucin. Rare tumours are entirely intramural.

Histopathology
Three variants of cervical adenomyoma have been described, the endocervical type, the endometrial type and atypical polypoid adenomyoma.

Endocervical type
The endocervical type, which may be confused with minimal deviation adenocarcinoma, is composed largely of endocervical mucinous glands surrounded by a mesenchymal component consisting predominantly of smooth muscle (1005). The glands are lined by tall mucin-secreting cells and are typically irregularly shaped with papillary infoldings. Occasionally, tubal-type epithelium or endometrial-type glands surrounded by endometrial-type stroma are focally pres-
Both the epithelial and smooth muscle components are uniformly bland without any significant mitotic activity. Differentiating features from minimal deviation adenocarcinoma include the well circumscribed nature of adenomyoma and the absence of a desmoplastic stromal reaction or focal atypia.

**Endometrial type**

Another variant of cervical adenomyoma is similar to that found within the corpus. It is composed of endometrial-type glands surrounded by endometrial-type stroma that is, in turn, surrounded by smooth muscle that predominates. The glands and stroma are bland. Minor foci of tubal, mucinous or squamous epithelium may be found. These adenomyomas may or may not be associated with uterine adenomyosis. The most likely differential diagnoses are atypical polypoid adenomyoma and low grade adenosarcoma.

**Atypical polypoid adenomyoma**

In atypical polypoid adenomyoma the glandular component exhibits architectural complexity that is usually marked. It is similar to the corresponding tumour within the uterine corpus and usually involves the lower uterine segment or upper endocervix (see chapter on uterine corpus).

**Prognosis and predictive factors**

Simple polypectomy or local excision cures most cervical adenomyomas. However, recurrences have been described following local excision, and residual tumour may be found at hysterectomy.

---

*Fig. 5.44* Wilms tumour. The tumour is composed of primitive tubules set in a background of renal blastema.
Melanotic, germ cell, lymphoid and secondary tumours of the cervix

C.B. Gilks
S. Carinelli

Definition
A variety of primary benign or malignant tumours of the uterine cervix that are not otherwise categorized as well as secondary tumours.

ICD-O codes
- Malignant melanoma 8720/3
- Blue naevus 8780/0
- Yolk sac tumour 9071/3
- Dermoid cyst 9084/0
- Mature cystic teratoma 9080/0

Malignant melanoma

Definition
A malignant tumour of melanocytic origin.

Epidemiology
Malignant melanoma of the cervix is considerably less common than vulvar or vaginal melanoma with fewer than 30 well documented cases reported [396, 667,940]. All occurred in adults, and approximately one-half had spread beyond the cervix at the time of presentation [396].

Clinical features
These tumours commonly present with abnormal vaginal bleeding. Malignant melanomas are typically described as polyoid or fungating, pigmented masses. However, they may be amelanotic and non-specific in appearance.

Histopathology
A junctional component was reported in approximately 50% of cases. In tumours lacking a junctional component, exclusion of the possibility of metastatic melanoma to the cervix requires clinical correlation. The histological appearance of cervical melanomas is noteworthy for the frequent presence of spindle-shaped cells. Desmoplastic and clear cell variants have also been reported [940, 1306]. The immunophenotype of cervical melanoma is indistinguishable from that of other sites.

Prognosis and predictive factors
The prognosis for patients with cervical melanoma is dismal, with only two reports of patients surviving more than 5 years [1360,2893].

Fig. 5.45 Blue naevus of the cervix. Note the aggregates of heavily pigmented dendritic melanocytes within the endocervical stroma.

Fig. 5.46 Malignant melanoma of the cervix. A The tumour shows junctional growth and transepidermal migration. B This tumour is composed of large epithelioid cells with pleomorphic nuclei in association with melanin pigment. C Note the spindle cell growth pattern of malignant melanocytes.
Blue naevus

Definition
A naevus composed of dendritic melanocytes that are typically heavily pigmented.

Clinical features
Benign pigmented lesions are asymptomatic and are typically incidental findings in hysterectomy specimens (2972, 2973). As most blue naevi occur in the endocervical canal, they are not visible colposcopically (2972,2973). Occasional examples are visible as pigmented macules on the ectocervix with a smooth overlying mucosa (1744).

Histopathology
Blue naevi are recognized histologically by the presence of poorly circumscribed collections of heavily pigmented, bland, spindle-shaped cells with fine dendritic processes in the superficial cervical stroma. They are most commonly located under the endocervical epithelium, but examples that involved the ectocervix have been reported (1744).

Differential diagnosis
The differential diagnosis includes other benign melanocytic lesions. In contrast to the frequency with which blue naevi are encountered, the cervical equivalent of common junctional, compound or intradermal naevi of skin is vanishingly rare in the cervix, with no convincing examples reported. Benign melanosis (3182) and lentigos (2568) of the ectocervical squamous mucosa are, however, occasionally encountered.

Yolk sac tumour

Definition
A primitive malignant germ cell tumour characterized by a variety of distinctive histological patterns, some of which recapitulate phases in the development of the normal yolk sac.

Synonym
Endodermal sinus tumour.

Epidemiology
The cervix is the second most common site in the lower female genital tract for yolk sac tumours after the vagina. It may be difficult or impossible to determine the primary site (vagina vs. cervix) in some cases (557).

Clinical features
These tumours commonly present with abnormal vaginal bleeding. Yolk sac tumours are polypoid, friable masses, protruding into the vagina (557).

Histopathology
The histological features are the same as for vaginal yolk sac tumours (557,3213).

Prognosis and predictive factors
The prognosis for patients with cervical vaginal yolk sac tumours is good with modern chemotherapy (1794).

Differential diagnosis
The differential diagnosis includes benign glial polyp of the cervix, a polypoid mass of mature glial tissue in women of reproductive age that is probably closely related to the cervical dermoid cyst. The former is thought to most probably arise from implantation of fetal tissue (1069,1711,2396).

Histogenesis
It has been proposed that these are not true neoplasms but are implanted fetal tissues (2968); molecular studies to determine whether the cells of cervical teratomas are genetically identical to the host and, thus, neoplastic rather than fetal in origin have not been performed.

Dermoid cyst

Definition
A mature teratoma characterized by a predominance of one or a few cysts lined by epidermis accompanied by its appendages.

Synonym
Mature cystic teratoma.

Clinical features
Cervical teratomas appear as smooth cervical polyps that may be pedunculated (1451).

Histopathology
The histological appearance is indistinguishable from mature teratomas at other sites. Gilial and squamous epithelial elements are common, but a wide range of mature tissue types have been reported (1451).

Dermoid cyst

Definition
A mature teratoma characterized by a predominance of one or a few cysts lined by epidermis accompanied by its appendages.

Synonym
Mature cystic teratoma.

Clinical features
Cervical teratomas appear as smooth cervical polyps that may be pedunculated (1451).

Histopathology
The histological appearance is indistinguishable from mature teratomas at other sites. Gilial and squamous epithelial elements are common, but a wide range of mature tissue types have been reported (1451).

Differential diagnosis
The differential diagnosis includes benign glial polyp of the cervix, a polypoid mass of mature glial tissue in women of reproductive age that is probably closely related to the cervical dermoid cyst. The former is thought to most probably arise from implantation of fetal tissue (1069,1711,2396).

Histogenesis
It has been proposed that these are not true neoplasms but are implanted fetal tissues (2968); molecular studies to determine whether the cells of cervical teratomas are genetically identical to the host and, thus, neoplastic rather than fetal in origin have not been performed.
Lymphoma and leukaemia

Definition
A malignant lymphoproliferative or haematopoetic neoplasm that may be primary or secondary.

Epidemiology
Involvement of the cervix by lymphoma or leukaemia may rarely be primary but is more commonly part of systemic disease with no specific symptoms referable to the cervix [1145].

Clinical features
With cervical involvement by lymphoma or leukaemia the cervix appears enlarged and barrel-shaped, although polypoid or nodular masses may be seen [1145,2457,3000]. For the histological description see chapter on the vagina.

Secondary tumours

Definition
Tumours of the uterine cervix that originate outside the cervix.

Incidence and origin
The majority of clinically significant secondary tumours of the cervix originate in the female genital system (endometrium, vagina and fallopian tube in that order) [1625,1939]. Endometrial carcinoma presents with stage II disease in 12% of patients [576]. Secondary cervical involvement is more common with high grade endometrial carcinoma, including serous carcinoma [576]. Extranodal primary sites include the breast, stomach and large bowel [1625,2608]. Cervical involvement by an extragenital tumour is almost always associated with disseminated disease and rapid progression to death. In occasional cases, however, cervical involvement may be the only evidence of disease at presentation or the first sign of recurrence [1087,1625,1802,2892].

Clinical features
The most common symptom of secondary cervical tumour is abnormal bleeding [1625,1939,2608]. Malignant cells may be detected on cervical cytologic preparations [1087]. On examination there are usually no abnormalities of the cervix [1939]. Occasionally, the cervix may appear enlarged, nodular or distorted, tumour may protrude from the os, or the cervix may be abnormally firm on palpation [1625,1802,2608,3179]. Secondary cervical involvement by endometrial carcinoma may present as raised nodules of tumour in the endocervical canal and have a similar appearance to the primary endometrial tumour. In most cases of stage II endometrial carcinoma, however, no clinical abnormality is evident [2608].

Histopathology
Secondary involvement of the cervix by endometrial carcinoma may be superficial with replacement of normal cervical epithelium by neoplastic cells of endometrial carcinoma (Stage IIA) or tumour may invade the underlying stroma (Stage IIB). The assessment of possible invasion into the cervical stroma poses the same problems in cases of secondary involvement of the cervix by endometrial carcinoma as for primary cervical adenocarcinoma. The cervical tumour may be either discontinuous or contiguous with the dominant endometrial tumour [2608]. Metastases of endometrial carcinoma to the cervix by lymphatic spread are less common than superficial mucosal implants and are present in only 6% of stage II endometrial carcinomas [2608]. The distinction of primary cervical adenocarcinoma from secondary involvement may be difficult or impossible in a small biopsy, as the different histological subtypes of adenocarcinoma seen in the female genital tract are not site-specific. Metastases from extragenital primary tumours may be suspected based on the submucosal location of tumour cells with a normal overlying cervical epithelium. Widespread lymphatic dissemination is also suggestive of a secondary origin. In the case of metastatic lobular carcinoma of the breast or diffuse gastric carcinoma, small nests, cords and individual cells infiltrate the cervical stroma, an appearance not characteristic of primary cervical adenocarcinoma.

Fig. 5.48 Metastatic gastric carcinoma to the uterine cervix. A Solid aggregates of metastatic carcinoma occur within the endocervical stroma. Note the surface endocervical mucinous epithelial lining and the endocervical glands in the upper portion of the field. B Note the cords of highly pleomorphic neoplastic cells within the endocervical stroma.
CHAPTER 6

Tumours of the Vagina

Although the incidence rate of vaginal intraepithelial neoplasia is increasing, that of squamous cell carcinoma is decreasing, reflecting earlier detection and more successful treatment. Human papillomavirus infection is a risk factor for both vaginal intraepithelial neoplasia and squamous cell carcinoma.

In past decades, clear cell adenocarcinoma occurred in young women, about two-thirds of whom had been exposed transplacentally to diethylstilbestrol. At that time, it was the most important glandular lesion of the vagina and the second most common epithelial malignancy. The precursor lesion appears to be atypical adenosis.

The most important non-epithelial tumours are malignant melanoma and sarcoma botryoides.
### WHO histological classification of tumours of the vagina

#### Epithelial tumours

<table>
<thead>
<tr>
<th>Squamous tumours and precursors</th>
<th>Morphology code (ICD-O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma, not otherwise specified</td>
<td>8070/3</td>
</tr>
<tr>
<td>Keratinizing</td>
<td>8071/3</td>
</tr>
<tr>
<td>Non-keratinizing</td>
<td>8072/3</td>
</tr>
<tr>
<td>Basaloid</td>
<td>8083/2</td>
</tr>
<tr>
<td>Verrucous</td>
<td>8051/3</td>
</tr>
<tr>
<td>Warty</td>
<td>8051/3</td>
</tr>
<tr>
<td>Squamous intraepithelial neoplasia</td>
<td></td>
</tr>
<tr>
<td>Vaginal intraepithelial neoplasia grade 3</td>
<td>8072/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma in situ</td>
<td>8070/2</td>
</tr>
</tbody>
</table>

#### Benign squamous lesions

<table>
<thead>
<tr>
<th>Condyloma acuminate</th>
<th>Squamous papilloma (vaginal micropapillomatosis)</th>
<th>Fibroepithelial polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>8210/0</td>
<td>8052/0</td>
<td>8260/0</td>
</tr>
</tbody>
</table>

#### Glandular tumours

<table>
<thead>
<tr>
<th>Clear cell adenocarcinoma</th>
<th>Endometrioid adenocarcinoma</th>
<th>Mesonephric adenocarcinoma</th>
<th>Müllerian papilloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>8310/3</td>
<td>8380/3</td>
<td>9103/3</td>
<td>8140/0</td>
</tr>
<tr>
<td>Tubular</td>
<td>Tubulovillosus</td>
<td>Villous</td>
<td></td>
</tr>
<tr>
<td>8211/0</td>
<td>8203/0</td>
<td>8261/0</td>
<td></td>
</tr>
</tbody>
</table>

#### Other epithelial tumours

<table>
<thead>
<tr>
<th>Adenosquamous carcinoma</th>
<th>Adenoid cystic carcinoma</th>
<th>Adenoid basal carcinoma</th>
<th>Carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>8560/3</td>
<td>8200/3</td>
<td>8098/3</td>
<td>8240/3</td>
</tr>
</tbody>
</table>

| Small cell carcinoma | Undifferentiated carcinoma | 8041/3                  | 8020/3    |

### Mixed epithelial and mesenchymal tumours

<table>
<thead>
<tr>
<th>Viscous squamous carcinoma (malignant müllerian mixed tumour; metastastic carcinoma)</th>
<th>8980/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant mixed tumour resembling synovial sarcoma</td>
<td>8940/3</td>
</tr>
<tr>
<td>Benign mixed tumour</td>
<td>8940/0</td>
</tr>
</tbody>
</table>

#### Glandular tumours

<table>
<thead>
<tr>
<th>Melanocytic tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Blue naevoid</td>
</tr>
<tr>
<td>Melanocytic naevoid</td>
</tr>
</tbody>
</table>

#### Miscellaneous tumours

<table>
<thead>
<tr>
<th>Tumours of germ cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yolk sac tumour</td>
</tr>
<tr>
<td>Dermoid cyst</td>
</tr>
</tbody>
</table>

#### Other epithelial tumours

| Peripherical primitive neuroectodermal tumour | 9260/3 |
| Enwil tumour | 9280/3 |
| Adenomatoid tumour | 9054/0 |

### Mesenchymal tumours and tumour-like conditions

| Sarcoma botryoides | 8910/3 |

### Secondary tumours

<table>
<thead>
<tr>
<th>Tumours of germ cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumours of germ cell type</td>
</tr>
<tr>
<td>Dermoid cyst</td>
</tr>
</tbody>
</table>

#### TNM and FIGO classification of carcinomas of the vagina

<table>
<thead>
<tr>
<th>TNM and FIGO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>T – Primary Tumour</td>
</tr>
<tr>
<td>N – Regional Lymph Nodes</td>
</tr>
<tr>
<td>M – Distant Metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FIGO Categories</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to vagina</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades paravaginal tissues but does not extend to pelvic wall</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades pelvic wall</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades mucosa of bladder or rectum, and/or extends beyond the true pelvis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IV</td>
</tr>
<tr>
<td>Stage IVA</td>
</tr>
<tr>
<td>Stage IVB</td>
</tr>
</tbody>
</table>
Squamous tumours

Definition
Primary squamous epithelial tumours of the vagina are the most frequent neoplasms at this site. They occur in all age groups but preferentially in the elderly. Vaginal intraepithelial neoplasia (VAIN) is considered a typical, though not obligatory, precursor lesion of squamous cell carcinoma.

ICD-O codes
- Squamous cell carcinoma 8070/3
- Vaginal intraepithelial neoplasia (VAIN), grade 3 8077/2
- Squamous cell carcinoma in situ 8070/2
- Squamous papilloma 8052/0

Squamous cell carcinoma

Definition
An invasive carcinoma composed of squamous cells of varying degrees of differentiation. According to the International Federation of Gynaecology and Obstetrics (FIGO), a tumour of the vagina involving the uterine cervix or the vulva should be classified as a primary cervical or vulvar cancer, respectively. Additionally, before the diagnosis of a primary vaginal carcinoma can be established, a 5-10 year disease free interval is required to rule out recurrent disease in those patients with a prior preinvasive or invasive cervical or vulvar neoplasm.

Epidemiology
Squamous cell carcinoma comprises up to 85% of vaginal carcinomas and accounts for 1-2% of all malignant tumours of the female genital tract (634, 1193). The mean age of patients is about 60 years.

Aetiology
In squamous cell carcinoma persistent infection with high-risk human papillomavirus (HPV) is probably a major aetiological factor. The same risk factors are observed as for vaginal intraepithelial neoplasia (VAIN), i.e. previous preinvasive or invasive disease of the lower genital tract, immunosuppression and prior pelvic irradiation (303). The development of VAIN and eventual progression to invasive disease is most likely, though the progression rate is unknown (347). Prior pelvic irradiation is a predisposing factor for vaginal squamous carcinoma (303,748,3075). Simultaneous or prior preinvasive or invasive disease elsewhere in the lower genital tract is observed in up to 30% of cases (220,2227,2480).

Clinical features
Signs and symptoms
The commonest symptom is a bloody vaginal discharge. Nearly 75% of patients present with painless bleeding, urinary tract symptoms or postcoital bleeding; however, the patient may be completely asymptomatic. Pelvic pain and dysuria usually signify advanced disease (2499). Most cases occur in the upper third of the vagina and are located on the posterior wall (2265).

Imaging
Magnetic resonance imaging (MRI) of the pelvis can be used to image vaginal tumours as well as to assess whether pelvic or inguinal lymphadenopathy is present. The MRI appearance, however, is not specific, and inflammatory changes and congestion of the vagina may mimic vaginal carcinoma (439).

Exfoliative cytology
Occasionally, cancer cells of vaginal origin may be observed in cervical smears.

Macroscopy
Tumours may be exophytic, ulcerative or annular and constricting. The lesions vary in size from being undetectable to greater than 10 cm. They may be polypoid, sessile, indurated, ulcerated or fun...
gating and may be found anywhere within the vagina. Squamous cell carcinoma, the commonest vaginal carcinoma, is ulcerative in half of cases, exophytic in a third and annular and constricting in the remainder.

Tumour spread and staging
Squamous cell carcinoma spreads predominantly laterally to the paravaginal and parametrial tissues when located in the lower and upper vagina, respectively. Tumours also invade lymphatics, metastasizing to regional lymph nodes and eventually distant sites including the lungs, liver and brain. The staging of vaginal tumours is by the TNM/FIGO classification (51,2976). Approximately 25% of patients present with stage I disease, one-third with stage II disease and 40% with stage III or IV disease (220,748, 1245,1524,2301,2480). Recurrences are typically local and usually happen within 2 years of treatment. The five-year survival rates are 70% for stage I, 45% for stage II, 30% for stage III and 15% for stage IV. The overall 5-year survival is about 42% (220,748,1245,1524,2301,2480).

Histopathology
Vaginal squamous cell carcinoma has the same histological characteristics as such tumours in other sites. Most cases are moderately differentiated and non-keratinizing (2301). Rarely, the tumours have spindle-cell features (2778). Warty carcinoma is another variant of vaginal squamous cell carcinoma (2339). The tumour is papillary with hyperkeratotic epithelium. Nuclear enlargement and koilocytosis with hyperchromasia, wrinkling of the nuclear membrane and multinucleation are typical changes (1541, 2936). Verrucous carcinoma has a papillary growth pattern with pushing borders and bulbous pegs of acanthotic epithelium with little or no atypia and surface maturation in the form of parakeratosis and hyperkeratosis. For a more detailed discussion of the subtypes of squamous cell carcinoma see chapter 5 or 7.

Prognosis and predictive factors
Radiation is the preferred treatment for most cases of vaginal carcinoma (1524, 2217,2981). In Stage I disease located in the upper part of the vagina, a radical hysterectomy, pelvic lymphadenectomy and partial vaginectomy may be considered (55,171). Otherwise, radiation therapy given as intracavitary therapy, interstitial implants and/or external pelvic/inguinal radiation, often in combination, is the most frequently adopted modality (1524,2217). In tumours of the middle or lower third of the vagina the external radiation field should include the inguinal and femoral lymph nodes. The clinical stage is the most significant prognostic factor (220,748,1245,1524, 2301,2480). Recurrences are typically local and usually happen within 2 years of treatment. The five-year survival rates are 70% for stage I, 45% for stage II, 30% for stage III and 15% for stage IV. The overall 5-year survival is about 42% (220,748,1245,1524,2301,2480). Tumour localization, grade or keratinization or patient age has not been demonstrated to have prognostic significance.

Vaginal intraepithelial neoplasia

Definition
A premalignant lesion of the vaginal squamous epithelium that can develop primarily in the vagina or as an extension from the cervix. VAIN is often a manifestation of the so-called lower genital tract neoplastic syndrome. Histologically, VAIN is defined in the same way as cervical intraepithelial neoplasia (CIN).

Synonyms
Dysplasia/carcinoma in situ, squamous intraepithelial lesion.

Epidemiology
VAIN is much less common than CIN, though its true incidence is unknown. There is some evidence that the incidence of VAIN has increased in recent decades, particularly among young and immunosuppressed women. The mean age for patients with VAIN is approximately 50 years. The majority of VAIN cases occur in women who have had a prior hysterectomy or who have a history of cervical or vulvar neoplasia (1626, 2403).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal intraepithelial neoplasia, grade 1</td>
<td>Mild dysplasia</td>
</tr>
<tr>
<td>Vaginal intraepithelial neoplasia, grade 2</td>
<td>Moderate dysplasia</td>
</tr>
<tr>
<td>Vaginal intraepithelial neoplasia, grade 3</td>
<td>Severe dysplasia and carcinoma in situ</td>
</tr>
</tbody>
</table>

VAIN = vaginal intraepithelial neoplasia
Aetiology
The fact that both VAIN and vaginal carcinoma are much less common than cervical neoplasia has been explained by the absence of a vulnerable transformation zone in the vagina. VAIN is associated with HPV infection in most cases. At least 15 different HPV types have been identified in VAIN. As in the cervix, VAIN 2 and VAIN 3 are associated with high-risk HPV types, of which type 16 is the most frequent. Mixed HPV types have also been identified in multifocal VAIN lesions and also in a single lesion (239, 2565). In VAIN 1 a mixture of low and high-risk HPV types can be detected.

Clinical features
Signs and symptoms
VAIN may be isolated but is more commonly multifocal (710,1626). Isolated lesions are mainly detected in the upper one-third of the vagina and in the vaginal vault after hysterectomy. VAIN is asymptomatic and cannot be diagnosed by the naked eye.

Colposcopy
VAIN may be suspected by a cervicovaginal cytology preparation, but the diagnosis can only be made by a colposcopically directed biopsy. If the colposcopy of the cervix is normal after an abnormal cytological smear, a careful colposcopic examination of all the vaginal epithelium should be performed. VAIN lesions are always iodine-negative. The presence of punctuation on a sharply demarcated acetowhite area is the single most reliable colposcopic feature suggestive of VAIN (2565).

Histopathology
The histopathology of VAIN is similar to that of CIN. Many VAIN 3 lesions also show hyperkeratosis. The so-called "flat condyloma" shows koilocytosis in the superficial layers of the epithelium with normal or only hyperplastic basal layers without nuclear atypia. However, the distinction between flat condyloma and VAIN 1 with koilocytosis is not always possible. Other differential diagnoses of VAIN include atrophy, squamous atypia and transitional cell metaplasia (3085) as well as immature squamous metaplasia in women with adenosis. A distinction is made based on the nuclear features of the epithelium. The relationship of the VAIN terminology to that of dysplasia and carcinoma in situ of the vagina is shown in Table 6.01.

Prognosis and predictive factors
The natural history of VAIN has been less extensively studied than that of CIN. In one study 23 patients with a mean age of 41 years were followed for at least 3 years with no treatment (49). One-half of the VAIN lesions were multifocal. Progression to invasive vaginal carcinoma occurred in only 2 cases, and VAIN persisted in 3 additional cases. Thus, VAIN spontaneously regressed in 78% of cases. A retrospective review of 121 women with VAIN showed that the recurrence rate was 33% (710). Progression to invasive vaginal cancer occurred in 2%. In another study of 94 patients with VAIN, the progression rate to cancer was 5% (2674).

Fig. 6.04 Condyloma acuminatum. Papillomatosis, acanthosis and hyperkeratosis are associated with a few koilocytes in the superficial layers.

Fig. 6.05 Spiked condyloma. Papillomatosis is associated with HPV-infected cells with a clear cytoplasm (koilocytes).

Fig. 6.06 Vaginal intraepithelial neoplasia, grade 1. Note the koilocytosis and the slightly thickened and disorganized basal layers.

Fig. 6.07 Flat condyloma. Note the cytopathic effects of human papillomavirus (koilocytosis) with a normal basal layer of the squamous epithelium.

Fig. 6.08 Atrophy. The cells are small, accounting for the nuclear crowding. Nuclei are uniform with discernible nucleoli. Mitoses are not detectable.
High grade VAIN appears to be an important precursor of invasive cancer; progression occurred in 8% of cases of high grade VAIN despite the fact that most of the patients were treated, whereas low grade VAIN regressed in 88% of women without treatment {2403}.

**Condyloma acuminatum**

**Definition**
A benign neoplasm characterized by papillary fronds containing fibrovascular cores and lined by stratified squamous epithelium with evidence of HPV infection, usually in the form of koilocytosis.

**Epidemiology**
Condylomas are sexually transmitted. There is strong evidence that their incidence has increased since the 1960s. The incidence is much higher in women than in men. They often occur on the mucosal epithelium of the vagina. However, because condylomas are often subclinical and not reported, their true incidence remains unknown.

**Aetiology**
Non-oncogenic HPV types 6 and 11 are found in the majority of condylomas {1837}. Patients with visible condylomas can be simultaneously infected by other HPV types (mixed HPV infection).

**Clinical features**

**Signs and symptoms**
Vaginal lesions are easily overlooked during a speculum examination. Vaginal condylomas present in the same way as those on the vulva and the cervix {1070, 2144}. They can be single or multiple. Condylomas can cover most of the vaginal mucosa and extend to the cervix and may be small or large. Most commonly, they occur adjacent to the introitus and in the vaginal fornices. Condylomas can be papular or macular. The latter has been also called “flat condyloma”, noncondylomatous wart virus infection or subclinical papillomavirus infection.

**Colposcopy**
Typical exophytic condylomas show digitate projections with vascularized cores producing loop-like patterns or punctation {1070, 2144}. The application of acetic acid augments the diagnosis of vaginal condylomas. Micropapillary vaginal condylomas may be diffuse and may completely cover the vagina. This manifestation is known as condylomatous vaginitis. Reverse punctation can be seen by colposcopy after acetic acid application. Spiked condylomas appear as small and elongated white spikes focally or diffusely distributed on the vaginal wall {1070, 2144}.

**Histopathology**
Condyloma acuminatum has a complex, arborizing architecture with hyperkeratosis, parakeratosis, acanthosis and papillomatosis as well as the typical cytopathic effects of HPV. It can be distinguished by clinical examination alone from vaginal micropapillomatosis, which has no significant relationship with HPV infection and is believed by some to be a normal anatomical variant of the lower genital tract {967}. The latter also lacks the histological features of condyloma.

**Squamous papilloma**

**Definition**
A benign papillary tumour in which squamous epithelium without atypia or koilocytosis lines a fibrovascular stalk.

**Synonyms**
Vaginal micropapillomatosis, squamous papillomatosis. These terms are applicable when numerous lesions are present.

**Epidemiology**
Squamous papillomas do not appear to be sexually transmitted.

**Aetiology**
Based on in situ hybridization studies using the polymerase chain reaction, vaginal micropapillary lesions appear unrelated to human papillomavirus {967}, and their aetiology is unknown.

**Clinical features**
Squamous papillomas may be single or multiple. When numerous, they occur near the hymenal ring and are referred to as vaginal micropapillomatosis. The lesions are usually asymptomatic but may be associated with vulvar burning or dyspareunia. They may be difficult to distinguish from condyloma by inspection. However, on colposcopic and histological examination papilloma is composed of a single papillary frond with a central fibrovascular core.

**Histopathology**
In squamous papilloma the squamous epithelium covers a central fibrovascular core and shows acanthosis but lacks koilocytosis. It has a smooth surface and lacks significant vascular structures. It lacks the complex arborizing architecture and koilocytes of condylomas.

---

![Fig. 6.09 Squamous papilloma. The fibrovascular core is covered by squamous epithelium with a smooth surface that lacks koilocytosis but shows acanthosis and papillomatosis.](image-url)
However, it is important to note that there may be a time during the evolution of condylomas when koilocytes are not easily identifiable.

**Fibroepithelial polyp**

**Definition**
A polyp lined by squamous epithelium that contains a central core of fibrous tissue in which stellate cells with tapering cytoplasmic processes and irregularly shaped thin-walled vessels are prominent features.

**Synonym**
Stromal polyp.

**Clinical features**
This lesion can occur at any age but has a predilection for pregnant women.

**Macroscopy**
These are polypoid lesions, usually solitary.

**Histopathology**
These polypoid lesions are characterized by a prominent fibrovascular stroma covered by squamous epithelium. They lack epithelial acanthosis and papillary architecture. Bizarre stromal cells, marked hypercellularity and elevated mitotic counts including atypical forms have been described that can lead to an erroneous diagnosis of sarcoma botryoides, but a cambium layer and rhabdomyoblasts are absent, and mitotic activity is typically low (2067).

**Glandular tumours and their precursors**

**ICD-O codes**
- Adenocarcinoma, NOS 8140/3
- Clear cell adenocarcinoma 8310/3
- Endometrioid adenocarcinoma 8380/3
- Mucinous adenocarcinoma 8480/3
- Mesonephric adenocarcinoma 9110/3
- Adenoma, NOS 8140/0
- Tubular 8211/0
- Tubulovillous 8263/0
- Villous 8261/0

**Clear cell adenocarcinoma**

**Definition**
An invasive neoplasm with an epithelial component that contains one or more cell types, most commonly clear cells and hobnail cells, but flat and/or eosinophilic cells may, on occasion, predominate.

**Epidemiology**
The occurrence of cases of vaginal clear cell adenocarcinoma associated with intrauterine exposure to diethylstilbestrol (DES) was responsible for an increase in incidence of adenocarcinoma in young women from the 1970s (1194). In the early 1970s the peak incidence of clear cell adenocarcinoma was around 19 years, the youngest patient being 8 years. With the ageing of the DES-exposed cohort, the peak incidence has been shifting towards an older age group.

**Aetiology**
DES was prescribed for threatened or repeated abortions from the 1940s to the early 1970s. Millions of women were exposed in utero to this and related drugs in several countries, including the United States, France and the Netherlands (2046). DES is a teratogen and causes a variety of congenital abnormalities of the lower genital tract in about 30% of the female offspring (1883). The absolute risk of clear cell adenocarcinoma of the vagina or cervix is estimated at 1:1000 (1843). About two-thirds of the cases of clear cell adenocarcinoma occurring in individuals under the age of 40 are linked to transplacental DES exposure. DES inhibits the development of urogenital sinus-derived squamous epithelium that is destined to become vaginal epithelium and normally grows up to the junction of the ectocervix and endocervix, replacing the pre-existing müllerian-derived columnar epithelium. The embryonic müllerian epithelium that is not replaced persists and develops into adenosis. Adenosis is found immediately adjacent to the tumour in over 90% of cases and is thought to be the precursor of clear cell adenocarcinoma. The rarity of clear cell adenocarcinoma in the exposed population suggests that DES is an incomplete carcinogen or that susceptibility factors are necessary for it to produce neoplastic transformation. Genetic factors and hormonal disruption by environmental toxins are implicated. A maternal history of prior spontaneous abortion increases the risk of clear cell adenocarcinoma (2161). Endogenous estrogens probably also play a role.

**Fig. 6.10** Fibroepithelial polyp. A multilobulated polypoid lesion arises from the vaginal wall.

**Fig. 6.11** Fibroepithelial polyp. A This polypoid lesion is composed of stroma and covered by squamous epithelium. B The stroma contains scattered bizarre multinucleated giant cells.
since most cases of clear cell adenocarcinoma are first detected around the time of puberty.

**Localization**

Whilst any part of the vagina may be involved, clear cell adenocarcinoma most often arises from its upper part. A primary vaginal clear cell adenocarcinoma may also involve the cervix. According to FIGO criteria about two-thirds of clear cell adenocarcinomas after DES exposure are classified as tumours of the vagina and one-third of the cervix \(^{1131}\). In non-DES exposed young women and postmenopausal women this ratio is reversed.

**Clinical features**

Vaginal bleeding, discharge and dyspareunia are the most common symptoms, but women may be asymptomatic. Abnormal cytologic findings may lead to detection, but care must be taken to sample the vagina as well as the cervix since cervical smears are relatively insensitive for the detection of clear cell adenocarcinoma \(^{1132}\).

Clear cell adenocarcinomas typically are polypoid, nodular, or papillary but may also be flat or ulcerated. Some clear cell adenocarcinomas are confined to the superficial stroma and may remain undetected for a long time \(^{1131,2386}\). Such small tumours may be invisible on macroscopic or even colposcopic examination and are only detected by palpation or when tumour cells are shed through the mucosa and detected by exfoliative cytology. Large tumours may be up to 10 cm in diameter.

**Histopathology**

Clear cell adenocarcinoma of the vagina has an appearance similar to those arising in the cervix, endometrium and ovary. Clear cell adenocarcinomas may show several growth patterns; the most common pattern is tubulocystic, but it also may be solid or mixed. A papillary growth pattern is seldom predominant. The main cell types are clear cells and hobnail cells. The appearance of the clear cells is due to the presence of abundant intracytoplasmic glycogen. Hobnail cells are characterized by inconspicuous cytoplasm and a bulbous nucleus that protrudes into glandular lumens. The tumour cells may also be flat with bland nuclei and scant cytoplasm in cystic areas or have granular eosinophilic cytoplasm without glycogen. The nuclei vary considerably in appearance. They may be significantly enlarged with multiple irregular nucleoli in clear and hobnail cells, or they may have fine chromatin and inconspicuous nucleoli in flat cells. The num-

![Fig. 6.12 Adenosis of the vagina. A By colposcopy red granular areas of adenosis are apparent. B Colposcopy after iodine application. The areas of adenosis do not stain.](image)

![Fig. 6.13 Clear cell adenocarcinoma. A Note the neoplastic tubules lined by hobnail cells on the right and adenosis of the tuboendometrial type on the left. B Cytological preparation shows hobnail cells with anisokaryosis, unevenly distributed chromatin, nucleoli and vacuolated cytoplasm.](image)
Number of mitoses varies but is usually less than 10 per 10 high power fields. Psammoma and intracellular hyaline bodies may occasionally be encountered.

**Cytopathology**
In cytological preparations the malignant cells may occur singly or in clusters and resemble large endocervical or endometrial cells. Typically, the nuclei are large with one or more prominent nucleoli. Nuclei may be bizarre. The bland cytopathological features of tumours that show only mild nuclear atypia may, however, hamper cytological detection.

**Prognosis and predictive factors**
Clear cell adenocarcinoma may be treated by radical hysterectomy, vaginectomy and lymphadenectomy or by external beam or local radiotherapy. The tumour spreads primarily by local invasion and lymphatic metastases and has a recurrence rate of 25%. The incidence of lymph node disease increases dramatically with tumour invasion beyond 3 mm in depth. Lymph node metastases occur in 16% of patients with stage I disease and 50% of those with stage II disease. Haematogenous metastases develop in 10% of patients with stage I disease and 25% of those with stage II disease. The 5-year survival of patients with stage I disease is approximately 70% and is close to 100% for patients with stage I tumours. Most recurrences occur within 3 years. Long disease-free intervals of more than 20 years have been observed. Factors associated with a favourable prognosis are: low stage, small tumour size, a tubulocystic pattern, low mitotic activity and mild nuclear atypia.

**Adenosis**

**Definition**
Adenosis is the presence of glandular epithelium in the vagina and is thought to be the result of the persistence of embryonic mullerian epithelium.

**Epidemiology**
Adenosis has been reported to occur in approximately 30% of women after in utero exposure to DES. Congenital adenosis may be present in up to 8% of unexposed women. Adenosis has been described after laser vaporization or intravaginal application of 5-fluorouracil (730).

**Localization**
The most frequent site of involvement is the anterior upper third of the vagina.

**Clinical features**

*Signs and symptoms*
Adenosis is usually asymptomatic. Some women present with a mucous discharge, bleeding or dyspareunia. Adenosis may spontaneously regress at the surface and be replaced by metaplastic squamous epithelium, particularly with increasing age. Because of the risk of development of clear cell adenocarcinoma within the vaginal wall, palpation, colposcopic examination and cytological smears are necessary to monitor patients with adenosis.

*Colposcopy*
Areas of adenosis and associated squamous metaplasia may be visible colposcopically and by iodine staining (2046). Adenosis may be occult or may present as cysts or as a diffusely red granular area.

**Histopathology**
Adenosis is characterized by the presence of glandular epithelium resembling mucus cell of the endocervix (mucinous type) and/or the endometrium or the fallopian tube (tuboneendometrial type). Adenosis may be found on the surface or deeper in the stroma. Mixtures of various types of adenosis may be encountered. Squamous metaplasia may occur as a result of healing.

**Atypical adenosis**

**Definition**
Atypical adenosis is the presence of atypical glandular epithelium in the vagina. It is reported to be a precursor lesion of clear cell adenocarcinoma.

**Histopathology**
Atypical adenosis occurs in the tuboendometrial type of adenosis and is a fre-
Tumours of the vagina

Quint finding immediately adjacent to clear cell adenocarcinoma. The atypical glands tend to be more complex than those of mucinous adenosis and are lined by cells with enlarged, atypical, pleomorphic, hyperchromatic nuclei that contain prominent nucleoli. Mitotic figures are infrequent, and hobnail cells may be present.

Differential diagnosis
A distinction from clear cell adenocarcinoma may be difficult if the atypical adenosis shows a pseudoinfiltrative pattern of small glands. Conversely, clear cell adenocarcinoma displaying a tubulocystic pattern may be erroneously interpreted as adenosis. However, unlike tubulocystic clear cell adenocarcinoma with bland flattened cells, atypical adenosis is composed of cuboidal or columnar epithelium.

Prognosis and predictive factors
Management may be local excision or follow-up {2609}.

Endometrioid adenocarcinoma

Only a few primary endometrioid adenocarcinomas of the vagina have been reported. The histological appearance resembles that of the much more common endometrioid adenocarcinoma of the endometrium. A few cases have been described in association with adenosis as well as cases arising in vaginal endometriosis {1155,3251}.

Mucinous adenocarcinoma

Primary mucinous adenocarcinoma of the vagina is rare. Only a few cases have been reported {745}. Like the other non-clear cell adenocarcinomas of the vagina, this type of tumour is predominantly reported in peri-menopausal women. Histologically, the tumour may resemble typical endocervical or intestinal adenocarcinomas of the cervix {909}. Due to its rarity, little is known about its aetiology and behaviour. A relationship to vaginal adenosis has been described {3168}, suggesting a müllerian origin. An unusual variant of mucinous adenocarcinoma has been described in neovaginas {1218,1941}.

Mesonephric adenocarcinoma

Mesonephric (Gartner) duct remnants are mostly situated deep in the lateral walls of the vagina. Only a few cases of carcinoma arising from mesonephric remnants in the vagina have been reported, and none since 1973. These tumours are composed of well-formed tubules lined by atypical, mitotically-active, cuboidal to columnar epithelium that resemble mesonephric duct remnants. Unlike clear cell adenocarcinoma, mesonephric carcinoma does not contain clear or hobnail cells, intracellular mucin or glycogen, and the tubules are often surrounded by a basement membrane.

Müllerian papilloma

Müllerian papilloma may arise in the vagina of infants and young women {2977} (see also chapter on the cervix). A few examples have arisen in the wall of the vagina {1817}. Occasional local recurrences have been reported {1719}, and in one instance repeated removal of recurrent müllerian papillomas was necessary {708}. The origin of the tumour is not clear, although reports support a müllerian origin {1719}.

Tubular, tubulovillous and villous adenoma

Definition
Benign glandular tumours with enteric differentiation {494}.

Clinical features
Patients may be premenopausal or post-menopausal. Clinical examination may reveal a polypoid mass.

Histopathology
The adenomas are histologically similar to colonic types and have been subclassified as tubular, tubulovillous or villous. The epithelium is stratified and contains columnar cells with mucin. The nuclei are oval to elongated and dysplastic. Adenocarcinoma arising from a vaginal adenoma has been reported {1935}.

Differential diagnosis
Aside from endometriosis and prolapsed fallopian tube, the most important lesions in the differential diagnosis are metastatic carcinoma and extension or recurrence of endometrial or endocervical adenocarcinoma. An adenoma is generally polypoid and lacks invasive borders, marked architectural complexity or high grade cytological features.

Uncommon epithelial tumours

Definition
Primary epithelial tumours of the vagina other than those of squamous or glandular type. These tumours are described in more detail in the chapter on the cervix.
<table>
<thead>
<tr>
<th>ICD-O codes</th>
<th>Adenosquamous carcinoma 8560/3</th>
<th>Adenoid cystic carcinoma 8200/3</th>
<th>Carcinoid 8240/3</th>
<th>Small cell carcinoma 8041/3</th>
<th>Undifferentiated carcinoma 8020/3</th>
</tr>
</thead>
</table>

**Adenosquamous carcinoma**

A carcinoma composed of a mixture of malignant glandular and squamous epithelial elements (2360).

**Adenoid cystic carcinoma**

An adenocarcinoma which resembles adenoid cystic carcinoma of salivary gland origin but usually lacks the myoepithelial cell component of the latter (2781).

**Adenoid basal carcinoma**

A carcinoma with rounded, generally well differentiated nests of basaloid cells showing focal gland formation; central squamous differentiation may be present as well (1906,1986).

**Carcinoid**

A tumour resembling carcinoids of the gastrointestinal tract and lung (936).

**Small cell carcinoma**

A carcinoma of neuroendocrine type that resembles small cell carcinomas of the lung (1571,1869,1877,2281).

**Undifferentiated carcinoma**

A carcinoma that is not of the small cell type and lacks evidence of glandular, squamous, neuroendocrine or other types of differentiation.
Mesenchymal tumours

A.G. Östör

### Vaginal sarcomas

**Definition**
Malignant mesenchymal tumours that arise in the vagina.

**ICD-O codes**
- Sarcoma botryoides 8910/3
- Leiomyosarcoma 8890/3
- Endometrioid stromal sarcoma, low grade 8931/3
- Undifferentiated vaginal sarcoma 8805/3

**Epidemiology**
Sarcomas are rare and comprise <2% of all malignant vaginal neoplasms (633).

**Aetiology**
There are virtually no clues to the pathogenesis of this group of tumours.

**Clinical features**
**Signs and symptoms**
Malignant tumours usually present with bleeding and/or discharge and a mass and are usually readily detected by clinical examination. Occasional cases are detected by an abnormal cytological examination. Some sarcomas, however, are asymptomatic, and the diagnosis is, therefore, delayed.

**Imaging**
The extent of tumour spread may be determined by transvaginal ultrasound.

**Tumour spread and staging**
Vaginal sarcomas spread by direct extension and by metastasis; the latter occurs both by lymphatic and haematogenous routes. The tumour initially grows into the vaginal wall and soft tissue of the pelvis, bladder or rectum. The staging of vaginal sarcomas in adults utilizes the TNM/FIGO classification (51,2976).

**Sarcoma botryoides**

**Definition**
A malignant mesenchymal tumour composed of small, round or oval to spindle-shaped cells, some of which show evidence of striated muscle differentiation.

**Synonym**
Embryonal rhabdomyosarcoma.

**Epidemiology**
Sarcoma botryoides (Greek bothryos: grapes) is the most common vaginal sarcoma and occurs almost exclusively in children and infants <5 years of age (mean 1.8 years) (633), although occasional cases are encountered in young adults or even postmenopausal women. At least two cases of sarcoma botryoides have been described in pregnancy (2709).

**Clinical features**
These tumours present typically as a vaginal mass that on clinical and macroscopic examination appears soft, oedematous and nodular, papillary, polypoid or grape-like, often protruding through the introitus.

**Macroscopy**
The tumours vary from 0.2-12 cm in maximum dimension and may be covered by an intact mucosa or be ulcerated and bleeding. The sectioned surface displays grey to red areas of myxomatous change and haemorrhage.

**Tumour spread and staging**
In children the Intergroup Rhabdomyosarcoma Study group clinical classification is used, which is based on the combined features of extent of disease, resectability and histological evaluation of margins of excision (99).

**Histopathology**
The neoplasm is composed of cells with round to oval or spindle-shaped nuclei and eosinophilic cytoplasm that may show differentiation towards striated muscle cells. Typically, there is a dense cambium layer composed of closely packed cells with small hyperchromatic nuclei immediately subjacent to the squamous epithelium that may be invaded. The nuclei have an open chromatin pattern and inconspicuous nucleoli. The central portion of the polypoid mass is typically hypocellular, oedematous or myxomatous. The mitotic rate is high. Rhabdo-myoblasts (strap cells), which may be sparse, may be found in any of the patterns. Their recognition may be facilitated by immunohistochemical staining with antibodies directed against actin, desmin or myoglobin. Although the first two antibodies are more sensitive than myoglobin, they are not specific for skeletal muscle differentiation. Ultrastructural examination may reveal characteristic features of rhabdomyoblastic differentiation, such as thick and thin filaments with Z-band material.

**Differential diagnosis**
The distinction from a benign fibroepithelial polyp with bizarre nuclei is important.

<table>
<thead>
<tr>
<th>Table 6.02</th>
<th>Clinical classification of vaginal sarcoma botryoides / rhabdomyosarcoma (99).</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Complete surgical resection</td>
</tr>
<tr>
<td>IIa</td>
<td>Excision, margin positive</td>
</tr>
<tr>
<td>IIb</td>
<td>Excision, lymph nodes positive</td>
</tr>
<tr>
<td>IIIa</td>
<td>Biopsy only</td>
</tr>
<tr>
<td>IIIB</td>
<td>Partial surgical excision (gross disease present)</td>
</tr>
<tr>
<td>IV</td>
<td>Metastatic disease</td>
</tr>
</tbody>
</table>
The clinical setting, the characteristic low power appearance, the absence of a cambium layer and striated cells and a typically low mitotic index establish the correct diagnosis of a fibroepithelial polyp (2055, 2067, 2141).

Genetic susceptibility
One instance of sarcoma botryoides has been reported in a child with multiple congenital abnormalities and bilateral nephroblastomas suggesting a possible genetic defect (1965).

Prognosis and predictive factors
The prognosis of sarcoma botryoides in the past was poor, but an 85% 3-year survival rate has recently been achieved with wide local excision and combination chemotherapy. Second malignancies in long-term survivors of vaginal embryonal rhabdomyosarcoma have not been reported to date.

Leiomyosarcoma

Definition
A malignant tumour composed of smooth muscle cells.

Epidemiology
Although leiomyosarcoma is the most common vaginal sarcoma in the adult and the second most common vaginal sarcoma, only approximately 50 cases have been reported (599). They accounted for only 5 of 60 cases in the only large series of vaginal smooth muscle tumours (2879). An epithelioid variant with a myxoid stroma has also been described (456). As in the uterus, occasional sarcomas arise from leiomyomas (1682).

Differential diagnosis
Leiomyosarcomas should be differentiated from the benign condition of post-operative spindle cell nodule (2861). The latter is a localized non-neoplastic lesion composed of closely packed spindle-shaped cells and capillaries occurring several weeks to several months postoperatively in the region of an excision. It may closely resemble a leiomyosarcoma, but the history of a recent operation at the same site facilitates its diagnosis.

Prognosis and predictive factors
Leiomyosarcomas are treated primarily by radical surgical excision (vaginectomy, hysterectomy and pelvic lymphadenectomy). In the only large series of 60 smooth muscle tumours, both benign and malignant, only 5 neoplasms recurred, and in one of these, a tumour with an infiltrative margin, the patient died of lung metastases (2879).

Endometrioid stromal sarcoma, low grade

Definition
A sarcoma with an infiltrating pattern that in its well differentiated form resembles normal endometrial stromal cells.

Histopathology
Low grade endometrioid stromal sarcomas have been rarely encountered in the vagina and resemble their counterparts in the endometrium. In two cases the tumours appear to have arisen from endometriosis (245). Before concluding that such a neoplasm is primary in the vagina, an origin within the uterus should be excluded (633, 1051, 2226). The term undifferentiated vaginal sarcoma is preferred for the high grade lesions.

Undifferentiated vaginal sarcoma

Definition
A sarcoma with an infiltrating pattern composed of small spindle-shaped cells lacking specific features.

Histopathology
Undifferentiated vaginal sarcomas are rare, polypoid or diffusely infiltrating lesions. Spindle to stellate cells with scanty cytoplasm are arranged in sheet-like, fascicular or storiform patterns. The cells exhibit various degrees of nuclear pleomorphism and hyperchromasia. The mitotic index is \( \geq 10 \) per 10 high power fields.

Mesenchymal tumours 303
Prognosis and predictive factors

Death from recurrent or metastatic tumour has occurred within 2 years of treatment in about 50% of patients [20, 3236].

Rare malignant mesenchymal tumours

Rare examples of malignant schwannoma (633), fibrosarcoma (2160), malignant fibrous histiocytoma (3078), angiosarcoma (1804, 2298, 2931), alveolar soft part sarcoma (402), synovial sarcoma (2095), malignant peripheral nerve sheath tumour (2226) and unclassifiable sarcoma (633) have all been described in the vagina, but they do not exhibit unique clinical or morphological features.

Benign mesenchymal neoplasms

Of the benign tumours only leiomyomas are relatively common.

ICD-O codes

Leiomyoma 8890/0
Genital rhabdomyoma 8905/0
Deep angiomyxoma 8841/1

Clinical features

Most benign tumours are asymptomatic, but depending on their size and position they may cause pain, bleeding, dyspareunia and urinary or rectal symptoms.

Leiomyoma

Definition

A benign neoplasm composed of smooth muscle cells having a variable amount of fibrous stroma.

Epidemiology

Approximately 300 cases of vaginal leiomyoma have been reported. Although the age at presentation ranges from 19-72 years, they typically occur during reproductive life (mean age 44 years) [2879]. Leiomyomas of the vagina are not related to those of the uterus, either in frequency or in racial distribution, the White to Black ratio for uterine and vaginal leiomyomas being 1:3 and 4:1 respectively [222].

Aetiology

There are virtually no clues to the pathogenesis of this group of tumours. Rare leiomyomas may recur in one or more pregnancies suggesting hormone dependency [2501].

Histopathology

Vaginal leiomyomas resemble their uterine counterparts. A case of bizarre (syncytial) leiomyoma has been described [264].

Histogenesis

The histogenesis of smooth muscle tumours is not clear, but myoepithelial cells such as are found in smooth muscle cells of venules or of the vaginal muscularis and myofibroblasts have all been implicated.

Prognosis and predictive factors

Nearly all are treated by local excision [1682, 2486, 2523]. An occasional tumour, especially if large, may recur [685, 1682].

Genital rhabdomyoma

Definition

An uncommon benign tumour of the lower female genital tract showing skeletal muscle differentiation.

Epidemiology

About 20 cases have been reported [1313, 2812].

Clinical features

These tumours occur in middle age women (range 30-48 years) and present as a well defined, solitary mass with the clinical appearance of a benign vaginal polyp [1397].

Macroscopy

Genital rhabdomyomas are solitary, nodular or polypoid, ranging in size from...
1-11 cm. They may arise anywhere in the vagina, and some protrude into the lumen. The overlying mucosa is usually intact since the tumour arises in the wall. The texture is rubbery and the sectioned surface is grey and glassy.

**Histopathology**
They are composed of mature, bland rhabdomyoblasts that are oval or strap-shaped with obvious cross striations in the cytoplasm. Mitotic activity and nuclear pleomorphism are absent. Abundant connective tissue stroma surrounds individual muscle cells. Rhabdo-myoma should not be confused with sarcoma botryoides.

**Prognosis and predictive factors**
No recurrences have been reported after complete local excision.

**Deep angiomyxoma**

**Definition**
A locally infiltrative tumour with a predilection for the pelvic and perineal regions and a tendency for local recurrence composed of fibroblasts, myofibroblasts and numerous, characteristically thick-walled, blood vessels embedded in an abundant myxoid matrix.

**Synonym**
Aggressive angiomyxoma.

**Clinical features**
Most patients present with a large, slowly growing, painless mass in the pelviperineal region that may give rise to pressure effects on the adjacent urogenital or anorectal tracts. Imaging studies often show the mass to be substantially larger than clinically suspected.

**Macroscopy**
Macroscopically, the tumour is lobulated but poorly circumscribed due to finger-like extensions into the surrounding tissue. The neoplasm is grey-pink or red-tan and rubbery or gelatinous.

**Tumour spread and staging**
Deep angiomyxoma is a locally infiltrative but non-metastasizing neoplasm that occurs for the most part during the reproductive years. At least two cases have been reported within the vagina, an uncommon site for this neoplasm (81, 496).

**Histopathology**
The tumour is of low to moderate cellularity and is composed of small, uniform, spindle-shaped to stellate cells with poorly defined, pale eosinophilic cytoplasm and bland, often vesicular nuclei. An abundant myxoid matrix contains a variable number of rounded, medium-sized to large vessels that possess thickened focally hyalinized walls. A characteristic feature is the presence of loosely organized islands of myoid cells around the larger nerve segments and vessels (3086). The neoplasm is positive for desmin in almost all cases, whereas stains for S-100 protein are consistently negative (1431,2082).

**Prognosis and predictive factors**
The treatment for this locally aggressive but non-metastasizing neoplasm is primarily surgical with close attention to margins. Approximately 30% of tumours recur locally.

**Postoperative spindle cell nodule**

**Definition**
A non-neoplastic localized lesion composed of closely packed proliferating spindle cells and capillaries simulating a leiomyosarcoma.

**Clinical features**
The lesion develops at the site of a recent operation several weeks to several months postoperatively (2861).

**Histopathology**
The lesion is composed of closely packed, mitotically active, spindle-shaped mesenchymal cells and capillaries often with an accompaniment of inflammatory cells.

**Differential diagnosis**
The history of a recent operation at the same site serves to distinguish this lesion from leiomyosarcoma. Postoperative spindle cell nodule may closely resemble a leiomyosarcoma or other spindle cell sarcoma, but the history of a recent operation at the same site facilitates its diagnosis.

Mesenchymal tumours 305
Mixed epithelial and mesenchymal tumours

Definition
Tumours in which both an epithelial and a mesenchymal component can be histologically identified as integral neoplastic components.

ICD-O codes
- Carcinosarcoma 8980/3
- Adenosarcoma 8933/3
- Malignant mixed tumour 8940/3
- Benign mixed tumour 8940/0

Epidemiology
These mixed tumours are among the rarest of vaginal primary tumours, which are themselves uncommon primary tumours of the female genital tract. No mixed tumours were found among 753 primary vaginal tumours compiled from ten reports in the literature [2714]. The U.S. National Cancer Data Base Report on Cancer of the Vagina [577] includes only 25 "complex mixed or stromal tumours" among 4,885 submitted cases of vaginal cancer. As expected, there are no epidemiological data available on mixed tumours [2226].

Aetiology
The aetiology of the tumours in this group that are more often primary in the endometrium, i.e. carcinosarcoma and adenosarcoma is discussed in the chapter on the uterine corpus of this publication. The aetiology of vaginal malignant mixed tumour is essentially unknown.

Carcinosarcoma

Definition
A tumour with malignant epithelial and mesenchymal components. Before the diagnosis of a primary vaginal tumour is made, extension from elsewhere in the female genital tract must be excluded.

Synonyms
Malignant müllerian mixed tumour, malignant mesodermal mixed tumour, metaplastic carcinoma.

Clinical features
These tumours present clinically as a palpable vaginal mass. Carcinosarcomas usually bleed and may occur years after therapeutic irradiation for some other lesion [2226,2714]. Imaging studies have not been reported for any of these lesions.

Macroscopy
Carcinosarcomas in their rare primary vaginal manifestations are identical in macroscopic appearance to their far more common endometrial counterparts. Although primary vaginal tumours of this sort are exophytic lesions, carcinosarcomas are more likely to be metastases from the endometrium or elsewhere in the female genital tract and may be deeper in the wall.

Tumour spread and staging
Staging and spread of these malignant tumours are identical to those of primary vaginal carcinomas [2714].

Histopathology
Primary vaginal carcinosarcoma is histologically identical to its endometrial counterpart. A vaginal metastasis from an endometrial or other primary carcinosarcoma may contain only the carcinomatous or rarely the sarcomatous component [1388,2692].

Prognosis and predictive factors
Most women with primary vaginal carcinosarcomas have rapidly developed metastases and died.

Adenosarcoma

Definition
A mixed tumour composed of a benign or atypical epithelial component of müllerian type and a malignant appearing mesenchymal component.

Clinical features
Adenosarcoma presents clinically as a palpable vaginal mass.

Macroscopy
Although primary vaginal adenosarcoma is typically an exophytic lesion, adenosarcomas are more likely to be metastases from the endometrium or...
Mixed epithelial and mesenchymal tumours

307

elsewhere in the female genital tract and may be deeper in the wall.

Histopathology
Primary vaginal adenosarcoma is histologically identical to its endometrial counterpart. Metastatic adenosarcoma generally consists of the sarcoma alone [2692].

Prognosis and predictive factors
Adenosarcomas of the vagina are not reported in enough numbers or detail to establish their prognosis.

Malignant mixed tumour resembling synovial sarcoma

Definition
An extremely rare biphasic malignant tumour resembling synovial sarcoma and containing gland-like structures lined by flattened epithelial-appearing cells and a highly cellular mesenchymal component. There is no evidence of müllerian differentiation.

Clinical features
The two reported cases of mixed tumour resembling synovial sarcoma presented as polypoid masses in the lateral fornix in women of ages 24 and 33.

Histopathology
The mixed tumour resembling synovial sarcoma, as its name suggests, is composed of gland-like structures lined by round to flattened epithelial-appearing cells embedded in a spindle cell matrix. In one reported case electron microscopic study suggested synovial-like differentiation [2095], whilst in another, a possible origin from mesonephric rests was proposed [2652].

Prognosis and predictive factors
Follow-up was too short to establish the clinical malignancy and survival rates of the two malignant mixed tumours resembling synovial sarcoma reported in the literature.

Benign mixed tumour

Definition
A well circumscribed benign tumour histologically resembling the mixed tumour of salivary glands with a predominant mesenchymal-appearing component and epithelial cells of squamous or glandular type.

Synonym
Spindle cell epithelioma.

Clinical features
The benign mixed tumour is usually asymptomatic, typically is a well-demarcated submucosal mass and has a predilection for the hymenal region [335, 2714]. It tends to occur in young to middle-aged women, with a mean age of 40.5 in the largest series reported [335].

Macroscopy
Benign mixed tumours are circumscribed, grey to white, soft to rubbery masses, usually measuring from 1-6 cm [335,2714].

Histopathology
The spindle cell component predominates histologically and lacks atypia or significant mitotic activity. Randomly interspersed are nests of benign-appearing squamous cells and, less frequently, glands lined by low cuboidal to columnar epithelium commonly demonstrating squamous metaplasia. Hyaline globular aggregates of stromal matrix are also frequently seen.

Immunoprofile
In an immunohistochemical study of a large series of cases, the spindle cells were strongly keratin-immunoreactive in 90% cases [335]. They showed only minimal expression for smooth muscle actin and were uniformly negative for S-100 protein, glial fibrillary acidic protein and factor VIII-related antigen [335,2717]. The tumours coexpressed CD34, CD99 and Bcl-2 [2717].

Histogenesis
The only benign vaginal tumour classically designated as a mixed tumour because of its histological resemblance to the benign mixed tumour (pleomorphic adenoma) of salivary glands has been renamed spindle cell epithelioma because of immunohistochemical and ultrastructural evidence suggesting purely epithelial differentiation [335]. Unlike mixed tumours of salivary glands, these vaginal tumours show no immunohistochemical or ultrastructural features of myoepithelial cells [2717]. Origin from a primitive/progenitor cell population has been postulated [2717].

Prognosis and predictive factors
The benign mixed tumour has never metastasized in reports of over forty cases; however, local recurrences have been noted.
Melanocytic tumours

Definition
A tumour composed of melanocytes, either benign or malignant.

ICD-O codes
Malignant melanoma 8720/3
Blue naevus 8780/0
Melanocytic naevus 8720/0

Malignant melanoma

Definition
A tumour composed of malignant melanocytes.

Epidemiology
Malignant melanoma is a rare but very aggressive tumour of the vagina. Patients have an average age of 60 years and most are White (492).

Clinical features
They typically present with vaginal bleeding, and some may have inguinal lymphadenopathy. The more common locations are in the lower third of the vagina and on the anterior vaginal wall.

Macroscopy
The lesions are pigmented and usually 2-3 cm in size.

Histopathology
The lesions are invasive and may display ulceration. Most have a lentiginous growth pattern, but junctional nests can be seen. In-situ or pagetoid growth is not typical. The cells are epithelioid or spindle-shaped and may contain melanin pigment. There is brisk mitotic activity. Tumour cells express S-100 protein, melan A and HMB-45.

Differential diagnosis
As “atypical” or dysplastic melanocytic lesions of the vagina have not been evaluated, histological separation of “borderline” melanocytic lesions from melanoma is not always possible. Nests of epithelioid cells raise the possibility of a poorly differentiated carcinoma. Spindle cell differentiation may create confusion with sarcomas.

Prognostic and predictive factors
Clinical criteria
Patients have been treated by a combination of surgery, radiation and chemotherapy. The prognosis is poor with a 5-year survival rate of 21% and a mean survival time of 15 months (314).

Histopathological criteria
Assessment of Clark levels, as is done for melanomas of skin, is not possible given the lack of normal cutaneous anatomical landmarks. Most tumours have a significant thickness, but even a thin melanoma does not necessarily portend a favourable prognosis. One study found that mitotic activity correlates better with the clinical outcome than the depth of invasion (314).

Blue naevus

Definition
A proliferation of subepithelial dendritic melanocytes.

Clinical features
Though rare, both common and cellular variants of blue naevus have been reported in the vagina (2400,2929). The common variant typically presents as a blue-black macule and the cellular variant as a nodule.

Histopathology
Classic blue naevi contain melanocytes with elongated dendritic processes and heavy cytoplasmic pigmentation. Cellular
variants have a biphasic composition with areas similar to common blue nae-
vus admixed with round nodules. The
cells are arranged in nests and short fas-
cicles with a whorled pattern and are
plump and spindle-shaped with oval
bland nuclei and pale cytoplasm.

Differential diagnosis
The common variant should not pose a
diagnostic problem. The cellular variant
may cause confusion with melanoma and
smooth muscle tumours. Nuclear atypia
and numerous mitotic figures would
favour melanoma. Well defined interlac-
ing fascicles, large thick-walled blood
vessels, immunohistochemical positivity
for muscle markers and negativity for
S-100 protein should assist in making the
diagnosis of a smooth muscle tumour.

**Melanocytic naevus**

Definition
Melanocytic nevi are defined as prolifer-
ation of nests of naevus cells.

Clinical features
Melanocytic nevi of the vagina are
thought to be similar to their counterparts
in the skin [1539].

**Yolk sac tumour**

Definition
A primitive malignant germ cell tumour
characterized by a variety of distinctive
histological patterns, some of which
recapitulate phases in the development
of the normal yolk sac.

ICD-O code 9071/3

Synonym
Endodermal sinus tumour.

Clinical features
Patients are usually under 3 years of age.
Vaginal bleeding and discharge are the
most common symptoms. Serum levels
of alpha-fetoprotein may be elevated. A
polypoid friable mass is seen on clinical
examination with a mean size of 3 cm.

Histopathology
Vaginal cases resemble their ovarian
counterparts.

Differential diagnosis
Although sarcoma botryoides may be
simulated clinically, the histological fea-
tures resolve any confusion. Clear cell
and endometrioid carcinomas may cr e-
 ate difficulty in histological separation.

Prognosis and predictive factors
Combined surgery and chemotherapy
may provide a favourable outcome. A
disease-free survival of up to 23 years is
possible [557].

Peripheral primitive neuroectodermal
tumour / Ewing tumour

Definition
Tumours of uncertain lineage within the
small round blue cell family of tumours.

ICD-O code Peripheral primitive
neuroectodermal tumour / 9364/3

Ewing tumour 9260/3

Clinical features
Peripheral primitive neuroectodermal
tumour/Ewing tumour (PNET/ET) is rare
within the vagina [3002]; A reported case
occurred in a 35-year-old woman who
presented with a vaginal mass.

Histopathology
Histological features are similar to
PNET/ET in non-vaginal sites. Typically,
PNET/ET grows as a diffuse sheet of uni-
form small cells with scant pale cyto-
plasm and an intermediate to high
nuclear to cytoplasmic ratio. The nuclei
are round with evenly dispersed chro-
matin. Mitotic figures may be numerous,
and rosettes may be seen.

Immunoprofile
Expression of CD99 would be expected
in almost all cases.

Differential diagnosis
PNET/ET should not be mistaken for
rhabdomyosarcoma, non-Hodgkin lym-
phoma (NHL), melanoma, small cell car-
icina or endometrial stromal sarcoma
because of differences in prognosis and
treatment. A broad immunohistochemical
panel and, if need be, molecular studies,
performed on paraffin-embedded tissue
should assist in making the correct diag-

Molecular genetics
Identification of the EWS/FLI1 fusion tran-
script derived from the t(11;22)(q24;q12)
chromosomal translocation by the
Reverse transcriptase-polymerase chain reaction and Southern blot hybridization would confirm the diagnosis.

**Prognosis and predictive factors**

The experience with PNET/ET of the vagina is limited, but patients with localized tumours in soft tissue sites can potentially be cured with a combination of surgery, chemotherapy and radiation therapy.

### Dermoid cyst

**Definition**

A cystic tumour composed of more than one germ cell layer in which all elements are mature.

**ICD-O code**

<table>
<thead>
<tr>
<th>Dermoid cyst</th>
<th>9084/0</th>
</tr>
</thead>
</table>

**Synonym**

Mature cystic teratoma.

**Macroscopy and histopathology**

These resemble the same tumour in the ovary.

### Adenomatoid tumour

**ICD-O code**

9054/0

A single case occurring in a 47-year-old woman has been reported [1697].

### Lymphoid and haematopoietic tumours

**Definition**

Tumours of the lymphoid and haematopoietic systems as well as secondary tumours of the vagina.

**Lymphoma**

**Definition**

Tumours with lymphoid differentiation arising as either primary (localized) or secondary (disseminated) disease.

**Clinical features**

Lymphomas of the vagina are predominantly of the non-Hodgkin’s type (3001). Patients with primary NHL have a mean age of 42 years, usually present with vaginal bleeding and have a mass on clinical examination. Patients with secondary NHL have a mean age of 65 years, present with vaginal bleeding and usually have a history of NHL.

**Histopathology**

Almost all NHLs primary in the vagina are diffuse large B-cell lymphomas.

---

<table>
<thead>
<tr>
<th>Immunohistochemical or molecular markers</th>
<th>Peripheral primitive neuroectodermal tumour/Ewing tumour</th>
<th>Rhabdomyosarcoma</th>
<th>B-cell non-Hodgkin lymphoma</th>
<th>Melanoma</th>
<th>Small cell carcinoma</th>
<th>Endometrial stromal sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Muscle specific actin/ desmin</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/ -</td>
</tr>
<tr>
<td>Chromogranin/ synaptophysin</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>S-100 protein</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMB-45</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leukocyte common antigen/ CD20</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD99</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>t(11;22)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>t(2;13)/ t(1;13)</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Monoclonal immunoglobulin heavy chain gene rearrangement</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Key:** +/-, variable rate of positivity; *, Not all markers have been thoroughly tested for each tumour, but expected results are listed.
growing in sheets. Some may have sclerosis. The neoplastic cells are large with round nuclei, vesicular chromatin and nucleoli. Secondary cases are usually diffuse large B-cell lymphomas and are histologically similar to the primary cases.

Immunoprofile
Almost all NHLs of the vagina (primary or secondary) are of B-cell lineage and typically express CD20.

Differential diagnosis
The main lesions in the differential diagnosis of NHL include granulocytic sarcoma and other haematological malignancies, carcinoma, melanoma and small round blue cell tumours such as rhabdomyosarcoma. Knowledge of the age, previous history of NHL or leukaemia, and the immunoprofile (keratin, CD20, CD3, CD43, myeloperoxidase, S-100 protein, desmin and other muscle markers) should help establish the correct diagnosis.

Somatic genetics
Southern blot analysis and polymerase chain reaction (PCR) can demonstrate monoclonal immunoglobulin heavy chain gene rearrangements in vaginal NHL. In situ hybridization has not confirmed the presence of human papillomavirus DNA or Epstein-Barr virus (EBV) RNA (2999); however, EBV DNA has been found by PCR (2718).

Prognosis and predictive factors
Vaginal NHL is usually treated by chemotherapy and radiation. The determination of the Ann Arbor stage is prognostically important for vaginal NHL. Patients with low stage tumours (stages IE and IIE) have a longer disease-free survival than those with high-stage disease have (stages IIE and IV).

Leukaemia
Definition
A malignant haematopoetic neoplasm that may be primary or secondary.

Synonym
Granulocytic sarcoma.

Epidemiology
Vaginal involvement by leukaemia may either be primary or secondary; however, the latter is much more common (428).

Clinical features
Leukaemia of the vagina is rare but is usually of the myeloid type (granulocytic sarcoma or “chloroma”) (2099). Patients are elderly, have a mass on clinical examination and may have other evidence of acute myeloid leukaemia.

Histopathology
A series of primary granulocytic sarcomas of the female genital tract including 3 cases of the vagina was reported (2099). Granulocytic sarcomas are usually composed of cells with finely dispersed nuclear chromatin and abundant cytoplasm that may be deeply eosinophilic. The identification of eosinophilic myelocytes is helpful in establishing the diagnosis; however, they are not always present. The tumours are positive for chloroacetate esterase.

Immunoprofile
Granulocytic sarcomas express lysozyme, myeloperoxidase, CD43 and CD68. Staining for CD45 may be seen, but the tumour cells are negative for CD20 and CD3.

Differential diagnosis
The most important differential diagnosis is malignant lymphoma. Enzyme histochemical stains for chloroacetate esterase or immunohistochemical stains for myeloperoxidase, CD68 and CD43 will establish the diagnosis in almost all cases (2099).

Prognosis and predictive factors
Granulocytic sarcoma of the vagina appears to behave in an aggressive fashion. Although experience is limited, the few reported granulocytic sarcomas of the vagina have also been treated with chemotherapy or radiation.

Secondary tumours
Definition
Tumours of the vagina that originate outside the vagina.

Incidence and origin
Metastatic tumours are more frequent than primary malignant tumours of the vagina. Tumours may spread by direct extension, most commonly from the cervix or vulva, vascular and lymphatic dissemination or by implantation. Metastatic adenocarcinomas originate from the endometrium, colon, rectum and, more rarely, the breast. Transitional cell carcinoma metastatic from the urethra and the bladder and renal cell carcinomas have been reported. In the past vaginal metastases were reported in up to 50% of cases of uterine choriocarcinoma.

Clinical features
The primary tumour is often clinically evident or has previously been treated. The most significant symptom is abnormal vaginal bleeding. Vaginal cytology may aid detection. A biopsy is contraindicated in metastatic trophoblastic disease due to the risk of excessive bleeding.
Squamous cell carcinoma of the vulva occurs predominantly in the older age group. Although the incidence rate of vulvar intraepithelial neoplasia is increasing, that of squamous cell carcinoma of the vulva is declining, reflecting earlier detection and more successful treatment. In addition to human papillomavirus infection, cigarette smoking is a putative risk factor for vulvar squamous cell carcinoma. There are three known precursor lesions: vulvar intraepithelial neoplasia, lichen sclerosis and chronic granulomatous disease.

Other important epithelial malignancies of the vulva are Paget disease and Bartholin gland carcinoma. They are much less common than squamous lesions, and the risk factors are largely unknown.

Prominent non-epithelial tumours are malignant melanoma and sarcoma botyoides.
WHO histological classification of tumours of the vulva

<table>
<thead>
<tr>
<th>Epithelial tumours</th>
<th>Tumours of skin appendage origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous and related tumours and precursors</td>
<td>Malignant sweat gland tumours</td>
</tr>
<tr>
<td>Squamous cell carcinoma, not otherwise specified 8070/3</td>
<td>Sebaceous carcinoma 8410/3</td>
</tr>
<tr>
<td>Keratinizing 8071/3</td>
<td>Syringoma 8407/0</td>
</tr>
<tr>
<td>Non-keratinizing 8072/3</td>
<td>Nodular hidradenoma 8402/0</td>
</tr>
<tr>
<td>Basaloid 8083/3</td>
<td>Trichoepithelioma 8100/0</td>
</tr>
<tr>
<td>Warty 8051/3</td>
<td>Trichilemmoma 8102/0</td>
</tr>
<tr>
<td>Verrucaus 8051/3</td>
<td>Others</td>
</tr>
<tr>
<td>Keratoacanthoma-like Variant with tumour giant cells</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma 8090/3</td>
<td></td>
</tr>
<tr>
<td>Squamous intraepithelial neoplasia</td>
<td></td>
</tr>
<tr>
<td>Vulvar intraepithelial neoplasia (VIN)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma in situ 8070/2</td>
<td></td>
</tr>
<tr>
<td>Benign squamous lesions</td>
<td></td>
</tr>
<tr>
<td>Condyloma acuminatum</td>
<td></td>
</tr>
<tr>
<td>Vestibular papilloma (micropapillomatosis) 8052/0</td>
<td></td>
</tr>
<tr>
<td>Fibroepithelial polyp</td>
<td></td>
</tr>
<tr>
<td>Seborrhoeic and inverted follicular keratosis</td>
<td></td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td></td>
</tr>
<tr>
<td>Glandular tumours</td>
<td></td>
</tr>
<tr>
<td>Paget disease 8542/3</td>
<td></td>
</tr>
<tr>
<td>Bartholin gland tumours</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma 8140/3</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma 8070/3</td>
<td></td>
</tr>
<tr>
<td>Adenoid cystic carcinoma 8200/3</td>
<td></td>
</tr>
<tr>
<td>Adenosquamous carcinoma 8560/3</td>
<td></td>
</tr>
<tr>
<td>Transitional cell carcinoma 8120/3</td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma 8041/3</td>
<td></td>
</tr>
<tr>
<td>Adenoma 8140/0</td>
<td></td>
</tr>
<tr>
<td>Adenomyoma 8932/0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Tumours arising from specialized anogenital mammary-like glands</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma of mammary gland type 8500/3</td>
<td></td>
</tr>
<tr>
<td>Papillary hidradenoma 8405/0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma of Skene gland origin 8140/3</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinomas of other types 8140/0</td>
<td></td>
</tr>
<tr>
<td>Adenoma of minor vestibular glands 8140/0</td>
<td></td>
</tr>
<tr>
<td>Mixed tumour of the vulva 8940/0</td>
<td></td>
</tr>
<tr>
<td>Soft tissue tumours</td>
<td></td>
</tr>
<tr>
<td>Sarcoma botryoides 8910/3</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma 8890/0</td>
<td></td>
</tr>
<tr>
<td>Proximal epithelioid sarcoma 8804/3</td>
<td></td>
</tr>
<tr>
<td>Alveolar soft part sarcoma 9581/3</td>
<td></td>
</tr>
<tr>
<td>Liposarcoma 8850/3</td>
<td></td>
</tr>
<tr>
<td>Dermatofibrosarcoma protubersans 8832/0</td>
<td></td>
</tr>
<tr>
<td>Deep angiomyxoma 8841/1</td>
<td></td>
</tr>
<tr>
<td>Superficial angiomyxoma 8841/0</td>
<td></td>
</tr>
<tr>
<td>Angiomyxofibroblastoma 8826/0</td>
<td></td>
</tr>
<tr>
<td>Cellular angiofibroma 9160/0</td>
<td></td>
</tr>
<tr>
<td>Leiomyoma 8830/0</td>
<td></td>
</tr>
<tr>
<td>Granular cell tumour 9580/0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Melanocytic tumours</td>
<td></td>
</tr>
<tr>
<td>Malignant melanoma 8720/3</td>
<td></td>
</tr>
<tr>
<td>Congenital melanocytic naevus 8761/0</td>
<td></td>
</tr>
<tr>
<td>Acquired melanocytic naevus 8720/0</td>
<td></td>
</tr>
<tr>
<td>Blue naevus 8780/3</td>
<td></td>
</tr>
<tr>
<td>Atypical melanocytic naevus of the genital type 8720/0</td>
<td></td>
</tr>
<tr>
<td>Dysplastic melanocytic naevus 8727/0</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous tumours</td>
<td></td>
</tr>
<tr>
<td>Yolk sac tumour 9071/3</td>
<td></td>
</tr>
<tr>
<td>Merkel cell tumour 8247/3</td>
<td></td>
</tr>
<tr>
<td>Peripheral primitive neuroectodermal tumour / Ewing tumour 9384/3</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Haematopoetic and lymphoid tumours</td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoma (specify type)</td>
<td></td>
</tr>
<tr>
<td>Leukaemia (specify type)</td>
<td></td>
</tr>
<tr>
<td>Secondary tumours</td>
<td></td>
</tr>
</tbody>
</table>

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

2. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are only available for lesions categorized as squamous intraepithelial neoplasia grade 3 (e.g. intraepithelial neoplasia/VIN grade 3 = 8077/2; squamous cell carcinoma in situ 8070/2).
TNM classification of carcinomas of the vulva

<table>
<thead>
<tr>
<th>TNM Classification</th>
<th>T – Primary Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (preinvasive carcinoma)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion no greater than 1 mm</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour confined to vulva or vulva and perineum, 2 cm or less in greatest dimension and with stromal invasion greater than 1 mm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined to vulva or vulva and perineum, more than 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades any of the following: lower urethra, vagina, anus</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades any of the following: bladder mucosa, rectal mucosa, upper urethra; or is fixed to pubic bone</td>
</tr>
</tbody>
</table>

Note: The depth of invasion is defined as the measurement of the tumour from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

| N – Regional Lymph Node s’ | | |
|-----------------------------|-----------------------------|
| NX                          | Regional lymph nodes cannot be assessed |
| N0                          | No regional lymph node metastasis |
| N1                          | Unilateral regional lymph node metastasis |
| N2                          | Bilateral regional lymph node metastasis |

<table>
<thead>
<tr>
<th>M – Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
</tr>
<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage Grouping (TNM and FIGO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
</tr>
<tr>
<td>Stage I</td>
</tr>
<tr>
<td>Stage IA</td>
</tr>
<tr>
<td>Stage IB</td>
</tr>
<tr>
<td>Stage II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Stage IVA</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Stage IVB</td>
</tr>
</tbody>
</table>

1. [B1,29,28].
3. The regional lymph nodes are the femoral and inguinal nodes.
Epithelial tumours

Squamous tumours

Definition
Malignant or benign epithelial tumours composed primarily of squamous cells.

ICD-O codes

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Keratinizing</td>
<td>8071/3</td>
</tr>
<tr>
<td>Non-keratinizing</td>
<td>8072/3</td>
</tr>
<tr>
<td>Basaloid</td>
<td>8083/3</td>
</tr>
<tr>
<td>Warty</td>
<td>8051/3</td>
</tr>
<tr>
<td>Verrucous</td>
<td>8051/3</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>8090/3</td>
</tr>
</tbody>
</table>

Squamous cell carcinoma

Definition
An invasive carcinoma composed of squamous cells of varying degrees of differentiation.

Epidemiology

Squamous cell carcinoma is the most common malignant tumour of the vulva. Primary squamous cell carcinoma of the vulva occurs more frequently in the older age group; the reported incidence rates are 1:100,000 in younger women and 20 in 100,000 in the elderly (2804).

Table 7.01
Currently recognized precursors of vulvar squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Precursor Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvar intraepithelial neoplasia (VIN), grade 3</td>
<td>8077/2</td>
</tr>
<tr>
<td>squamous cell carcinoma in situ</td>
<td>8070/2</td>
</tr>
<tr>
<td>Vestibular papilloma</td>
<td>8052/0</td>
</tr>
</tbody>
</table>

Aetiology

In addition to human papillomavirus (HPV), cigarette smoking is a risk factor for vulvar carcinoma (611). However, the specific aetiology of most vulvar epithelial tumours is unknown. The carcinomas associated with HPV include warty and basaloid carcinomas with the corresponding intraepithelial precursor lesions [584,1106,1541,2180,2936]. Verrucous carcinoma is associated with HPV, usually of type 6 or 11. In some cases there is no recognized precursor lesion. Squamous cell hyperplasia per se is apparently not a precursor of vulvar squamous cell carcinoma (1461).

There are currently four recognized precursors of vulvar carcinoma (See table 7.1). Vulvar intraepithelial neoplasia (VIN) of the simplex (differentiated) type is usually associated with lichen sclerosus. The latter is also considered to be a precursor of keratinizing squamous cell carcinoma and is not HPV associated (3175). In the retrospective evaluation of vulvectomy specimens from women with vulvar squamous cell carcinoma, the frequency of identifying associated lichen sclerosus ranges from 15-40%, the higher rate being observed in deeply invasive carcinomas (403,1621,3240). The lifetime risk of squamous cell carcinoma arising in vulvar lichen sclerosus is unknown but may exceed 6% (403,1621,1824,2369,2606). The squamous cell carcinomas associated with lichen sclerosus involving the vulva are usually of the keratinizing type.

Localization

Vulvar squamous cell carcinoma is usually solitary and is found most commonly on the labia minora or majora; the clitoris is the primary site in approximately 10% of cases.

Clinical features

Signs and symptoms

Squamous cell carcinoma may present as an ulcer, nodule, macule or pedunculated mass. Symptoms may be similar to those seen with VIN, although in more advanced cases discharge, bleeding, pain, odour or self-palpation of a mass may bring the patient to the physician.

Imaging

Imaging studies are generally not applicable for the detection of vulvar tumours. When the regional lymph nodes are clinically suspicious, imaging studies, including computed tomography or magnetic resonance, are employed, where available, to evaluate pelvic and para-aortic lymph nodes. Dye and technetium-99m labelled colloid have been used to detect inguino-femoral sentinel lymph nodes (646).

Colposcopy

Colposcopic examination employing topically applied 3% acetic acid to enhance visualization of lesions and photographic recording of vulvar lesions may be of value in clinical management and follow-up (3124).

Exfoliative and aspiration cytology

Although exfoliative cytology has been applied to the evaluation of primary tumours of the vulva, this practice is not commonly used, and directed biopsy of identified lesions is the most effective method of primary diagnosis. Fine needle aspiration cytology is of value in assessing suspicious lymph nodes or subcutaneous nodules (1283).

Macroscopy

Most vulvar squamous carcinomas are solitary. The tumours may be nodular, verruciform or ulcerated with raised firm edges.

Tumour spread and staging

The staging of vulvar tumours is by the TNM/FIGO classification (51,2976). Superficially invasive vulvar carcinoma, stage 1A as defined by FIGO, is a single focus of squamous cell carcinoma having a diameter of 2 cm or less and a depth of invasion of 1 mm or less. The definition includes cases that have capillary-like space involvement by tumour. The term “microinvasive carcinoma” is not recommended.
Squamous cell carcinoma is an invasive neoplasm composed of squamous cells of varying degrees of differentiation. Several morphological variants have been described:

**Keratinizing**
Keratinizing squamous cell carcinoma contains keratin pearls.

**Non-keratinizing**
Non-keratinizing squamous cell carcinoma does not form appreciable keratin; it may contain small numbers of individually keratinized cells but lacks keratin pearls. Rarely, the tumour is composed predominantly of spindle-shaped cells (2529). In some cases the carcinoma may have a sarcoma-like stroma (2778).

**Basaloid**
Basaloid squamous cell carcinoma is composed of nests of immature, basal type squamous cells with scanty cytoplasm that resemble closely the cells of squamous carcinoma in situ of the cervix. Some keratinization may be evident in the centres of the nests, but keratin pearls are rarely present. This tumour may be associated with HPV infections, predominantly type 16 (1541, 2936).

**Warty**
Warty (condylomatous) squamous cell carcinoma has a warty surface and cellular features of HPV infection (720, 1541, 2936).

**Verrucous**
Verrucous carcinoma is a highly differentiated squamous cell carcinoma that has a hyperkeratinized, undulating, warty surface and invades the underlying stroma in the form of bulbous pegs with a pushing border. Verrucous carcinoma accounts for 1-2% of all vulvar carcinomas and has little or no metastatic potential. The cellular features include minimal nuclear atypia and abundant eosinophilic cytoplasm. Mitotic figures are rare and, when present, are typical. There is usually a prominent chronic inflammatory cell infiltrate in the stroma. HPV, especially type 6, has been identified in a number of cases. Giant condyloma (Buschke-Lowenstein tumour) is considered by some to be synonymous with verrucous carcinoma (100, 348, 1336, 1501).

**Variant with tumour giant cells**
Squamous cell carcinoma with a prominent tumour giant cell component is a highly aggressive neoplasm that can be confused with malignant melanoma (3122).

**Tumour measurements**
It is recommended that the following features should be included in the pathology report (2601, 3119):
1. Depth of invasion (mm).
2. Tumour thickness.
3. Method of measurement of depth of invasion and thickness of the tumour.
4. Presence or absence of vascular space involvement by tumour.
5. Diameter of the tumour, including the clinically measured diameter, if available.

In the event that invasion is equivocal growing but are usually self-limited. Histologically, they consist of a central crater filled with a glassy squamous epithelial proliferation in which horny masses of keratin are pushed upward, while tongues of squamous epithelium invade the dermis. Metastasis of so-called keratoacanthoma has been described (1227). Complete excision with a clear histological margin is the recommended treatment.
even with additional sectioning, it is recommended that invasion should not be diagnosed [3119].

The following criteria apply to the measurement of vulvar squamous cell carcinoma:

1. **Thickness:** measurement from the surface, or the granular layer if keratinized, to the deepest point of invasion.
2. **Depth of invasion:** measurement from the epithelial-stromal junction of the adjacent most superficial dermal papillae to the deepest point of invasion.

The preferred measurement is the depth of invasion, as defined above.

### Somatic genetics

Cytogenetic data exist on 11 squamous cell carcinomas of the vulva [2897,3156]. The most common karyotypic changes are loss of 3p, 8p, 22q, Xp, 10q and 18q and gain of 3q and 11q21. There is an inverse correlation between histological differentiation and karyotypic complexity. Furthermore, a comparative genomic hybridization study of 10 cases revealed losses of 4p, 3p, and 5q and gains of 3q and 8p [1338]. Loss of 10q and 18q seems to be particularly associated with a poor prognosis in squamous cell carcinoma [2897,3156]. For patients with stage 1A carcinoma, the therapy is usually local excision with at least a 1-cm margin of normal tissue [2818].

TP53 mutation or HPV can independently lead to cell cycle disruption relevant to vulvar squamous cell carcinogenesis. Besides mutational inactivation, TP53 can be inactivated through binding of HPV protein E6. PTEN is another gene that is frequently mutated in carcinomas of the vulva [1234]. Both TP53 and PTEN mutations have also been detected in VIN, indicating that they are early events in vulvar carcinogenesis [1234,1866].

High frequencies of allelic imbalance have been detected at 1q, 2q, 3p, 5q, 8p, 8q, 10p, 10q, 11q, 15q, 17p, 18q, 21q and 22q, most of these irrespective of HPV status [2256]. This finding suggests that despite a different pathogenesis both HPV-positive and HPV-negative vulvar squamous cell carcinomas share several genetic changes during their progression.

### Prognosis and predictive factors

Risk factors for recurrence include advanced stage, tumour diameter >2.5 cm, multifocality, capillary-like space involvement, associated VIN 2 or VIN 3 and involved margins of resection [1235,2004]. The extent of lymph node involvement and mode of treatment may also influence survival [721]. Patients whose tumours have a "spray" or finger-like pattern of invasion have a poorer survival than those with a "pushing" pattern [1235].

For patients with stage 1A carcinoma, the therapy is usually local excision with at least a 1-cm margin of normal tissue [3, 1428]. Inguinofemoral lymph node dissection is usually unnecessary [247,373,374,1105,1428]. The risk of recurrence in stage 1A cases is very low, with 5 and 10-year recurrence-free tumour specific survivals of 100% and 94.7%, respectively [1732]. Late recurrence or "reoccurrence" of a second squamous carcinoma in another site within the vulva is rare but can occur, and therefore long-term follow-up is warranted.

For tumours greater than stage 1A partial or total deep vulvectomy with ipsilateral or bilateral inguino-femoral lymph node resection may be required. If superficial lymph nodes contain tumour, radiotherapy to the deep pelvic nodes or chemoradiation may be necessary [360,373,1749,2783].

### Basal cell carcinoma

#### Definition

An infiltrating tumour composed predominately of cells resembling the basal cells of the epidermis.

#### Clinical features

This tumour presents as a slow growing, locally invasive, but rarely metastasizing lesion in the vulva [218,833,1872,2260].
Epithelial tumours

Histopathology

The tumour is composed of aggregates of uniform basal cells with peripheral palisading. Squamous cell differentiation may occur at the centre of the tumour nests. Tumours containing gland-like structures are referred to as "adenoid basal cell carcinoma" (1850). Those containing infiltrating malignant-appearing squamous cells may be diagnosed as metatypical basal cell carcinoma or basosquamous carcinoma. Immunohistochemical findings reflect these histological subtypes (183). Basal cell carcinoma has been reported in association with vulvar Paget disease (1084).

Histogenesis

This tumour is derived from the basal cells of the epidermis or hair follicles.

Prognosis and predictive factors

Basal cell carcinoma of the vulva is usually treated by local excision; however, groin metastases have been reported (1017).

Vulvar intraepithelial neoplasia

Definition

An intraepithelial lesion of the vulvar squamous epithelium characterized by disordered maturation and nuclear abnormalities, i.e. loss of polarity, pleomorphism, coarse chromatin, irregularities of the nuclear membrane and mitotic figures, including atypical forms.

Synonym

Dysplasia/carcinoma in situ.

Epidemiology

The incidence of VIN, unlike that of vulvar carcinoma, has been increasing over the past 20 years, especially in women of reproductive age, with the highest frequency reported in women 20-35 years old (538,1312,2804).

Aetiology

VIN is predominately of the warty or basaloïd types, and both are associated with HPV, most commonly type 16 (1106, 1197,1663,2936). Women with HPV-related vulvar disease have an increased risk of associated cervical intraepithelial neoplasia (CIN) (2766). Women infected with human immunodeficiency virus (HIV) have a high frequency of HPV infection of the lower genital tract and associated CIN and/or VIN (2766).

Clinical features

Women with VIN may present with vulvar pruritus or irritation or may observe the lesions and seek medical assistance (919). VIN is typically a macular or papular lesion or lesions, which in approximately one-half of the cases are white or aceto-white. Approximately one-quarter of VIN lesions are pigmented. VIN is multifocal in approximately two-thirds of the cases. The remaining patients usually present as a solitary lesion, a more common finding in older women (431). Large confluent lesions are uncommon (919, 3123).

Tumour spread and staging

Up to one-fifth of the women presenting with VIN are found to have an associated squamous cell carcinoma (431,1197,1272). In most cases these squamous cell carcinomas are superficially invasive.

Histopathology

The epithelial cells are typically crowded, and acanthosis may be present. A prominent granular layer may be associated with parakeratosis, hyperkeratosis or both. Involvement of skin appendages is seen in over one-third of the cases, which in hairy skin may be as deep as 2.7 mm. Skin appendage involvement should not be misinterpreted as invasion (219,2636). There may be associated HPV changes. The term "bowenoid papulosis" should not be used as a histological diagnosis (see below). The grading of HPV-related VIN is similar to that used in the cervix. The simplex type of VIN (carcinoma in situ, simplex

Vulvar intraepithelial neoplasia, differentiated (simplex) type. The atypia is confined to the basal and parabasal layers. The epithelial cells are crowded and show minimal maturation. C VIN 3 (carcinoma in situ, basaloïd type). Nearly the entire epithelium is composed of closely packed basaloïd cells.
is a highly differentiated lesion resembling well differentiated squamous cell carcinoma in which the atypia is most prominent in or confined to the basal and parabasal layers of the epithelium, where the cells have abundant cytoplasm and form pearls and the nuclei are relatively uniform in size and contain coarse chromatin and prominent nucleoli [3175].

**Somatic genetics**

The only cytogenetically analysed case of VIN 3 (squamous cell carcinoma in situ) of the vulva had a rearrangement of 11p as the sole anomaly [2818]. Genomic deletions have been demonstrated in the simplex (differentiated) form of VIN and its subsequent squamous carcinoma unrelated to HPV infection [1663]. These also express TP53 [1824,3175].

**Prognosis and predictive factors**

VIN is usually treated by local excision. Laser or other ablative procedure may also have a role [1197,1369,3124]. Spontaneous regression of VIN 2 and 3 in younger women with papular pigmentated lesions is recognized, and such lesions are referred to clinically as Bowenoid papulosis by some investigators [1369]. The recurrence of VIN is well recognized, especially in women who are heavy cigarette smokers or positive for HIV.

**Condyloma acuminatum**

**Definition**

A benign neoplasm characterized by papillary fronds containing fibrovascular cores and lined by stratified squamous epithelium with evidence of HPV infection, usually in the form of koilocytosis.

**Tumour spread and staging**

Co-infection of the vulva and cervix is well recognized [1528]. Vulvar carcinoma in young women has been associated with genital condyloma [2945].

**Histopathology**

The lesions are typically multiple and papilomatous or papular. The epithelium is acanthotic with parabasal hyperplasia and koilocytosis in the upper portion. Hyperkeratosis and parakeratosis are usual, and binucleated and multinucleated keratinocytes are often present. The rete ridges are elongated and thickened. A chronic inflammatory infiltrate is usually present within the underlying connective tissue. HPV infection in the vulvar epithelium is expressed in three broad categories: (1) Fully expressed, with morphological features of HPV infection, as seen in condyloma acuminatum (2) Minimally expressed, with only mild morphological changes, e.g. koilocytosis (3) Latent, in which no characteristic morphological changes are seen, although HPV can be detected with the use of molecular techniques [1013].

**Vestibular papilloma**

**Definition**

A benign papillary tumour with a squamous epithelial mucosal surface that overlies a delicate fibrovascular stalk.

**Synonyms**

Micropapillomatosis labialis, vestibular micropapillomatosis. These terms are applicable when numerous lesions are present.

**Clinical features**

The lesions may be solitary but frequently are multiple, often occurring in clusters near the hymenal ring, resulting in a condition referred to as vestibular papillomatosis or micropapillomatosis or micropapillomatosis labialis [238,644,980,1930,2277]. They are less than 6 mm in height. Unlike condylomas, they do not typically respond to podophyllin and/or interferon [2277].

**Histopathology**

These lesions have papillary architecture and a smooth surface without acanthosis or koilocytic atypia. They lack the complex arborizing architecture of condyloma.

**Aetiology**

The great majority of studies of vestibular micropapillomatosis as defined above have demonstrated no relationship of these lesions to HPV [238,644,1856,2118,2277].

**Fibroepithelial polyp**

**Definition**

A polypoid lesion covered by squamous epithelium and containing a central core of fibrous tissue in which stellate cells with tapering cytoplasmic processes and
Epithelial tumours

irregularly shaped thin-walled vessels are prominent features.

Histopathology
These polyoid lesions are characterized by a prominent fibrovascular stroma covered by squamous epithelium without evidence of koilocytes. In contrast to vulvar condylomas, fibroepithelial polyps do not show epithelial acanthosis or papillary architecture. Bizarre stromal cells have been described in these polyps that do not influence behaviour (416).

Aetiology
In contrast to condylomas, fibroepithelial polyps appear unrelated to HPV infection and rarely contain HPV nucleic acids (1837).

Prognosis and predictive factors
Although benign, the lesion may recur if incompletely excised (2141).

Seborrheic keratosis and inverted follicular keratosis

Definition
A benign tumour characterized by proliferation of the basal cells of the squamous epithelium with acanthosis, hyperkeratosis and the formation of keratin-filled pseudohorn cysts. Some cases may have an incidental HPV infection (3263). Inverted follicular keratosis is a seborrheic keratosis of follicular origin and contains prominent squamous eddies. An inverted follicular keratosis of the vulva has been reported that may have been related to close shaving (2467).

Keratoacanthoma
This rare squamoproliferative lesion commonly occurs on sun-exposed skin. It is thought to arise from follicular epithelium and was originally considered to be benign. It has a central keratin-filled crater and focal infiltration at its dermal interface. In some instances the lesion regresses spontaneously (2361). Two cases have been described in the vulva (997). At present the lesion originally described as keratoacanthoma is generally accepted as a well differentiated squamous cell carcinoma, keratoacanthoma type (1227), and the latter diagnosis is recommended (see section on squamous cell carcinoma).

Vulvar Paget disease

Definition
An intraepithelial neoplasm of cutaneous origin expressing apocrine or eccrine glandular-like features and characterized by distinctive large cells with prominent cytoplasm referred to as Paget cells. It may also be derived from an underlying skin appendage adenocarcinoma or anorectal or urothelial carcinoma (3121).

Epidemiology
Primary cutaneous Paget disease is an uncommon neoplasm, usually of postmenopausal White women. In approximately 10-20% of women with vulvar Paget disease, there is an invasive component or an underlying skin appendage adenocarcinoma (825,3121).

Clinical features
Paget disease typically presents as a symptomatic red, eczematoid lesion that may clinically resemble a dermatosis (1028,3121,3267). Paget disease that is related to anorectal adenocarcinoma

Glandular tumours

ICD-O codes
Paget disease 8542/3
Bartholin gland tumours
Adenocarcinoma 8140/3
Squamous cell carcinoma 8070/3
Adenoid cystic carcinoma 8200/3
Adenosquamous carcinoma 8560/3
Small cell carcinoma 8041/3
Transitional cell carcinoma 8120/3
Adenoma 8140/0
Adenomyoma 8932/0
Papillary hidradenoma 8405/0
Adenocarcinoma of Skene gland origin 8140/3
Adenoma of minor vestibular glands 8140/0
Mixed tumour of the vulva 8940/0

Vulvar Paget disease

Definition
An intraepithelial neoplasm of cutaneous origin expressing apocrine or eccrine glandular-like features and characterized by distinctive large cells with prominent cytoplasm referred to as Paget cells. It may also be derived from an underlying skin appendage adenocarcinoma or anorectal or urothelial carcinoma (3121).

Epidemiology
Primary cutaneous Paget disease is an uncommon neoplasm, usually of postmenopausal White women. In approximately 10-20% of women with vulvar Paget disease, there is an invasive component or an underlying skin appendage adenocarcinoma (825,3121).

Clinical features
Paget disease typically presents as a symptomatic red, eczematoid lesion that may clinically resemble a dermatosis (1028,3121,3267). Paget disease that is related to anorectal adenocarcinoma
clinically involves the perianal mucosa and skin, as well as the adjacent vulva.

Histopathology
The Paget cell of cutaneous origin is typically a large, round cell with a large nucleus and prominent nucleolus. The cytoplasm is pale on routine hematoxylin and eosin stain, is often vacuolated and stains with mucicarmine. The cytoplasm contains PAS-positive material that is resistant to diastase. The Paget cells may also express CA125 and Her-2/neu but do not express estrogen receptor (573,3119,3121).

Paget disease that is related to urothelial origin. Clusters of large pale cells resembling transitional cell carcinoma involve predominantly the parabasal area of the epidermis with sparing of the basal layer.

Clinical features
Bartholin gland carcinoma occurs predominantly in women over 50 years of age and presents as an enlargement in the Bartholin gland area that may clinically resemble a Bartholin duct cyst.

Tumour spread and staging
Approximately 20% of cases are associated with ipsilateral inguinofemoral lymph node metastases at presentation [556,1634,3108].

Histopathology
The tumour is typically solid and deeply infiltrative. A transition from an adjacent Bartholin gland to tumour is of value in identifying its origin. Various types of carcinoma have been described.

Adenocarcinoma
Adenocarcinoma accounts for approximately 40% of Bartholin gland tumours [556,1634]. Adenocarcinomas may be mucinous, papillary or mucoepidermoid in type. They are usually carcinoembryonic antigen immunoreactive.

Squamous cell carcinoma
This tumour accounts for approximately 40% of Bartholin gland tumours and is composed of neoplastic squamous cells.

Adenoid cystic carcinoma
Adenoid cystic carcinoma accounts for approximately 15% of Bartholin gland tumours [556,675]. It is composed typically of rounded islands of uniform malignant epithelial cells with a cribriform pattern. A hyaline stroma may form cylinders separating rows of tumour cells. The intraluminal material is basement membrane-like rather than a secretion, supporting a squamous rather than glandular origin.

The cytogenetic analysis of an adenoid cystic carcinoma of Bartholin gland revealed a complex karyotype involving chromosomes 1, 4, 6, 11, 14 and 22 [1457].

Adenosquamous carcinoma
Adenosquamous carcinoma accounts for approximately 5% of Bartholin gland tumours. It is composed of neoplastic mucin-containing glandular and neoplastic squamous cells.

Transitional cell carcinoma
Transitional cell carcinoma is a rare tumour of Bartholin gland composed of
neoplastic urothelial-type cells, occasionally with a minor component of glandular or squamous cells.

**Small cell carcinoma**
This rare highly malignant neoplasm is composed of small neuroendocrine cells with scant cytoplasm and numerous mitotic figures [1361].

**Benign neoplasms of Bartholin gland**

**Adenoma and adenomyoma**
Bartholin gland adenoma is a rare benign tumour of Bartholin gland characterized by small clustered closely packed glands and tubules lined by columnar to cuboidal epithelium with colloid-like secretion arranged in a lobular pattern and contiguous with identifiable Bartholin gland elements. Bartholin gland adenoma has been reported in association with adenoid cystic carcinoma [1487]. Bartholin gland nodular hyperplasia can be distinguished from adenoma by the preservation of the normal duct-acinar relationships present in hyperplasia. Bartholin gland adenomyoma has a fibromuscular stromal element that is immunoreactive for smooth muscle actin and desmin as well as a lobular glandular architecture with glands lined by columnar mucin-secreting epithelial cells adjacent to tubules [1487].

**Tumours arising from specialized anogenital mammary-like glands**

**Definition**
Malignant and benign tumours, usually of glandular type and resembling neoplasms of the breast, may arise in specialized anogenital mammary-like glands. These glands and the tumours that arise from them are usually identified in or adjacent to the intralabial sulcus. Adenocarcinoma with morphological features of breast carcinoma has been reported as a primary vulvar tumour [687]. Such tumours are currently thought to arise from the specialized anogenital glands and not from ectopic breast tissue [2991,2992]. The papillary hidradenoma is an example of a benign neoplasm [2991,2992]. Intraductal adenocarcinoma of mammary-type within a hidradenoma has been reported [2212].

**Papillary hidradenoma**

**Definition**
A benign tumour composed of epithelial secretory cells and underlying myoepithelial cells lining complex branching papillae with delicate fibrovascular stalks.

**Epidemiology**
This tumour is rare in the vulva but is the most common benign glandular neoplasm at this site.

**Clinical features**
It usually presents as an asymptomatic mass within or adjacent to the intralabial sulcus and may cause bleeding resembling carcinoma if the gland prolapses and/or ulcerates.

**Histopathology**
The tumour is distinctly circumscribed and composed of complex papillae and

---

**Table 7.02**
Immunohistochemical findings of Paget disease.

<table>
<thead>
<tr>
<th>Type of Paget disease</th>
<th>CK-7</th>
<th>CK 20</th>
<th>GCDFP-15</th>
<th>CEA</th>
<th>UP-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary skin neoplasm</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Related to anorectal carcinoma</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Related to urothelial carcinoma</td>
<td>+</td>
<td>[+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Abbreviations for antibodies used as follows:**
CK = cytokeratin; CEA = carcinoembryonic antigen; GCDFP-15 = gross cystic disease fluid protein-15; UP-III = uroplakin III [2088,3121].

---

![Fig. 7.11 Paget disease of the vulva. Note the red, eczematous appearance.](image)

![Fig. 7.12 Bartholin gland neoplasms. A Squamous cell carcinoma. Aggregates of neoplastic squamous cells infiltrate Bartholin gland seen on the left. B Adenoid cystic carcinoma. Note the cribriform pattern with the lumens containing basophilic mucin. C Bartholin gland adenoma. A nodule is composed of clustered glands lined by mucinous epithelium.](image)
glandular elements surrounded by fibrous tissue. Relatively uniform columnar epithelial secretory cells with underlying myoepithelial cells cover the glands and papillary stalks. **Adenocarcinoma of Skene gland origin**

An adenocarcinoma of Skene gland with associated metastasis has been reported [2726]. Skene gland is the female homologue of the male prostate, and the tumour expresses prostate antigens by immunohistochemistry [2726]. A carcinoma of Skene duct origin was associated with systemic coagulopathy [2895].

**Adenocarcinomas of other types**

These tumours may arise from endometriosis or ectopic cloacal tissue [307,3126,3237].

**Adenoma of minor vestibular glands**

Adenoma of minor vestibular glands is a rare benign tumour composed of clusters of small glands lined by mucin-secreting columnar epithelial cells arranged in a lobular pattern without intervening Bartholin duct elements. It is usually an incidental finding measuring 1-2 mm in diameter, although one example was as large as 10 mm. Nodular hyperplasia of the minor vestibular glands may also occur [141,2295].

**Mixed tumour of the vulva**

**Definition**

A benign epithelial tumour composed of epithelial cells arranged in tubules or nests mixed with a fibrous stromal component that may include chondroid, osseous and myxoid elements. **Synonyms**

Pleomorphic adenoma, chondroid syringoma.

**Clinical features**

Mixed tumour of the vulva usually presents as a subcutaneous nodule involving the labum majus and/or the Bartholin gland area.

**Histopathology**

The histological features are similar to those of mixed tumours of salivary glands. The tumour with its stromal-like elements is believed to arise from pluripotential myoepithelial cells that are present in Bartholin gland, sweat glands and the specialized anogenital (mammary-like) glands of the vulva [2410].

**Prognosis and predictive factors**

Although these tumours are considered benign, insufficient cases of vulvar mixed tumours have been reported to determine their natural history at this site. The tumour may recur locally. A carcinoma arising in a mixed tumour has been described [2117]. Complete local excision with free margins is the recommended therapy for the primary tumour as well as for local recurrences.

**Tumours of skin appendage origin**

**Definition**

Benign or malignant tumours differentiating towards hair follicles or sweat or sebaceous glands.

**ICD-O codes**

- Malignant sweat gland tumour 8400/3
- Sebaceous carcinoma 8410/3
- Syringoma 8407/0
- Nodular hidradenoma 8402/0
- Trichoepithelioma 8100/0
- Trichilemmoma 8102/0

**Malignant sweat gland tumours**

Vulvar malignant sweat gland tumours include eccrine adenocarcinoma, porocarcinoma, clear cell hidradenocarcinoma, and apocrine adenocarcinoma, the last of which may be associated with Paget disease [3112].

**Sebaceous carcinoma**

Vulvar sebaceous carcinoma resembles its cutaneous counterpart. It is a malignant tumour composed of cords and nests of basalkid appearing neoplastic glandular elements with cellular features of sebaceous epithelium. The tumour may be associated with neoplastic sebaceous cells present in pagetoid nests within the parabasal component of the overlying epithelium and in larger clusters near the epithelial surface [405,795]. Sebaceous carcinoma of the vulva may be associated with VIN [1318].
**Syringoma**

**Definition**
A benign epithelial tumour believed to arise from eccrine ducts that is composed of small and relatively uniform epithelial-lined tubules and cysts within a densely fibrous dermis.

**Clinical findings**
It presents as asymptomatic or pruritic papules that are small, clustered and non-pigmented and involve the deeper skin layers of the labia majora. The nodules are often bilateral.

**Histopathology**
Histologically, small epithelial cysts and dilated duct-like spaces lined by two rows of cells, an inner epithelial and an outer myoepithelial, are seen. The ductular structures typically form comma-like shapes. The tumour lacks a clearly defined capsule or margin; the dermis surrounding the neoplastic ducts has a fibrotic appearance.

**Nodular hidradenoma**

**Definition**
Nodular hidradenoma is an infrequent benign tumour of sweat gland origin composed of epithelial cells with clear cytoplasm arranged in lobules and nests.

**Synonym**
Clear cell hidradenoma.

**Histopathology**
It is composed of epithelial cells with clear cytoplasm arranged in lobules and nests.

**Prognosis and predictive factors**
Complete local excision is considered adequate therapy.

**Trichoepithelioma**

**Definition**
A benign tumour composed of complex interconnected nests of basaloid cells that form small “horn cysts” (cysts containing keratin).

**Clinical features**
On clinical examination single or multiple cutaneous nodules with overlying skin abnormalities are identified.

**Histopathology**
Nests of cells form small keratin-containing cysts. The neoplastic epithelial cells are monomorphic without nuclear hyperchromasia or atypia. The tumour has a defined dermal interface and lacks an infiltrative appearance. Rupture of the keratin-containing cysts may result in a granulomatous reaction with foreign body giant cells. Hair follicles may be identified in some cases.

**Histogenesis**
The tumour is considered to be of follicular origin.

**Prognosis and predictive factors**
The treatment is complete local excision.

**Trichilemmoma**

**Definition**
A benign epithelial tumour composed of relatively uniform epithelial cells with pale-staining cytoplasm that may have some nuclear pleomorphism. It is thought to arise from the proliferation of outer root sheath epithelial cells of the hair follicle.

**Synonym**
Proliferating trichilemmal tumour.

**Clinical findings**
Clinically, these tumours have been reported in the dermis of the labium majus, presenting as a slow-growing solid mass.

**Histopathology**
The tumour has a lobulated appearance with a dermal pushing border that may show no connection with the overlying epithelium. The cells show peripheral palisading and increased clear cytoplasm as they stratify toward the centre. Amorphous keratin is present in the lumens, although no granular layer is formed. Calcification may occur.

**Uncommon vulvar skin appendage tumours**

Proliferating trichilemmal cysts (pillar tumours), trichoblastic fibroma and apocrine cystadenoma have been described on the vulva. A local excision is therapeutic.
Mesenchymal tumours

Definition
A variety of benign and malignant soft tissue tumours that occur in the vulva.

Malignant soft tissue tumours

Definition
Malignant soft tissue tumours that arise in the vulva.

ICD-O codes
- Sarcoma botryoides 8910/3
- Leiomyosarcoma 8890/3
- Proximal-type epithelioid sarcoma 8804/3
- Alveolar soft part sarcoma 9581/3
- Liposarcoma 8850/3
- Dermatofibrosarcoma protuberans 8832/3

Sarcoma botryoides

Definition
A malignant neoplasm exhibiting striated muscle differentiation that occurs almost exclusively in children younger than 10 years of age [555,558,2002].

Synonym
Embryonal rhabdomyosarcoma.

Clinical features
In girls the neoplasm typically arises from the labial or perineal area and presents with bleeding and ulceration. The neoplasm usually presents as a solid vulvar mass; the distinctive “bunch of grapes” appearance is more characteristic of vaginal primaries.

Tumour spread and staging
When both the vulva and vagina are involved, the tumour is regarded as vaginal for staging purposes.

Histopathology
For the typical histological features of sarcoma botryoides see the chapter on the vagina. Vulvar rhabdomyosarcoma sometimes exhibits an alveolar pattern, usually a focal finding, but occasionally diffuse. In this pattern tumour cells grow in loosely cohesive nests separated by fibrous septa. Towards the centre of the nests, the cells show loss of cohesion and float freely within a space, whilst the cells at the periphery are adherent to the septa, a pattern that simulates pulmonary alveoli. The tumour cell cytoplasm stains with a variety of muscle markers including actin, myosin, desmin, myogenin and myoD-1.

Prognosis and predictive factors
The prognosis depends both upon the clinical stage and the histological type (99). An alveolar histology, even when focal, is an unfavourable prognostic feature, whereas classic botryoid embryonal rhabdomyosarcoma is associated with a greater than 90% survival [558].

Leiomyosarcoma

Definition
A rare malignant neoplasm showing smooth muscle differentiation.

Clinical features
These neoplasms occur in adults in any part of the vulva and present as a rapidly enlarging mass, sometimes with pain.

Histopathology
Most reported cases are high grade neoplasms with the usual features of necrosis, infiltrative margins, cytological atypia and mitotic indices in excess of 10 mitotic figures per 10 high power fields. Problematic tumours are those with no necrosis and a low mitotic index [2880].

Differential diagnosis
Leiomyosarcoma should be differentiated from postoperative spindle cell nodule [1397]. The latter is mitotically active and may infiltrate the underlying tissue. The distinction from leiomyosarcoma or other malignant spindle cell tumours depends to a large extent on the history of a recent operation at the same site [1762].

Proximal-type epithelioid sarcoma

Definition
A malignant tumour histologically similar to epithelioid sarcoma of soft parts.
**Synonym**
Malignant rhabdoid tumour, adult type.

**Histopathology**
This tumour, which has histological and immunological features similar to epithelioid sarcoma of the extremities, has a predilection for the vulva (1078). The growth pattern is frequently nodular, and the tumour cells are large with abundant amphophilic cytoplasm. The nuclei are either large and pleomorphic with small nucleoli or vesicular with prominent nucleoli. Keratin and vimentin stains are positive in essentially all tumours, and CD34 is positive in approximately one-half of the cases.

**Prognosis and predictive factors**
Frequent recurrences and a high incidence of metastasis mark the clinical course.

**Alveolar soft part sarcoma**

**Definition**
A sarcoma characterized by solid and alveolar groups of large epithelial-like cells with granular, eosinophilic cytoplasm.

**Histopathology**
The rare cases of alveolar soft part sarcoma reported in the vulva have the same distinctive histology as those neoplasms occurring in more conventional soft tissue locations (2639). The tumour is composed of large uniform cells with abundant granular to vacuolated eosinophilic cytoplasm; the cells are compartmentalized into packets by thin-walled often sinusoidal vessels. Most of the tumours contain characteristic intracytoplasmic PAS-positive, diastase resistant, rod-shaped crystals.

**Liposarcoma**
Liposarcomas are extremely rare in this location (354,2062). Both atypical lipomatous tumours (well differentiated liposarcomas) and myxoid liposarcomas have been reported.

**Dermatofibrosarcoma protuberans**
Dermatofibrosarcoma protuberans is a highly recurrent low grade cutaneous sarcoma that is usually located on the trunk. Although rare, more than 10 cases have been reported in the vulva, and in one such case a supernumerary ring chromosome with the characteristic COL1A1/PDGFB fusion gene was found (3004).

**Benign soft tissue tumours**

**Definition**
Benign soft tissue tumours that arise in the vulva.

**ICD-O codes**
- Deep angiomyxoma 8841/1
- Superficial angiomyxoma 8841/0
- Angiomyofibroblastoma 8826/0
- Cellular angiofibroma 9160/0
- Leiomyoma 8890/0
- Granular cell tumour 9580/0

---

**Fig. 7.16** Epithelioid sarcoma of the vulva. A The tumour forms a multinodular mass beneath the skin with areas of haemorrhage. B The neoplasm is composed of large epithelioid cells with pleomorphic nuclei, prominent nucleoli and frequent mitotic figures.

**Fig. 7.17** Deep angiomyxoma. A The tumour forms a large bulging mass with a pale myxoid surface. B The neoplasm contains vessels of variable calibre, some of which are thick-walled. C The tumour is sparsely cellular and composed of uniform stellate cells set in a myxoid matrix.
Table 7.03
Differential diagnosis of myxoid soft tissue lesions of the vulva.

<table>
<thead>
<tr>
<th></th>
<th>Sarcoma botryoides</th>
<th>Deep angiomyxoma</th>
<th>Angiomyofibroblastoma</th>
<th>Superficial angiomyxoma</th>
<th>Fibroepithelial polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at presentation</strong></td>
<td>Pre-pubertal</td>
<td>Reproductive years</td>
<td>Reproductive years</td>
<td>Reproductive years</td>
<td>Reproductive years</td>
</tr>
<tr>
<td><strong>Size, site and macroscopic configuration</strong></td>
<td>Polypoid, exophytic or mass</td>
<td>Often larger than 5 cm, never exophytic</td>
<td>Subcutaneous, less than 5 cm</td>
<td>Small, dermal lobulated, superficial</td>
<td>Small, subepithelial, exophytic</td>
</tr>
<tr>
<td><strong>Margins</strong></td>
<td>Infiltrative</td>
<td>Infiltrative</td>
<td>Compressive</td>
<td>Poorly circumscribed</td>
<td></td>
</tr>
<tr>
<td><strong>Cellularity and cells</strong></td>
<td>Largely paucicellular with a variably pronounced cambium layer; Spindle shaped cells including rhabdomyoblasts in the myxoid zones</td>
<td>Paucicellular; Cytologically bland, stellate</td>
<td>More cellular than DA; Perivascular concentration of cells is usual; Cytologically bland; Plasmacytoid or epithelioid cells may be prominent.</td>
<td>Bland spindle cells in addition to enlarged, pleomorphic stromal cells with smudged chromatin</td>
<td></td>
</tr>
<tr>
<td><strong>Vessels</strong></td>
<td>Inconspicuous</td>
<td>Medium calibre, thick-walled vessels; pinwheel collagen</td>
<td>Smaller vessels than DA; Perivascular concentration of stromal cells</td>
<td>Elongated thin-walled vessels</td>
<td></td>
</tr>
<tr>
<td><strong>Matrix</strong></td>
<td>Paucicellular, myxoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mitotic index</strong></td>
<td>Usually easily found</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>Actin and desmin positive; Myogenin and myoD positive.</td>
<td>Actin, desmin and vimentin positive.</td>
<td>Strongly desmin positive. Minority of cells in occasional cases show positivity for either smooth muscle actin or panmuscle actin (HHF35); Negative for S-100 protein, keratin, fast myosin and myoglobin.</td>
<td>Desmin negative</td>
<td>Often desmin positive</td>
</tr>
<tr>
<td><strong>Associated findings</strong></td>
<td>Stromal neutrophils. When multiple, consider Carney syndrome</td>
<td></td>
<td></td>
<td></td>
<td>Overlying epithelium may demonstrate intraepithelial neoplasia</td>
</tr>
<tr>
<td><strong>Clinical course</strong></td>
<td>Fully malignant neoplasm; Alveolar histology adverse prognostic factor</td>
<td>Local recurrence common; never metastasizes</td>
<td>Does not recur; Occasional lesions have hybrid features of DA and AMFB and should be treated as DA</td>
<td>Benign, no recurrences</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DA = Deep angiomyxoma; AMFB = Angiomyofibroblastoma
**Deep angiomyxoma**

**Definition**
A locally infiltrative tumour composed of fibroblasts, myofibroblasts and numerous, characteristically thick-walled, blood vessels embedded in an abundant myxoid matrix.

**Synonym**
Aggressive angiomyxoma.

**Clinical features**
Most patients present with a relatively large, often greater than 10 cm, slowly growing, painless mass in the pelvic-perineal region that may give rise to pressure effects on the adjacent urogenital or anorectal tracts. Imaging studies often show the mass to be substantially larger than clinically suspected.

**Macroscopy**
Macroscopically, the tumour is lobulated but poorly circumscribed due to finger-like extensions into the surrounding tissue. The neoplasm is grey-pink or tan and rubbery or gelatinous.

**Tumour spread and staging**
Deep angiomyxoma is a locally infiltrative but non-metastasizing neoplasm that occurs during the reproductive years.

**Histopathology**
The constituent cells of this paucicellular neoplasm are small, uniform, spindle-shaped to stellate with poorly defined, pale eosinophilic cytoplasm and bland, often vesicular nuclei. The abundant myxoid matrix contains a variable number of rounded medium-sized to large vessels that possess thickened focally hyalinized walls. Multinucleated cells may be present, and occasionally there is morphological overlap with angiomyo-fibroblastoma (see below). Actin and desmin stains are positive in almost all cases, whereas S-100 protein is consistently negative.

**Differential diagnosis**
The differential diagnosis includes angiomyo-fibroblastoma, fibroepithelial polyp (so-called pseudosarcoma botryoides) and superficial angiomyxoma.

Other less common lesions that may enter the differential diagnosis are:
1. Myxoid neurofibroma, which has more buckled or wavy nuclei and whose cells are S-100 protein positive.
2. Low grade myxofibrosarcoma, which has thin–walled curvilinear vessels, shows more nuclear atypia and is essentially always desmin negative.
3. Myxoid liposarcoma, which contains delicate arborizing vessels and small lipoblasts.
4. Cellular angiofibroma, which is well circumscribed.

**Prognosis and predictive factors**
The treatment for this locally aggressive but non-metastasizing proliferation is primarily surgical with close attention to margins. Approximately 30% of patients develop one or more local recurrences.

**Superficial angiomyxoma**

**Definition**
A multilobulated, dermal or subcutaneous lesion composed of fibroblasts and thin-walled vessels in a myxoid matrix that occurs in adults.

**Clinical features**
The tumour occurs as a subcutaneous mass during the reproductive years.

**Histopathology**
Scattered multinucleated fibroblasts are often seen. There is no cytological atypia or pleomorphism, but scattered mitoses may be found. The stroma generally contains an inconspicuous mixed inflammatory infiltrate that is notable for the presence of neutrophils despite the absence of ulceration or necrosis. Up to one-third contain an epithelial component, usually squamous epithelium.

**Prognosis and predictive factors**
Approximately one-third of the lesions recur locally in a non–destructive fashion, usually as a consequence of an incomplete or marginal excision. Less than 5% of cases recur repeatedly.

**Angiomyofibroblastoma**

**Definition**
A benign, non-recurring, well circumscribed, myofibroblastic lesion composed of spindle-shaped to round cells

---

*Fig. 7.18 Angiomyofibroblastoma. A Alternating hypercellular and hypocellular areas are associated with a prominent vascular pattern. B Binucleate and trinucleate tumour cells are common, and some cells have a plasmacytoid appearance.*
that tend to concentrate around vessels.

Clinical features
Angiomyofibroblastoma occurs in the reproductive years and usually presents as a slowly growing, painless, well-circumscribed, subcutaneous mass measuring less than 5 cm in maximum diameter.

Macroscopy
Macroscopically, a narrow fibrous pseudocapsule delimits these tumours.

Histopathology
At low power angiomyofibroblastoma shows alternating hypercellular and hypocellular areas associated with a prominent vascular pattern throughout. Binucleate or multinucleate tumour cells are common, and some cells have denser, more hyaline cytoplasm, imparting a plasmacytoid appearance. Mitoses are very infrequent. The constituent cells are desmin positive. The major differential diagnostic considerations are deep angiomyxoma and fibroepithelial polyp.

Cellular angiofibroma
Definition
A recently described distinctive benign mesenchymal tumour composed of bland spindle-shaped cells admixed with numerous hyalinized blood vessels.

Clinical features
The tumour typically presents as a circumscribed solid rubbery vulvar mass in middle-aged women.

Histopathology
Cellular angiofibroma is usually a well-circumscribed cellular lesion that is composed of bland spindle-shaped cells interspersed with medium to small blood vessels, which typically have thick hyalinized walls [597,1818,2063]. Mature adipocytes, especially around the periphery of the lesion, are a characteristic feature. Cellular angiofibroma is vimentin-positive and desmin-negative, an immunoprofile that differentiates this tumour from deep angiomyxoma and angiomyofibroblastoma.

Prognosis and predictive factors
A local recurrence following excision has been described in a single case [1818].

Leiomyoma
These benign neoplasms do not differ macroscopically or histologically from leiomyomas encountered elsewhere in the female genital tract and are treated by simple excision. Problematic smooth muscle neoplasms are those that are greater than 7.0 cm in greatest dimension, have infiltrative margins and a mitotic index in excess of 5 per 10 high power fields [2880] (see section on leiomyosarcoma).

Granular cell tumour
Definition
A tumour composed of cells with uniform central nuclei and abundant granular, slightly basophilic cytoplasm.

Histopathology
These have the same appearance as in other more common sites. A proliferation of cells with small uniform nuclei and abundant, slightly basophilic cytoplasm diffusely involves the superficial connective tissue [2554]. The tumour cells are uniformly S-100 protein positive. Of particular importance in the vulva is the tendency for the overlying squamous epithelium to undergo pseudopseudoepitheliomatous hyperplasia and simulate a well-differentiated squamous carcinoma [3138]. Malignant varieties are rare and show high cellularity, nuclear pleomorphism, tumour cell necrosis and frequent mitotic figures [824].

Other benign tumours and tumour-like conditions
Other benign tumours and tumour-like conditions that occur in the vulva include lipoma, haemangioma, angiofibroma, pyogenic granuloma (lobular capillary haemangioma), lymphangioma, neurofibroma, schwannoma, glomus tumour, rhabdomyoma and post-operative spindle cell nodule [1762]. The histological features are similar to their appearance in more common sites.
Melanocytic tumours

Malignant melanomas account for 2-10% of vulvar malignancies [2316] and occur predominantly in elderly White women. A variety of naevi that must be distinguished from melanoma also occur in the vulva.

ICD-O codes
- Malignant melanoma 8720/3
- Congenital melanocytic naevus 8761/0
- Acquired melanocytic naevus 8720/0
- Blue naevus 8780/0
- Atypical melanocytic naevus of the genital type 8720/0
- Dysplastic melanocytic naevus 8727/0

**Malignant melanoma**

**Definition**
A malignant tumour of melanocytic origin.

**Clinical features**

*Signs and symptoms*
Symptoms include vulvar bleeding, pruritus and dysuria. Although vulvar malignant melanoma usually presents as a pigmented mass, 27% are non-pigmented [2320]. Satellite cutaneous nodules occur in 20% of cases [2320]. Melanoma may arise in a prior benign or atypical appearing melanocytic lesion. [1912, 3151]. The majority present as a nodule or polypoid mass. Approximately 5% are ulcerated [2320]. They occur with nearly equal frequency in the labia majora, labia minora or clitoris.

**Imaging**
Radiological, magnetic resonance imaging and/or radiolabelled isotope scan studies may be used to assess tumour that is present outside the vulva.

**Histopathology**
Three histological types of melanoma are identified: superficial spreading, nodular and mucosal/acral lentiginous [216, 1355,2261,2864]. Approximately 25% of the cases are unclassifiable [2320]. Melanomas may be composed of epithelioid, spindle, dendritic, nevoid or mixed cell types. The epithelioid cells contain abundant eosinophilic cytoplasm, large nuclei and prominent nucleoli. The dendritic cells have tapering cytoplasmic extensions resembling nerve cells and show moderate nuclear pleomorphism. Spindle-shaped cells have smaller, oval nuclei and may be arranged in sheets or bundles. Certain cell types may predominate within a given tumour. The amount of melanin within the tumour cells is highly variable, and cells may contain no melanin.

Both mucosal/acral lentiginous and superficial spreading melanomas can be entirely intraepithelial. When invasive, both histological types have vertical and radial growth phases, the vertical growth component representing the invasive focus of tumour. Nodular melanomas display predominately a vertical growth phase. Atypical melanocytes characteristic of melanoma in situ usually can be identified within the epithelium adjacent to mucosal/acral lentiginous and superficial spreading melanomas. Superficial spreading melanomas have melanocytic cells within the area of invasion that are typically large with relatively uniform nuclei and prominent nucleoli, similar to the adjacent intraepithelial melanoma. The intraepithelial component is considered to be the radial growth portion of the tumour. Nodular melanomas may have a small neoplastic intraepithelial component adjacent to the invasive tumour and are generally not considered to have a significant radial growth phase. The cells of nodular melanomas may be epithelioid or spindle-shaped. These tumours are typically deeply invasive. Mucosal/acral lentiginous melanomas are most common within the vulvar vestibule, including the clitoris. They are characterized by spindle-shaped neoplastic melanocytes within the junctional zone involving the adjacent superficial stroma in a diffuse pattern. The spindle-shaped cells are relatively uniform, lacking significant nuclear pleomorphism. Within the stroma the tumour is usually associated with a desmoplastic response. There is some variation in the reported frequency of melanoma types involving the vulva; however, in a large series of 198 cases mucosal/acral lentiginous melanoma comprised 52% of the cases, nodular melanoma 20% and superficial

**Fig. 7.20** Malignant melanoma of the vulva. A Low power micrograph of a heavily pigmented melanoma. B The neoplastic cells involve the epithelium and the junctional areas as well as the adjacent dermis. Note the large, pleomorphic nuclei with prominent nucleoli. Some cells contain melanin. C This neoplasm is composed of spindle-shaped cells with elongated nuclei resembling a spindle cell sarcoma.
spreading melanoma 4%, with the remainder of the cases being unclassifiable [2320,3120].

**Immunoprofile**
Melanomas usually are immunoreactive for S-100 protein, HMB-45 and Melan A [3119]. Unlike some tumours of epithelial origin, including Paget disease, they are not immunoreactive for AE1/3, cytokeratins 7 and 20, epithelial membrane antigen, carcinoembryonic antigen or gross cystic disease fluid protein-15 [3120].

**Somatic genetics**
The only two malignant melanomas of the vulva so far karyotyped showed trisomy 20 and del(18)(p11), respectively [2897].

**Prognosis and predictive factors**

**Clinical criteria**
Treatment for a vulvar melanoma with a thickness of 0.75 mm or less is usually a wide local excision with a 1-cm circumferential margin and a 1-2 cm deep margin. Melanomas with a thickness of 1-4 mm require a 2 cm circumferential margin and a deep margin of at least 1-2 cm [2949]. Melanomas with a thickness greater than 4 mm are usually treated by radical vulvectomy [2950]. Depending on the tumour size, bilateral inguino-femoral lymphadenectomy may also be performed [1912,2261,2864, 3151].

**Histopathological criteria**
Clark levels and Breslow thickness measurements are used to assess cutaneous vulvar melanomas. Breslow thickness measurements for cutaneous malignant melanoma require measurement from the deep border of the granular layer of the overlying epithelium to the deepest point of tumour invasion. If a melanoma is less than 0.76 mm in thickness, it has little or no metastatic potential [1694,3120]. Survival following a diagnosis of vulvar melanoma is adversely influenced by numerous factors including a tumour thickness exceeding 2 mm, a tumour interpreted as Clark level IV or greater, a mitotic count within the tumour exceeding 10 mitoses per square mm, surface ulceration of the tumour and advanced tumour stage [3120].

**Congenital melanocytic naevus**
The congenital melanocytic naevus is a benign tumour of melanocytes that is present at birth. Tumours may be small or involve a large area.

**Acquired melanocytic naevus**
The acquired melanocytic naevus appears in childhood and continues to grow with increasing age. This lesion may be junctional, i.e. at the epidermal-dermal junction, intradermal or compound (junctional and intradermal).

**Blue naevus**
The blue naevus is located entirely within the dermis and is composed of spindle-shaped or dendritic melanocytes that are typically heavily pigmented. A subtype known as the cellular blue naevus has a low potential for metastasis.

**Atypical melanocytic naevus of the genital type**

**Definition**
One type of atypical melanocytic proliferation in the genital area that forms a distinctive clinicopathological entity that can be distinguished from melanoma and dysplastic naevus.

**Synonym**
Atypical vulvar naevus.

**Clinical features**
The atypical melanocytic naevus of the genital type occurs primarily in young women of reproductive age. Unlike the dysplastic naevus, it is not associated with dysplastic naevi in other sites. Vulvar naevi can be influenced by hormonal changes and may appear more active or atypical during pregnancy.

**Histopathology**
The atypical melanocytic naevus of the genital type has junctional melanocytic nests that are variably sized and include some atypical superficial melanocytes. These lesions lack significant atypia or mitotic activity in the deeper dermal melanocytes and do not involve skin appendages. In addition the lesion is small, well circumscribed and lacks pagetoid spread or necrosis [31,498].
**Dysplastic melanocytic naevus**

**Definition**
A naevus that exhibits slight to moderate nuclear atypia that occurs only in the cells in the superficial portion.

**Clinical features**
These naevi occur predominantly in young women of reproductive age and present as elevated pigmented lesions with irregular borders typically exceeding 0.5 cm in diameter. Dysplastic naevi are rare on the vulva and may be associated with similar naevi elsewhere on the trunk and extremities.

**Histopathology**
They are composed of large epithelioid or spindle-shaped naevus cells with nuclear pleomorphism and prominent nucleoli. The atypical naevus cells are clustered in irregularly spaced junctional nests and involve hair shafts and the ducts of sweat glands and other skin appendages (31,498). The dysplastic naevus may be compound or junctional. Features that distinguish a dysplastic naevus from malignant melanoma include symmetrical growth evident on full cross-section and the predominance of atypical cells in the superficial cellular component of the naevus. Limited pagetoid spread of single melanocytes with minimal or no involvement of the upper one-third of the epithelium may also be seen (31,498,2362).

**Genetic susceptibility**
These vulvar naevi may occur in patients with the dysplastic naevus syndrome.

**E.J. Wilkinson**

---

**Germ cell, neuroectodermal, lymphoid and secondary tumours**

**Definition**
Primary tumours of the vulva that are not epithelial, mesenchymal or melanocytic in type, as well as secondary tumours.

**ICD-O codes**

- Yolk sac tumour: 9071/3
- Merkel cell tumour: 8247/3
- Peripheral primitive neuroectodermal tumour: 9364/3
- Ewing tumour: 9260/3

**Yolk sac tumour**

**Definition**
A primitive malignant germ cell tumour characterized by a variety of distinctive histological patterns, some of which recapitulate phases in the development of the normal yolk sac.

**Synonym**
Endodermal sinus tumour.

**Epidemiology**
Yolk sac tumour is rare in the vulva and has been reported primarily in children and young women (888).

**Histopathology**
For the histological features see the chapter on the ovary.

**Prognosis and predictive factors**
Vulvar yolk sac tumour is treated by local wide excision and chemotherapy, which is usually platinum-based (888).

**Merkel cell tumour**

**Definition**
A malignant tumour composed of small neuroendocrine type cells of the lower dermis.

**Synonym**
Neuroendocrine carcinoma of the skin.

**Epidemiology**
Merkel cell tumours are rare in the vulva and aggressive (324,554,996).

**Histopathology**
The neoplastic cells have scanty cytoplasm and nuclei with finely stippled chromatin. Glandular and squamous differentiation has been reported (2607).

---

Fig. 7.22 A highly cellular peripheral primitive neuroectodermal tumour of vulva in an 18 year old.
Immunohistochemical stains for cytokeratin demonstrate a distinctive perinuclear globular cytoplasmic pattern, and markers of neuroendocrine differentiation are usually positive (1209). Electron microscopic examination demonstrates intermediate filaments in a globular paranuclear arrangement and dense core granules (554,996,1209).

**Histogenesis**

These neoplasms are derived from small, neuroendocrine cells of the lower epidermis.

**Peripheral primitive neuroectodermal tumour / Ewing tumour**

**Definition**

An embryonal tumour arising outside of the central nervous system composed of undifferentiated or poorly differentiated neuroepithelial cells.

**Clinical features**

This is a rare primary tumour of the vulva that has been in reported in children and adult women of reproductive age (2839, 3002) and presents as a subcutaneous mass.

**Histopathology**

It is circumscribed but not encapsulated and composed of relatively small cells with minimal cytoplasm and ill defined cell borders. The nuclei are hyperchromatic with finely granular chromatin. Small nucleoli are evident. The mitotic count is variable, with an average of 3 per 10 high power fields reported (3002). The tumour is usually multilobulated but is variable in appearance with solid areas, sinusoidal-appearing areas with cystic spaces containing eosinophilic proteinaceous material and Homer Wright rosettes (2839,3002).

The tumour cells are immunoreactive for CD99 and vimentin and may be reactive for synaptophysin. Pan-cytokeratin may also be focally positive in some cases. Dense core neurosecretory granules are not identified by electron microscopy.

**Somatic genetics**

A vulvar peripheral primitive neuroectodermal tumour/Ewing tumour has been shown to express the EWS/FLI1 chimeric transcript due to the chromosome translocation t(11;22)(q24;q12), which is pathognomonic for this tumour type and is present in approximately 90% of tumours of this type (3002).

**Malignant lymphoma**

**Definition**

A malignant lymphoproliferative neoplasm that may be primary or secondary.

**Clinical features**

This is a rare neoplasm that presents as a vulvar mass (1279,2266,3002). In the largest series two-thirds of the cases were diffuse large B-cell lymphomas (3002).

**Prognosis and predictive factors**

Malignant lymphoma of the vulva is usually an aggressive disease (3002).

**Leukaemia**

**Definition**

A malignant haematopoetic neoplasm that may be primary or secondary.

**Clinical features**

Rarely, granulocytic sarcoma presents as a vulvar mass (1583).

**Histopathology**

See chapters on the cervix and vagina.

**Secondary tumours of the vulva**

**Definition**

Tumours of the vulva that originate outside the vulva.

**Incidence and origin**

The vulva is a rare site of secondary involvement by tumour. Tumours may involve the vulva by lymphatic spread or contiguous growth. The primary site of a secondary tumour of the vulva is most commonly the cervix, followed by the endometrium or ovary. Occasionally, breast carcinoma, renal cell carcinoma, gastric carcinoma, lung carcinoma, and, rarely, gestational choriocarcinoma, malignant melanoma or neuroblastoma spread to the vulva. Vaginal, urethral, urinary bladder and anorectal carcinomas may extend directly into the vulva (1631, 1802,3121).
Inherited Tumour Syndromes

Inherited cancer susceptibility is now recognized as a significant risk for cancer of the breast and female genitals organs. For many inherited tumour syndromes, the underlying germline mutations have been identified. This allows genetic testing and counseling of at risk family members and to estimate the associated disease burden. The genetic basis involves mutational inactivation of tumour supressor and DNA repair genes. Such germline mutations follow a mendelian inheritance pattern and usually confer substantial cancer risks, with breast and ovary as most frequent target organs. Additional familial aggregations have been observed but the responsible genes have not yet been identified and may involve multigenic traits.
Familial aggregation of cancers of the breast and female genital organs

Evidence of familial aggregation of breast, ovarian, and other tumours of the female genital organs derived from anecdotal observation of large families and from systematic analyses of cancer incidence in relatives of cancer cases. Although there are a number of potential measures of familial aggregation, the most commonly used is the familial relative risk (FRR) or standardized incidence rate (SIR). This is defined as the ratio of the incidence of disease among relatives of an individual with disease compared with the incidence in the population as a whole. The FRR is most often estimated through comparison of family history data between cases and controls, with the resulting odds ratio used as an estimator of the familial risk. Using genealogical resources linked to cancer registries has a number of advantages; the number of cases is usually large compared to case-control studies and, more importantly, all cancers found among relatives are confirmed in the cancer registry.

Breast cancer
Evidence that women with a positive family history of breast cancer are at increased risk for developing the disease has been accumulating for over 50 years; virtually every study has found significantly elevated relative risks to female relatives of breast cancer patients. Most studies have found relative risks between 2 and 3 for first-degree relatives of breast cancer patients selected without regard to age at diagnosis or laterality. A recent review of 74 published studies [2238] calculated familial relative risks of 2.1 (95% CI 2.0, 2.2) for breast cancer in any first degree relative, 2.3 for a sister affected, and 2.0 for an affected mother, and a relative risk of 3.6 if an individual had both a mother and sister affected. For individuals with a first degree relative diagnosed with breast cancer under age 50, the relative risk to develop breast cancer before age 50 was 3.3 (CI 2.8, 3.9).

In a population-based study of familial cancer using the Utah Population Database, Goldgar et al. [1029] studied the incidence of breast and other cancers among 49,202 first-degree relatives of 5559 breast cancer probands diagnosed before age 80. This study estimated a relative risk of 1.8 in first degree relatives of these breast cancer probands. When restricted to early-onset cancer (diagnosed before age 50), the relative risk of breast cancer among first-degree relatives increased to 2.6 and the risk for early-onset breast cancer among these relatives was 3.7 (95% CI 2.8–4.6). The Swedish family cancer database [715] contains >9.6 million individuals, with data on nearly 700,000 invasive cancers and consists of individuals born in Sweden after 1934 and their parents. Analyzing cancers diagnosed between the years 1958 to 1996, the standardized incidence ratio for breast cancer was 1.85 (95% CI 1.74–1.96) for having an affected mother, 1.36 (1.79–2.18) for having an affected sister, and 2.4 (1.72–3.23) if both mother and sister were affected. Other studies found larger familial effects among relatives of young bilateral probands compared with young probands with unilateral breast cancer [700,1246,2129]. The issue of relationship of histology to familial breast cancer is less clear [700,1246,2129].

Danish case-control study of 237 cases and 2123 controls) Parazzini et al. [2173] found a smaller effect, with an OR of 1.5 (CI 1.0–2.3). This may partly be explained by the fact that in the former study, cases were restricted to ages 20-54, while in the latter, the median age at diagnosis was 61. A Danish case-control study of 237 cases of endometrial cancer diagnosed under age 50 and 538 population controls reported an OR for family history of 2.1 (1.1–3.8). In contrast to most other sites, the two registry/genealogy based studies of endometrial cancer produced conflicting results, with the Utah study finding a FRR of 1.32 and the Swedish family cancer database reporting a SIR of 2.85. The reason for this discrepancy is unclear, but may to some extent reflect differences in the age distribution of the two populations.

Cervical cancer
In the Utah Population Database [1029], a FRR to first degree relatives of 999 cervical cancer cases of 1.74 was obtained (95% CI 1.03-2.53) while in the Swedish...
family cancer database (715), a slightly higher risk of 1.93 (1.52-2.42) in mothers of invasive cervical cancer cases and 2.39 (1.59-3.46) in sisters. Unlike many other cancers, there did not appear to be a significant effect of age at diagnosis in familial risk of cervical cancer, although the risks to mothers did depend on the number of affected daughters. In this study, significant familial aggregation was also found for in situ carcinoma of the cervix (FRR 1.79, (1.75-1.84).

**Multiple cancer sites**

In most but not all studies, a familial association between cancers of the breast and ovary have been found, particularly when the breast cancer cases have been diagnosed at a young age. Undoubtedly, the majority of the association between breast and ovarian cancer detected in these population studies is due to the BRCA1 gene, which is known to be involved in a large proportion of extended kindreds with clearly inherited susceptibility to breast and ovarian cancer. It is likely that some of the discrepant results are linked to the frequency of BRCA1 deleterious alleles in the respective populations in these studies. For breast cancer, the most consistent finding has been a small (FRR/SIR = 1.2) but highly significant familial association with prostate cancer. Other sites found to be associated in at least two studies with breast cancer in the familial context have been thyroid cancer and other endocrine-related tumours. For endometrial cancer, there is a familial association with colorectal cancer which is consistently found in a number of studies with statistically significant OR/SIRs ranging from from 1.3 to 1.9. Some, but not all studies have also reported associations with ovarian cancer, particularly among relatives of younger patients. The strongest and most consistent familial association between cervical and other sites is for lung cancer with statistically significant OR/SIRs of 1.8 and 1.64 found in the Swedish FCDB and the Utah UPDB, respectively. Other cancers with possible associations in both studies are lip/skin (SIR 2.4 and 1.83) and bladder cancer (SIR=1.6), though the latter was not statistically significant in the UPDB study.

In addition to this statistical and observational evidence for the role of genetic factors in the development of these cancers, a number of specific genes have been identified. Of these, the most important in terms of both risk and frequency are the breast cancer susceptibility loci BRCA1 and BRCA2, and the mismatch repair genes MSH2, MLH1, and MSH6 in the context of the hereditary non-polyposis colorectal cancer (HNPCC).

**Search for additional genes**

While some of the familial clustering may be due to shared environmental factors, it seems likely that a number of additional loci remain to be identified for cancers of the breast and female genital tract. Some studies have shown that only about one-fifth of the familial aggregation of breast cancer is attributable to the BRCA1 and BRCA2 genes [107,592,2230] and that these genes only explain less than half of all high risk site-specific breast cancer families [898,2631]. Whether the remaining familial aggregation is due to additional moderate to high risk loci or to the combined effects of a number of more common, but lower risk, susceptibility alleles is unknown [2236]. In contrast, it appears that almost all of the familial clustering in ovarian cancer can be ascribed to the effects of the BRCA1/2 and HNPCC loci [2802]. Although no systematic studies have been done for endometrial cancer, it is also likely that the HNPCC loci account for a substantial fraction of familial aggregation in this cancer as well.

### Table 8.01

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>MIM</th>
<th>Gene</th>
<th>Location</th>
<th>Associated sites / tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 syndrome</td>
<td>113705</td>
<td>BRCA1</td>
<td>17q</td>
<td>Breast, ovary, colon, liver, endometrium, cervix, fallopian tube, peritoneum</td>
</tr>
<tr>
<td>BRCA2 syndrome</td>
<td>600185</td>
<td>BRCA2</td>
<td>13q</td>
<td>Breast (female and male), ovary, fallopian tube, prostate, pancreas, gallbladder, stomach, melanoma</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>151623</td>
<td>TP53</td>
<td>17p</td>
<td>Breast, sarcoma, brain, adrenal, leukemia</td>
</tr>
<tr>
<td>Cowden</td>
<td>153050</td>
<td>PTEN</td>
<td>10q</td>
<td>Skin, thyroid, breast, cerebellum, colon</td>
</tr>
<tr>
<td>HNPCC</td>
<td>114500</td>
<td>MLH1</td>
<td>3p</td>
<td>Colon, endometrium, small intestine, ovary, ureter/renal pelvis, hepatobiliary tract, brain, skin</td>
</tr>
<tr>
<td>Muir Torre</td>
<td>158320</td>
<td>MLH1</td>
<td>3p</td>
<td>HNPCC sites plus sebaceous glands</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>175200</td>
<td>STK11</td>
<td>19p</td>
<td>Small intestine, ovary, cervix, testis, pancreas, breast</td>
</tr>
<tr>
<td>Ataxia Telangiectasia</td>
<td>208900</td>
<td>ATM</td>
<td>11q</td>
<td>Breast (heterozygotes)</td>
</tr>
</tbody>
</table>
BRCA1 syndrome

Definition
Inherited tumour syndrome with autosomal dominant trait and markedly increased susceptibility to breast and ovarian tumours, due to germline mutations in the BRCA1 gene. Additional organs include colon, liver, endometrium, cervix, fallopian tube, and peritoneum.

MIM No. 113705 (1835)

Synonyms
Breast cancer 1, early onset breast ovarian cancer syndrome.

Incidence
The prevalence of BRCA1 mutations in most Caucasian populations is estimated to be 1 in 883 (897). However, in certain populations, this is higher, e.g. 1% in Ashkenazi Jews (3065). Using recombination techniques, BRCA1 mutations have been dated to the early Roman times (1997). De novo mutations are rare.

Diagnostic criteria
A definitive diagnosis is only possible by genetic testing. BRCA1 mutations are common in certain populations and in families with numerous early onset breast cancer cases (>4 cases of breast cancer at <60 years) or in those with ovarian cancer at any age in addition to early onset breast cancer. The chance of a mutation in either BRCA1 or BRCA2 is lower (<30%) when only two or three breast cancer cases are present in a family. The main difference between BRCA1 and BRCA2 is the increased risk of male breast cancer in BRCA2. The American Society of Clinical Oncology (ASCO) guidelines suggest offering testing at a probability of mutation of >10% but many other countries will only offer testing to those with a chance >30% because of the need to concentrate resources.

Breast tumours
Penetrance
Analyses of worldwide data submitted to the Breast Cancer Linkage Consortium (BCLC) have provided general estimates of penetrance [8]. Estimates for specific populations have shown that the Ashkenazim have a lower than average lifetime breast cancer penetrance of about 50-60% (3065). Population based studies in UK breast cancer patients also revealed a lower penetrance and indicate that the presence of a mutation within a familial breast cancer cluster does confer a higher penetrance (2230). This may be due to an association with other genes or epidemiological factors that are present in the family. There are also reports of variable penetrance dependent on the position of the mutation within the BRCA1 gene (2914).

Clinical features
Breast cancer in BRCA1 mutation carriers occurs more often at a younger age, typically before age 40 (1687). It tends to progress directly to invasive disease without a precancerous DCIS component [8,1574]. Accordingly, there appears to be a lower chance of early detection by mammographic screening and a higher proportion of invasive cancers (1025). There is an almost linear increase in the lifetime risk of contralateral breast cancer from the age of 35 years, reaching a level of 64% by the age of 80 (742).

Pathology
Certain morphological types of breast cancer, including medullary carcinoma, tubular carcinoma, lobular carcinoma in situ, and invasive lobular carcinoma, have been reported more commonly in patients with a positive family history of breast cancer [191,1566,1684,1724,2441]. Patients with BRCA1 germline mutations have an excess of medullary or atypical medullary carcinoma compared to controls [8,764,1767]. Tumours in BRCA1 mutation carriers are generally of a higher grade than their sporadic counterparts [8,764,1767]. Ductal carcinoma in situ (DCIS) adjacent to invasive cancer is observed less frequently while the frequency of lobular neoplasia in situ is similar in both groups [8]. However, in a multifactorial analysis of the BCLC database, the only features significantly associated with BRCA1 were total mitotic count, continuous pushing margins, and lymphocytic infiltrate. All other features, including the diagnosis of medullary and atypical medullary carcinoma, were not found to be significant (1572). BRCA1-associated tumours are more likely to be estrogen (ER) and progesterone receptor (PgR) negative (766, 1352,1574,2121). Data on ERBB2 are limited but BRCA1-linked tumours are more likely to be negative than controls (1352,1574). BRCA1-linked tumours show a higher frequency of TP53 mutations and p53 expression than sporadic breast cancer (580,581,765,1574). BRCA1-associated tumours show very low expression of Cyclin D1 in both the invasive and in situ components (2122). The absence of Cyclin D1 in these tumours could be an additional evidence

<table>
<thead>
<tr>
<th>Chance of mutation</th>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>Single breast cancer / ovarian cancer case at &lt;60 years in non Ashkenazim</td>
</tr>
<tr>
<td>10-30%</td>
<td>2-3 female breast cancers &lt;60 years (no ovarian / male breast cancer)</td>
</tr>
<tr>
<td>30%</td>
<td>One female breast cancer &lt;60 and one ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>Female breast cancer &lt;60 in Ashkenazi</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>Four cases of female breast cancer at &lt;60 years</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cases female breast cancer &lt;60 and ovarian cancer any age</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cases female breast cancer &lt;60 and male breast cancer any age</td>
</tr>
</tbody>
</table>

Table 8.02
Probability of BRCA1/2 mutation in women with breast/ovarian cancer.

From R.A. Eeles (749).
of hormone independence of BRCA1-associated breast cancers.

**Prognosis and prognostic factors**

Studies on the prognosis of breast cancer associated with BRCA1 range from poorer prognosis, to no difference, to a better prognosis [441]. There is a potential survival bias since at least one patient in each family must have survived in order to have blood taken for gene testing. The most optimal studies are therefore those which have taken this into consideration, either by discounting the proband in a family who has presented for testing [3022] or by testing specific founder mutations in archival tumour tissue material from all cases in a specific population (for example, see Foulkes et al. [904]).

**Ovarian tumours**

**Age distribution and penetrance**

About 7-10% of ovarian carcinomas are due to inherited BRCA1 (or BRCA2) mutations; as these are on autosomes, they can be inherited from either the mother or the father. Although ovarian cancer can occur earlier in BRCA1 (and indeed BRCA2) carriers, the presence of an older onset ovarian cancer still can indicate an underlying mutation in either of these genes. The penetrance for ovarian cancer in BRCA1 mutation carriers is shown in Fig. 8.02; it starts to rise at an earlier age than the curve for BRCA2, which starts to rise at about 50 years. The penetrance is 44-60% by age 70. This is markedly higher than the lifetime risk of 1.8% (1 in 55) for sporadic ovarian cancer in women living in developed countries.

**Clinical features**

In a retrospective cohort study of Jewish subjects, women with advanced-stage ovarian cancer and a BRCA1 or BRCA2 founder mutation had a longer survival than women with non-hereditary ovarian cancer (P = 0.004) and a longer median time to recurrence (14 months versus 7 months) (P < 0.001) [329]. BRCA1/2 heterozygotes had higher response rates to primary therapy compared with patients who had sporadic disease (P = 0.01), and those with advance-stage disease had improved survival compared with patients who had advanced stage sporadic carcinoma [422].

**Pathology**

In patients with BRCA1 germline mutations, epithelial tumours (canceromas) are the most common histological diagnosis. All subtypes of malignant epithelial ovarian neoplasms have been reported, including the very rare entity of malignant transitional cell carcinoma [3102]. Interobserver variation in typing of ovarian carcinoma is likely to account, at least in part, for the different results reported to date [572,1716,2513]. Some studies indicate that papillary serous adenocarcinoma is the predominant ovarian cancer that occurs in familial ovarian cancer syndromes [229,2479,2800] while others report that they occur with similar frequency in BRCA1/2 mutation carriers and sporadic cases [329,2239,3102]. The frequency of endometrioid and clear cell carcinoma occurring in BRCA1 mutation carriers is similar to that of sporadic cases [50,229,1353,2239,2479,2800,3102,3272]. The current data suggest that germline mutations in BRCA1/2 genes do not pre-

---

**Table 8.03**

Lifetime cancer risks of BRCA1 carriers.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Relative risk (95% CI)</th>
<th>Cumulative risk by age 70, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Age-dependent</td>
<td>87</td>
</tr>
<tr>
<td>Ovary</td>
<td>Age-dependent</td>
<td>44</td>
</tr>
<tr>
<td>Colon</td>
<td>4.11 (2.36-7.15) (996)</td>
<td>2.03 (1.42-2.95) [2915]</td>
</tr>
<tr>
<td>Cervix</td>
<td>3.72 (2.26-6.10)</td>
<td>3.57 (3.16-4.04)</td>
</tr>
<tr>
<td>Uterus</td>
<td>2.65 (1.69-4.16)</td>
<td>2.47 (2.02-3.04)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.26 (1.26-4.06)</td>
<td>1.29 (0.9-1.7)</td>
</tr>
<tr>
<td>Prostate</td>
<td>3.32 (1.78-6.20) (996)</td>
<td>1.82 (1.01-3.29) [2915]</td>
</tr>
<tr>
<td>All cancers</td>
<td>2.30 (1.93-2.75)</td>
<td>2.27 (2.13-2.49)</td>
</tr>
</tbody>
</table>

From D. Ford et al. [996] and D. Thompson et al. [2915].

1 When considered together with rectal cancer, the relative risk was no longer significantly elevated above 1.0; no excess risk was noted among men.

2 For men under the age of 65.

3 All cancers other than non-melanoma skin cancer, breast cancer, or ovarian cancer.
dispose individuals to the development of borderline neoplasms (1044,1704). However, occasional invasive (2479, 3272) and borderline (50) mucinous neoplasms have been reported. Stromal tumours and malignant germ cell ovarian neoplasms appear not to be associated with BRCA1/2 germline mutations. However, several families in which more than one relative had been diagnosed with a malignant ovarian germ cell tumour have been published (2790). Single cases of dysgerminoma (3103) and transitional cell ovarian carcinoma (3101) have been observed in BRCA1 carriers with a family history of breast and ovarian cancer. The development of these lesions may be unrelated to the germline BRCA1 mutations in these cases.

The first report on BRCA1-associated ovarian carcinoma found that overall the tumours were of higher grade and higher stage than their historic age-matched controls (2479). These findings have been largely reproduced by a number of other groups (50,229,2239,3102,3272). In contrast, Berchuck et al. (229) found that although the BRCA1 cases in their study were all of advanced stage (III/IV), they were half as likely to be as poorly differentiated as cases without mutations. Johannsson et al. (1353) did not identify a difference in grade between the ovarian cancers in their BRCA1 mutation carriers and the control population-based cancer registry group.

Prognosis and prognostic factors
The majority of BRCA1 ovarian cancers are serous cystadenocarcinomas which have a poor prognosis generally if diagnosed when they have spread outside the ovary. Studies of ovarian cancer occurring in BRCA1 carriers have reported a somewhat better prognosis (213), but it is uncertain whether this is because of the bias in carrier detection in this population or whether they are more sensitive to treatment. If the latter were true, this would refer to platinum treatments as these data have been reported prior to the use of taxanes.

Tumours of the fallopian tube
Definition
Hereditary fallopian tube carcinoma arises from epithelium overlying the lamina propria of the endosalpinx in women at high hereditary risk to develop ovarian carcinoma, typically due to loss of the wild-type allele of BRCA1 or BRCA2. The tumour has to fulfill the clinical and histological criteria for tubal carcinoma (1256) as well as clinical genetic criteria shown in Table 8.02.

Incidence
From 1997 to 2002, a total of 15 hereditary breast/ovarian family related tubal tumours have been reported in literature. In 8 cases a BRCA1 mutation was detected. However, the true incidence of both hereditary and sporadic tubal carcinoma is probably much higher. This is caused by the fact that primary tubal tumours are often mistaken for primary ovarian carcinomas (3150). Moreover, some primary ovarian carcinomas might actually derive from inclusion cysts lined by tubal epithelial cells included into the ovarian stroma (2247).

Age distribution
In general the age of onset is younger in hereditary cases when compared to sporadic cases.

Diagnostic criteria
The criteria of Hu et al. (1256) as modified by Sedlis (2614) and Yoonessi (3185) are applied to differentiate hereditary tubal carcinomas from ovarian- and endometrial tubal carcinomas. These criteria require that: a) the main tumour is in the fallopian tube and arises from the endosalpinx, b) the histological features resemble a tubal pattern, c) if the tubal wall is involved, the transition between malignant and benign tubal epithelium should be detectable, d) the fallopian tube contains more tumour than the ovary or endometrium.

Clinical features
Symptoms and signs. To date, there is no indication that clinical hereditary tubal carcinoma features are different from those of its sporadic counterpart. In addition to occasional abdominal discomfort, the classical triad of symptoms include: (i) prominent watery vaginal discharge, (ii) pelvic pain and (iii) a pelvic mass (158). Cervical cytology reveals adenocarcinomatous cells in approximately 10% of patients (3185).

Tumour marker. As in ovarian carcinoma, elevation of serum CA125 levels are found in approximately 80% of cases (1173).

Imaging. CT/MRI are inconclusive with respect to the differential diagnosis of tubal or ovarian carcinomas. However, these techniques can be helpful in determining the extent of disease. Likewise, ultrasonography can not distinguish tubal from ovarian disease (2720).

Histopathology and grading
Serous papillary carcinoma is the most common form of hereditary tubal carcinoma. Grading is of limited value in these tumours and, if used, is based on the papillary architecture, nuclear atypia and mitotic activity. Grade I cancers show papillary growth with well differentiated columnar cells and low mitotic rate. Grade II cancers are papillary with evi-
dent gland formation with intermediate
differentiated cells with moderate mitotic
activity. Grade III shows solid growth with
loss of papillae and a medullary/glandu-
lar pattern. The cells are poorly differen-
tiated and the mitotic activity is high.

Immunohistochemistry. Being predomi-
nantly of serous papillary type, hereditary
tubal carcinomas are positive for cytoker-
atin 7 and 8, MUC1, CEA, OVTL3,
OV632, CA125, and negative or showing
only low expression for cytokeratin 20,
CEA and vimentin. Also, p53 is often
expressed, and cyclins E and A and Ki67
show a varying number of proliferating
cells, whereas staining for ERBB2 and
cyclin D1 is usually negative. Steroid
receptor content varies. In the rare clear
cell cancers, p21 is highly expressed.

Seeding and metastasis
Hereditary tubal carcinomas presumably
spread like their sporadic counterparts.
Empirical data are available to date point
to a mode of spread similar to ovarian
cancer.

Prognosis
The five-year survival rate of 30% in spo-
radic cases varies with stage (158,3185),
but not with grade. The survival rate of
hereditary tubal carcinomas has yet to
be established since only small numbers
of patients have been reported and most
patients have still not completed their 5-
year follow-up.

Other tumours
BRCA1 predominantly predisposes to
female breast cancer and ovarian can-
cer. Unlike BRCA2, it is not thought to
predispose to male breast cancer. A few
families with male breast cancer and a
BRCA1 mutation have been described,
but these may be within the numbers
expected by chance. A study of causes of
mortality by Ford et al. (896) reported
an increased risk of colon cancer and
prostate cancer. However, a reanalysis
(2914) has shown a small pancreatic
cancer excess, as is seen in BRCA2 car-
riers and an excess of prostate cancer
risk only at age <60 years. The excess of
colonic cancer was counteracted by a
deficit of rectal cancer. See Table 8.03 for
details on risk estimates.

Genetics
Chromosomal location and
gene structure
The BRCA1 gene is located on chromo-
some 17q21 [1109]. The 24 exons of the
BRCA1 gene (22 coding exons; alterna-
tive 5'UTR exons, 1a & 1b) span an 81-
kb chromosomal region, that has an
unusually high density of Alu repetitive
dNA (41.5%) [1864,2735]. A partial
pseudogene (BRCA1m) consisting of a
tandem duplication of exons 1a, 1b and
2 lies 44.5kb upstream of BRCA1
(356,2303). Exon 11 of BRCA1 (3.4 kb)
encodes 61% of the 1863 amino acid
protein. The amino-terminal RING finger
domain and the carboxy-terminal BRCT
repeats [316] of BRCA1 are highly con-
served among vertebrates [2825], while
the rest of the protein bears little homolo-
gy to other known genes.

Gene expression
Several alternatively spliced transcripts
have been described for the BRCA1
gene, the most prevalent of these lead to
in-frame deletions of exon 11 (BRCA1-
Δ11). Both full length and Δ11 transcripts
are ubiquitously expressed. The 100-
and 97-kDa Δ11 protein isoforms lack the
nuclear localization signal and are cyto-
plasmic (1864,2904). However, the full-
length 220-kDa protein is predominantly
observed in the nucleus. Its expression
and phosphorylation is cell-cycle
dependent, commencing in G1 and
reaching maximal levels by early S-
phase. BRCA1 colocalizes with the
BRCA2 and Rad51 proteins in discrete
foci during S-phase. DNA damage leads
to hyperphosphorylation of BRCA1, dis-
persal of the BRCA1/BRCA2/Rad51
nuclear foci, and their relocalization to
PCNA-containing DNA replication struc-
tures. In meiotic cells, BRCA1, BRCA2
and Rad51 colocalize on the axial ele-
ments of developing synaptonemal com-
plexes [450,2594,2596]. A large protein
complex consisting of other tumour sup-
pressor and DNA repair proteins, known
as BASC (BRCA1-associated genome
surveillance complex) has been identi-
fied. Among these, partial colocalization
of BRCA1 with Rad50, MRE11 and BLM
in nuclear foci analogous to those
observed with BRCA2 and Rad51 has
been demonstrated [3054]. In addition to
its interactions with BRCA2, Rad51, and
BASC, the BRCA1 protein has been
shown to form complexes with a number
of other proteins involved in diverse cel-
lular functions, including DNA repair,
transcription, chromatin remodeling, and
protein ubiquination (reviewed in [3018]).
During mouse embryonic development,
Brca1 exhibits a dynamic expression

![Fig. 8.04](A) Normal endosalpinx, stained for bcl-2, which is a differentiation marker of serous tubal cells. (B) Tubal cell-lined inclusion cyst in the ovary stained for bcl-2. (C) Dysplastic lesion in a fallopian tube of a
BRCA1 mutation carrier, stained for p53. (D) Serous adenocarcinoma of the fallopian tube stained for bcl-2
(note: not all serous carcinomas are bcl-positive).
To assess whether wild-type and/or mutated BRCA1 alleles are lost in dysplastic tubal epithelium of a BRCA1 mutation carrier, light-cycler polymerase chain reaction (PCR) melting curve analysis is performed. This technique utilizes the properties of probes to anneal less stringent to mutated DNA than to wild-type DNA, resulting in a lower denaturation temperature for mutated DNA. Two peaks, indicating different denaturing temperatures, are detected in non-dysplastic epithelium, indicating the presence of both wild-type and mutated BRCA1 DNA. One clear peak at the melting temperature for the mutated BRCA1 DNA in the dysplastic epithelium indicates loss of wild-type BRCA1 DNA. From J.M. Piek et al. (2246).

Fig. 8.05 To assess whether wild-type and/or mutated BRCA1 alleles are lost in dysplastic tubal epithelium of a BRCA1 mutation carrier, light-cycler polymerase chain reaction (PCR) melting curve analysis is performed. This technique utilizes the properties of probes to anneal less stringent to mutated DNA than to wild-type DNA, resulting in a lower denaturation temperature for mutated DNA. Two peaks, indicating different denaturing temperatures, are detected in non-dysplastic epithelium, indicating the presence of both wild-type and mutated BRCA1 DNA. One clear peak at the melting temperature for the mutated BRCA1 DNA in the dysplastic epithelium indicates loss of wild-type BRCA1 DNA. From J.M. Piek et al. (2246).

pattern, which parallels Brca2 expression in that the highest expression levels occur in epithelial tissues undergoing concurrent proliferation and differentiation. In adult mice, Brca1 and Brca2 expression is induced during mammary gland ductal proliferation, morphogenesis and differentiation occurring at puberty and again during proliferation of the mammary epithelium during pregnancy (1582,1769,2323).

Consistent with its role as a tumour-suppressor gene, the wild-type allele of BRCA1 is lost in the majority of tumours of individuals with inherited mutations, presumably leading to absence of normal protein (560). In sporadic cancer, BRCA1 protein expression is absent or reduced in the majority of high grade breast carcinomas and sporadic ovarian tumours (2493,3130). Although few somatic mutations in the BRCA1 coding sequence have been identified (1846), somatic inactivation of protein expression may occur through several mechanisms, including gross chromosomal rearrangements – approximately 50% of primary breast tumours show loss of heterozygosity of chromosome 17q21 (559, 1134), or epigenetic inactivation of expression, such as promoter hypermethylation (426).

Gene function

The BRCT domain of BRCA1 is a protein-protein interaction module found in proteins involved in DNA repair and cell cycle control (316). The RING domain mediates the interaction with BARD1 and the dimer displays ubiquitin ligase (E3) activity (159). The physiologic substrates of this activity remain unknown although the Fanconi anaemia D2 protein is a likely candidate (958). The integrity of the RING and BRCT domains is indispensable for the functions of BRCA1 as demonstrated by the presence of cancer-associated mutations in these regions.

A number of different mutations have been introduced into mouse Brca1, all resulting in embryos with γ-irradiation hypersensitivity and genetic instability. Mice with a conditional mutation of Brca1 in the mammary gland developed tumorigenesis associated with genetic instability, providing an important link to human disease (3167). Interestingly, mouse cells lacking Brca1 are deficient in repair of chromosomal double-strand breaks (DSB) by homologous recombination (1901). Taken together, these results suggest a role for BRCA1 in the DNA damage response.

Expression of wild type but not disease-associated BRCA1 alleles in BRCA1-deficient human cells restores resistance to DNA-damaging agents (2595) and several BRCA1-containing complexes involved in DNA repair have been identified. These include S-phase nuclear foci containing BRCA2 and Rad51 (450), the hRad50-HMre11-NBS1 (R/M/N) complex, involved in a wide variety of DNA repair processes (3255), and the BASC complex which contains ATM, the BLM helicase, mismatch repair proteins MSH2, MSH6, MLH1 and the R/M/N complex (3054). DNA damaging agents induce BRCA1 hyperphosphorylation, which is likely to modulate the association of BRCA1 with these different protein complexes (2597). These biochemical approaches corroborate the notion that BRCA1 participates in the cellular response to promote DNA break recognition and repair, as shown in Fig. 8.08.

The involvement of BRCA1 in a variety of DNA repair processes suggests that it may be an upstream effector common to various responses to DNA damage (3018). In line with the idea of BRCA1’s pleiotropic role, it also acts as a negative regulator of cell growth. Ectopic expression of BRCA1 causes cell cycle arrest at G1 via the induction of the cdk inhibitor p21 (2745). Conversely, inhibition of BRCA1 expression with antisense oligonucleotides results in the acceleration of mammary epithelial cell lines (2917). Also, BRCA1 seems to be required for efficient radiation-induced G2/M and S-phase checkpoints pointing to a broad involvement of BRCA1 in checkpoint control (3166,3178).

Several lines of evidence suggest that one of the molecular functions of BRCA1 is the regulation of transcription. The BRCA1 C-terminus acts as a transactivation domain and germline mutations found in BRCA1 abolish this activity (1899). BRCA1 can be copurified with RNA polymerase II and upon replication blockage, a novel complex containing BRCA1 and BARD1 is formed, suggesting that BRCA1 protein redistributes to different complexes in response to replication stress (476,2593). BRCA1 also associates and, in some cases, modulates the activity of several proteins involved in the regulation of gene expression such as transcription factors, coactivators, corepressors, and chromatin remodeling complexes (297,1247, 1899,3255). A recent exciting development, of yet unknown physiologic signifi-
cance, was the discovery of direct DNA binding by BRCA1 in vitro which may be important for its function in transcription and DNA repair [2198]. Putative BRCA1 transcriptional target genes identified so far play a role in some aspect of the DNA damage response: BRCA1 induces the transactiva-

tion of p21WAF1/CIP1 in p53-dependent and independent manners, insuring a potent cell cycle arrest, reinforcing the connection between cell cycle check-

point control and transcription regulation [2130,2745]. Experiments using cDNA arrays identified the DNA-damage-

response gene GADD45 as a major tar-

get of BRCA1-mediated transcription [1138,1727]. These results, coupled with studies showing that disruption of p53 partially resuces embryonic lethality in Brca1-/- mice, link the p53 pathway and BRCA1 function [1106,1710]. Import-

antly, the majority of tumours derived from BRCA1-linked patients or from Brca1-/- mice present mutations in p53 [581,3167].

Mutational spectrum

Germline mutations in BRCA1 have been detected in 15-20% of clinic-based breast cancer families, and in 40-50% of breast-ovarian cancer families [2657, 3023]. Mutations occur throughout the entire coding region, and hence the mutation spectrum has taught us rela-
tively little about the gene’s function. The majority of the mutations are predicted to lead to a prematurely truncated protein when translated. In conjunction with the observed loss of the wildtype allele in tumours arising in mutation carriers [560], this indicates that inactivation of the gene is an important step in tumori-
genesis. Despite the strong variability in mutations detected in families, founder effects have led to some mutations being very prevalent in certain populations of defined geographical or ethnic back-
ground. An example is the 185delAG mutation, which is present in approxi-
mately 1% of all individuals of Ashkenazi Jewish descent [1151]. As a result, muta-
tion spectra may vary according to ethnic background of the sampled popula-
tion [2824]. In some populations, specif-
ic large interstitial deletions or insertions, which are difficult to detect by conven-
tional PCR-based mutation scanning technologies, have been observed to be particularly frequent. They may comprise between 10 and 20% of the total muta-
tion spectrum [944,1229]. In recent years, an increasing number of missense changes are being detected in BRCA1, of which the clinical sig-
nificance is uncertain. These already comprise up to 40% of all known sequence changes in BRCA1. The Breast Cancer Information Core (BIC) maintains a website providing a central repositary for information regarding mutations and polymorphisms [http://research.nhgri.nih.gov/bic/].

Genotype-phenotype correlations

Initially, the breast and ovarian cancer cancer risks conferred by mutations in BRCA1 were estimated from BRCA1-linked, multiple-case families (see Figs. 8.01 and 8.02) [896,898]. More recently, estimates from specific populations have come up with lower estimates [106,3065]. This could point to 1) the existence of mutation-specific risks (because different populations have dif-
ferent mutation spectra, the overall cancer risks would differ), 2) the existence of genetic variants in other genes, particu-
larly prevalent in certain populations, which might modify the BRCA1-related cancer risks, 3) population-specific dif-
ferences in environmental risk modifiers.

BRCA1 mutation position

One report observed a significant corre-
lation between the location of the muta-
tion in the gene and the ratio of breast to ovarian cancer incidence within each family [974], suggesting a transition in risk such that mutations in the 3’ third of the gene were associated with a lower propor-
tion of ovarian cancer. It wasn’t clear, however, whether this was due to higher breast cancer risks, or lower ovar-
ian cancer risks. A much larger study of 356 BRCA1-linked families [2914] found the breast cancer risk associated with mutations in the central region to be sig-
nificantly lower than for other mutations (relative risk, 0.71), and the ovarian can-
cer risk associated with mutations 3’ to nucleotide 4191 to be significantly reduced relative to the rest of the gene (relative risk, 0.81). Recent work sug-

gests that the risk to ovarian cancer might also be influenced by genetic vari-

ation in the wildtype BRCA1 copy in BRCA1 carriers [1009].

Genetic risk modifiers

One study showed that the risk for ovari-

an cancer was 2.11 times greater for BRCA1 carriers harbouring one or two rare HRAS1 alleles, compared to carriers with only common alleles (P = 0.015). Susceptibility to breast cancer did not appear to be affected by the presence of rare HRAS1 alleles [2240]. Likewise, a length-variation of the polyglutamine repeats in the estrogen receptor co-activ-

ator NCOA3 and the androgen receptor influences breast cancer risk in carriers of BRCA1 and BRCA2 [2342,2345]. The variant progesterone receptor allele named PROGINS was associated with an odds ratio of 2.4 for ovarian cancer among 214 BRCA1/2 carriers with no past exposure to oral contraceptives, compared to women without ovarian cancer and with no PROGINS allele [2487]. These results support the hypothesis that pathways involving endocrine signalling may have a substantial effect on BRCA1/2-associated cancer risk. Genetic variation in the genes constitut-

ing the DNA repair pathways might also be involved. A C/G polymorphism in the 5’ untranslated region of RAD51 was found to modify both breast and ovarian
cancer risk, initially only in carriers of BRCA2 [1328, 1644, 3053].

**Hormonal factors as risk modifiers**

**Oral contraceptives**

Because of the observed protective effects of oophorectomy and tamoxifen, it is of concern that supplemental estrogen, in the form of oral contraceptives or hormone replacement therapy, may increase the risk of breast cancer. In the Oxford overview analysis, current use of birth control pills was associated with a relative risk of 1.2 (539). However, in a recent large American case-control study, no adverse effect was noted (2607). In a large international case-control study of oral contraceptives and hereditary breast cancer (1977) a mild increase in risk was seen among BRCA1 carriers (relative risk 1.2) but not among BRCA2 carriers (relative risk 0.89). The overall result was not significant, but risk increases were found for women who first took a contraceptive before age 30, for women who developed breast cancer before age 40, for women with five or more years of pill use, and for women who first took an oral contraceptive prior to 1975. It appears that short-term use of modern contraceptives poses no increase in risk; but further studies are needed in this regard. No studies have been conducted yet regarding whether or not HRT increases the risk of breast cancer in BRCA1/2 mutation carriers.

It is important to establish whether oral contraceptives are hazardous to the breast, because their use has been proposed as a preventive measure against ovarian cancer. A protective effect of oral contraceptives on ovarian cancer risk has been observed in three case-control studies of BRCA1/2 mutation carriers (1976, 1979, 1980) but there has been one conflicting report (1886). In a recent study of 232 ovarian cancer cases and 232 controls, oral contraceptive use was associated with a 56% reduction in the risk of ovarian cancer (p = 0.002) (1976). A protective effect among BRCA1 carriers was greater than that observed for members of the general population (224).

**Pregnancy**

Hormonal levels rise dramatically during pregnancy and two groups found pregnancy to be a risk factor for early breast cancer in BRCA1/2 mutation carriers. Johansson et al. reported ten pregnancy-related breast cancers in 37 BRCA1/2 mutation carriers, versus the expected 3.7 (1351). Jernstrom et al. reported that the risk of breast cancer increased with each pregnancy in BRCA1/2 carriers before the age of 40 (1348). This was found for BRCA1 and BRCA2 mutation carriers, but was only significant for the former group. In the general population, pregnancy offers protection against breast cancer after the age of 40, but appears to increase the risk for very early-onset breast cancer [227]. This is consistent with the hypothesis that the ovarian hormones produced during pregnancy are mitogenic, and accelerate the growth of existing tumours. During pregnancy breast differentiation occurs and thereafter the population of susceptible cells is reduced. This may explain why pregnancy prevents breast cancers at a later age. In the general population, only a small proportion of breast cancers occur before age 40, and pregnancy confers an overall advantage. Early-onset breast cancers are typical among BRCA1 mutation carriers, however, and a high proportion of cancers occur before age 40. A case-control study of breast-feeding and breast cancer in BRCA1/2 mutation carriers reported a protective effect in women with BRCA1 mutations, but not with BRCA2 mutations (1347). BRCA1 mutation carriers who breast-fed for more than one year were 40% less likely to have breast cancer than those who breast-fed for a shorter period (p = 0.01). The observed protective effect among BRCA1 carriers was greater than that observed for members of the general population (224).

**Prognosis and preventive options**

The overall life expectancy of unaffected women with a BRCA1 or BRCA2 mutation clearly is decreased due to their high risk of developing breast cancer and ovarian cancer, in particular at young ages. The overall mortality from breast and ovarian cancer within 10 years of diagnosis of cancer is still significant, 40% and 60% respectively. Currently the following avenues are being explored to improve the prognosis of women with a BRCA1 or BRCA2 mutation, all aiming for either early detection or prevention of breast cancer and/or ovarian cancer: i) regular surveillance, ii) prophylactic surgery, and iii) chemoprevention.

**Preventive surveillance**

No evidence exists that regular breast surveillance using mammography leads to earlier detection of cancers in mutation carriers [1442]. Preliminary results on
breast surveillance using MRI suggest that there is an increased frequency of early detection of tumours, but definite conclusions cannot yet be made (1875, 2835). Also, no evidence exists that regular ovarian surveillance detects ovarian cancer at curable stages.

**Prophylactic surgery**

Prophylactic bilateral mastectomy lowers the risk of breast cancer in mutation carriers by more than 90%, also on the long-term (178,1407). Prophylactic bilateral salpingo-oophorectomy prevents ovarian cancer, though a minimum long-term risk of 4% of peritoneal cancer remains after this procedure (2344). The incidence of breast cancer in BRCA1 carriers is maximal in the age group 40 to 55 and then declines slightly thereafter (1978). This observation suggests that ovarian hormones may have a promoting role in breast carcinogenesis. In support of this, oophorectomy has been found to be protective against breast cancer in BRCA1/2 mutation carriers in several studies (1976,2504). Rebbeck et al. compared the breast cancer risk in a historical cohort of BRCA1 mutation carriers, some of whom had undergone an oophorectomy and some of whom had both ovaries intact (2343,2344). The estimated relative risk of breast cancer associated with oophorectomy was approximately one-half. This was confirmed in a case-control study (763) and in a prospective follow-up study of 170 women (1413). Among BRCA1 mutation carriers; the risk of breast cancer among women who had an oophorectomy was decreased by 61% (odds ratio 0.39; 95% CI 0.20 to 0.75). These studies suggest that oophorectomy might be used as a strategy to decrease the risk of breast cancer among BRCA1 mutation carriers. However, in young women the procedure is associated with acute and long-term side effects.

Members of a BRCA1-linked family are at risk also to develop tubal carcinoma (3271). Piek et al. studied prophylactically removed fallopian tubes of 12 women with a predisposition for ovarian cancer, in 7 of whom a BRCA1 mutation was detected (2246). Six showed dysplasia, including one case of severe dysplasia. Five harboured hyperplastic lesions, and in one woman no histological aberrations were found. Therefore, it is recommend-

<table>
<thead>
<tr>
<th>Table 8.05</th>
<th>Effects of modifying factors on breast and ovarian cancer risk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>BRCA1</td>
<td>BRCA2</td>
</tr>
<tr>
<td><strong>Genetic factors</strong></td>
<td></td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>↓↑</td>
</tr>
<tr>
<td>NCOA3</td>
<td>↑</td>
</tr>
<tr>
<td>RAD51</td>
<td>–</td>
</tr>
<tr>
<td>HRAS1</td>
<td>?</td>
</tr>
<tr>
<td><strong>Lifestyle factors</strong></td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>↓</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>↓</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>–</td>
</tr>
<tr>
<td>Pregnancy*</td>
<td>↑</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>↓</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>↑?</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>↓</td>
</tr>
<tr>
<td>Hormone-replacement therapy</td>
<td>?</td>
</tr>
</tbody>
</table>

↑↓ = significant decrease in cancer risk
↑↓ = significant increase in cancer risk
↑ = suggested increase in cancer risk, but uncertain
↓ = suggested decrease in cancer risk, but uncertain
↑ = significant increase in cancer risk
↓ = significant decrease in cancer risk
? = not studied
– = no modifying effect seen

From S.A. Narod (1976).

* The pregnancy effect was seen for early-onset (40 years) breast cancer only.

**Chemoprevention**

Tamoxifen is an anti-estrogenic drug that is routinely used in the treatment of estrogen-receptor positive breast cancer that has also been demonstrated to be of value in reducing the risk of primary invasive and pre-malignant breast cancer in high risk women (865,1464,1976) and of contralateral breast cancer in unselected women (10). Narod, et al. (1976) studied tamoxifen and contralateral breast cancer in a case-control study of BRCA1 and BRCA2 mutation carriers. Tamoxifen use was equivalent to a 62% risk reduction in BRCA1 carriers. A reduction in risk of contralateral cancer was also seen with oophorectomy and chemotherapy. This result implies that the combination of tamoxifen and oophorectomy may be more effective than either treatment alone, and that the two prevention strategies may be complementary. Until more definitive guidelines are established, the interest in participation in chemoprevention trials is likely to remain small (2285).
**BRCA2 syndrome**

**Definition**
Inherited tumour syndrome with autosomal dominant trait and markedly increased susceptibility to early onset breast cancer and an additional risk for the development of male breast cancer and, less frequently, pancreatic and ovarian cancer. Occasionally, carriers of a BRCA2 germline mutation present with skin melanoma, gall bladder and bile duct tumours, and cancer of the fallopian tube.

**MIM No.** 600185 {1835}

**Synonyms**
Site specific early onset breast cancer syndrome, breast cancer 2, FANC D1.

**Incidence**
The BRCA2 syndrome is generally uncommon (about 1 in 1000 individuals), but in certain populations, it is more prevalent. For example, a specific mutation (6174delT) is present in 1.5% of the Ashkenazim and another (999del5) in 0.6% of Icelanders, due to founder effects (2382,2921).

**Diagnostic criteria**
BRCA2 mutations are more often present in families with multiple female breast cancer (>4 cases of early onset at <60 years) and male breast cancer. The risk of ovarian cancer is lower than in BRCA1 families. The definitive diagnosis relies on the identification of a BRCA2 germline mutation.

**Breast tumours**

- **Penetrance and age distribution**
  Analyses of the worldwide data submitted to the Breast Cancer Linkage Consortium (BCLC) studies have been used to provide general estimates of penetrance (see Fig. 8.01) [8]. Population based studies of mutations in breast cancer patients from the UK have shown a lower penetrance than the BCLC, indicating that the presence of a mutation within a familial breast cancer cluster does confer a higher penetrance (2230). This may be due to association with other genes or exposure and lifestyle factors that are present in the family. Specific estimates for different populations have shown that the Ashkenazim have a somewhat lower lifetime breast cancer penetrance of about 50-60% (3065). There are also reports of variable penetrance, dependent upon mutation position [2914]. There is an increased risk of contralateral breast cancer of about 56% lifetime after a diagnosis of a first breast primary. Breast cancer in BRCA2 carriers occurs more often at younger ages than in the general population, but at older ages than in BRCA1 carriers.

- **Pathology**
  Although lobular and tubulo-lobular carcinoma has been reported to be associated with BRCA2 germline mutation in one study [1767], this has not been confirmed in a larger study and no specific histological type is thought to be associated with BRCA2 (8,1572). In a multifactorial analysis, the only factors found to be significant for BRCA2 were tubule score, fewer mitoses and continuous pushing margins. All other features were not found to be significant [1572]. BRCA2 tumours are overall higher grade than sporadic cancers [8,43,1767]. Ductal carcinoma in situ (DCIS) is observed less frequently in BRCA2 cases than in controls, but this is not the case for BRCA1. Lobular carcinoma in situ shows no difference between the groups [8]. Invasive lobular carcinoma clearly does have a familial association and a trend has been identified in familial breast cancer not linked to BRCA1 or BRCA2 (i.e. BRCA X) [1571].

- **BRCA2 tumours are similar to sporadic cancers in steroid receptor (ER, PgR) expression** [766,1574,2121]. Data on ERBB2 are limited but BRCA1 and BRCA2 tumours are more likely to be negative than controls [1574]. BRCA2 tumours do not show a higher frequency...
of TP53 mutation and p53 expression compared to sporadic breast cancer [590,581,1574].

Prognosis and prognostic factors
Since the breast cancers associated with BRCA2 mutations are more often estrogen receptor positive and are associated with DCIS, they would be expected to have a better prognosis. The most systematic study to investigate prognosis has analysed the survival of Ashkenazi women with breast cancer who have mutations as tested from paraffin-stored tissue. This is possible because they have a single 6174delT founder mutation. There was no difference in survival between carriers and non-carriers [441].

Risk modifiers and prevention
The preventive effect of oophorectomy and tamoxifen, mastectomy, and the possible hazard associated with oral contraceptives are similar in both BRCA syndromes have been dealt with in the preceding section on BRCA1.

Ovarian tumours
Penetrance and age distribution
About 7-10% of ovarian carcinomas are due to inherited BRCA1 or BRCA2 mutations; as these are on autosomes, they can be inherited from either the mother or the father. Although ovarian cancer can occur earlier in BRCA1 and indeed BRCA2 carriers, the presence of an older onset ovarian cancer still can indicate an underlying mutation in either of these genes. The penetrance of ovarian cancer in BRCA2 carriers is shown in Fig. 8.02; the risk of developing ovarian cancer by age 70 in BRCA2 families is approximately 27% [898]. It should be noted that the penetrance curve starts to rise later than for BRCA1 which could have implications for the timing of prophylactic oophorectomy.

Pathology
Compared with the information on the pathology of BRCA1-associated ovarian cancers, little is reported on BRCA2 mutation-related ovarian tumours. The paucity of information is accounted for by the low incidence of this disease compared with that of BRCA1-linked cases [329,973]. Some recent studies indicate that the histological phenotype of these ovarian neoplasms is similar to that of BRCA1-associated carcinomas and are predominantly of papillary serous type [329,2239,3272]. A single case of an ovarian malignant mixed müllerian tumour (carcinosarcoma), has been reported as occurring in a BRCA2 mutation carrier [2748].

The data on grade are similar to those of BRCA1 ovarian cancers with an association with higher grade but limited numbers in study and interobserver variation [329,2239,2479,3102,3272] in the scoring of grade should be taken into account when considering the evidence. There are no data to support a role of BRCA2 in borderline ovarian lesions [1044,1704] nor are there germ cell or sex cord stromal tumours.

Prevention by oral contraceptives
Although it has been long known that oral contraceptives can decrease the risk of developing ovarian cancer in the general population [2], recently there is evidence that this may also be true for hereditary ovarian cancer [1976,1979,1980]. See the preceding section on BRCA1 syndrome for further details.

Prognosis and prognostic factors
In a retrospective cohort study, women with BRCA1 or BRCA2 founder mutation advanced-stage ovarian cancer had a longer survival compared with women with non-hereditary ovarian cancer (P = 0.004) and a longer median time to recurrence (14 months versus 7 months) (P< 0.001) [329].

Studies of ovarian cancer occurring in BRCA2 carriers have reported a better prognosis [329], but it is uncertain whether this is because of the bias in carrier detection in this population or whether they are more sensitive to treatment. If the latter is true, this would be platinum treatments as these data are prior to the use of taxanes.

Tumours of the fallopian tube
Hereditary fallopian tube carcinoma arises from epithelium overlying the lamina propria of the endosalpinx in women at high hereditary risk to develop ovarian carcinoma. Loss of the wild-type breast cancer 1 or 2 gene (BRCA1/2) allele is most likely pivotal in carcinogenesis of these tumours. To be unequivocally identified, the tumour has to fulfill the clinical and histological criteria for tubal carcinoma [1256] as well as clinical genetic criteria.

Incidence
From 1997 to 2002, a total of 15 hereditary breast/ovarian family related tubal tumours have been reported in literature. In 4 cases, a BRCA2 mutation was detected. However, the true incidence of hereditary tubal carcinoma is probably much higher, as is suggested for its sporadic counterpart. This is caused by the fact that primary tubal tumours are often mistaken for primary ovarian carcinomas (3150). Moreover, some primary ovarian carcinomas might actually derive from inclusion cysts lined by tubal epithelial cells included into the ovarian stroma [2247].

Age distribution
In general the age of onset is younger in hereditary cases when compared to sporadic cases.

Diagnostic criteria
The criteria of Hu et al. [1256] as modified by Sedlis [2614] and Younessi [3185] are applied to differentiate hereditary tubal carcinomas from ovarian and endometrial carcinoma. These criteria require that: (i) the main tumour is in the fallopian tube and arises from the endosalpinx, (ii) the histological features resemble a tubal pattern, (iii) if the tubal wall is involved, the transition between malignant and benign tubal epithelium should be detectable, (iv) the fallopian tube contains more tumour than the ovary or endometrium.

Clinical features

Symptoms and signs. To date, there is no indication that clinical hereditary tubal carcinoma features are different from those of its sporadic counterpart; abdominal discomfort is more or less common, but an atypical complaint. The classical but rare triad of symptoms include: (i) prominent watery vaginal discharge, (ii) pelvic pain and (iii) pelvic mass [158]. It has been reported that approximately 10% of patients will have adenocarcinomatous cells in cervical cytology [3185].

Tumour markers. As in ovarian carcinoma, elevation of serum CA125 levels can be found in approximately 80% of cases [1173].

Imaging. CT / MRI are inconclusive with respect to the differential diagnosis of
tubal or ovarian carcinomas. However, these techniques can be helpful in determining the extent of disease. Likewise, ultrasonography can not distinguish tubal from ovarian disease (2720).

Pathology

Histopathology and grading. Serous papillary carcinoma is one of the most common forms of hereditary tubal carcinoma. Grading is of limited value in these tumours and, if used, is based on the papillary architecture, nuclear atypia and mitotic activity. Grade I cancers show papillary growth with well differentiated columnar cells and low mitotic rate. Grade II cancers are papillary with evident gland formation with intermediated differentiated cells with moderate mitotic activity. Grade III shows solid growth with loss of papillae and a medullary/glandular pattern. The cells are poorly differentiated and the mitotic activity is high.

Immunoprofile. Being predominantly of serous papillary type, hereditary tubal carcinomas are positive for cytokeratins 7 and 8, MUC1, CEA, OVTL3, OV622, CA125, and negative or showing only low expression for cytokeratin 20, CEA and vimentin. Also, p53 is often expressed, and cyclins E and A and Ki67 show a varying number of proliferating cells, whereas staining for HER-2/neu and cyclin D1 is usually negative. Steroid receptor content varies. In the rare clear cell cancers, p21 is highly expressed.

Seeding and metastasis

Hereditary tubal carcinomas presumably spread like their sporadic counterparts. However, only empirical data are available to date, pointing to a mode of spread similar to ovarian cancer.

Survival

The five-year survival rate of 30% in sporadic cases varies with stage (159,3185), but not with grade. The survival rate of hereditary tubal carcinomas has yet to be established since only small numbers of patients have been reported and most patients have still not completed their 5-year follow-up.

Prophylactic interventions

In one study, 30 women with either a documented deleterious BRCA1 or BRCA2 mutation or a suggestive family history underwent prophylactic oophorectomy (1617). Five of these (17%) were found to have clinically occult malignancy, 3 of which involved a primary fallopian tube malignancy. Three of the five were known BRCA1 mutation carriers, one had a documented BRCA2 mutation. Therefore, it is recommended to perform a complete adnexitomy in women carrying a BRCA1 or a BRCA2 mutation. Whether an abdominal hysterectomy should be performed to dissect the intra-uterine part of the tube, is still in debate. However, most studies indicate that tubal carcinomas in fact predominantly arise in distal parts of the tube.

Other tumours

BRCA2 confers an increased risk of ovarian cancer, but not as high as that for BRCA1. Statistically significant increases in risk were observed for a number of other tumour types, including prostate, pancreatic and stomach cancer. The risk for male breast cancer, although the hallmark of BRCA2 mutations, is based on only four observed cases and hence is very imprecise.

Table 8.06
Cancer risks of BRCA2 carriers.

<table>
<thead>
<tr>
<th>Cancer site or type</th>
<th>Relative risk (95% CI)</th>
<th>Cumulative Risk By Age 70, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (female)</td>
<td>Age-dependent</td>
<td>84 (43 – 95)</td>
</tr>
<tr>
<td>Breast (male)</td>
<td>150</td>
<td>6.3 (1.4 – 25.6)</td>
</tr>
<tr>
<td>Ovary</td>
<td>Age-dependent</td>
<td>27 (0 – 47)</td>
</tr>
<tr>
<td>Gall bladder and bile ducts</td>
<td>4.97 (1.50 – 16.5)</td>
<td>-</td>
</tr>
<tr>
<td>Prostate</td>
<td>4.65 (3.48 – 6.22)</td>
<td>7.5 (9.7 – 9.3)</td>
</tr>
<tr>
<td>Prostate before age 65</td>
<td>7.33 (4.66 – 11.52)</td>
<td>-</td>
</tr>
<tr>
<td>Pancreas*</td>
<td>3.51 (1.87 – 6.58)</td>
<td>Males: 2.1 (1.2 – 3.0) Females: 1.5 (0.9 – 2.1)</td>
</tr>
<tr>
<td>Stomach*</td>
<td>2.59 (1.46 - 4.61)</td>
<td>-</td>
</tr>
<tr>
<td>Malignant melanoma*</td>
<td>2.58 (1.28 – 5.17)</td>
<td>-</td>
</tr>
<tr>
<td>All cancers*</td>
<td>2.46 (2.15 – 2.78)</td>
<td>-</td>
</tr>
</tbody>
</table>

- Relative risks were slightly higher for individuals aged 65 or under.
- All cancers other than nonmelanoma skin cancer, breast cancer, or ovarian cancer.

Genetics

Chromosomal location and gene structure

BRCA2 is located on chromosome 13q12.3. It consists of 27 exons, of which exon 11 is remarkably large (4.9 kb). The open reading frame is 10,254 basepairs, encoding a protein of 3,418 amino acids that has no significant similarity to any known protein. Exon 11 encodes a structural motif consisting of eight ‘BRC’ repeats, through which BRCA2 controls the function of RAD51, a recombinase enzyme, in pathways for DNA repair by homologous recombination.

Gene expression

A wide range of human tissues express BRCA2 mRNA, in a pattern very similar to that of BRCA1, but the highest levels were observed in breast and thymus, with slightly lower levels in lung, ovary, and spleen (2891). In normal cells, BRCA2 is a nuclear protein, preferentially expressed during the late-G1/early-S phase of the cell cycle (258,480,3012). In mice, Brca1 and Brca2 are coordinately upregulated during ductal proliferation, morphogenesis and differentiation of breast epithelial cells occurring at puberty, pregnancy and lactation (1582,1769,
Both proteins co-exist with RAD51 in subnuclear foci during S phase, which redistribute following DNA damage (450, 2193). Exon 12 of the messenger is alternatively spliced, and there is some suggestion that this splice variant is expressed at higher levels in about a third of sporadic breast tumour when compared to normal epithelial cells (266). In sporadic breast tumours, BRCA2 mRNA-expression was higher than that in normal surrounding tissues in 20% of the cases, and lower in 11% (267). In agreement with this, no hypermethylation of the BRCA2 promotor region has been detected in breast and ovarian cancer (541).

**Gene function**

Loss, or mutational inactivation, of the single wild-type allele in heterozygous carriers of mutations in the BRCA2 gene is a key step in tumourigenesis. The mechanism by which the encoded protein contributes to disease progression is not yet completely understood but is thought to be related, at least in part, to the proposed role of BRCA2 in the repair of damaged DNA. BRCA2 encodes a very large (3,418 amino acids in humans) protein that is expressed during S phase of the cell cycle when it is present in the cell nucleus. Although the amino acid sequence of the BRCA2 protein presents few direct clues as to its normal cellular role, some functional domains have been defined. The C-terminal region of BRCA2 contains a functional nuclear localization sequence; many pathogenic truncating mutations in human BRCA2 are proximal to this domain and would therefore be predicted to encode cytoplasmic proteins. The central part of the protein encoded by the large exon 11 contains eight copies of a novel sequence (the BRC repeat) that has been shown to be capable of binding RAD51 protein. RAD51 is a key protein involved in double-strand DNA break repair and homologous recombination and the interaction with BRCA2 was the first evidence implicating the protein in these processes. BRCA2-deficient cells and tumours characteristically accumulate aberrations in chromosome structure (3018). These lesions include breaks involving one of the two sister chromatids, as well as tri-radial and quadri-radial chromosomes typical of Bloom syndrome and Fanconi anaemia. Thus, BRCA2 deficiency may be similar in its pathogenesis to other genetic diseases in which unstable chromosome structure is linked to cancer predisposition. Chromatid-type breaks, tri-radial and quadri-radial chromosomes are thought to arise from defects in the repair of DNA double-strand breaks (DSBs) during the S phase of cell cycle. During S phase, DSB repair proceeds preferentially through mechanisms involving homologous recombination. These mechanisms enable error-free repair of broken DNA, taking advantage of the availability of the replicated sister chromatid as a substrate for recombination reactions. In BRCA2-deficient cells, DSB repair by homologous recombination is defective. However, alternative – but error-prone – mechanisms for DSB repair such as end-joining or strand-annealing are still present. The end result is that DSBs in BRCA2-deficient cells are mis-repaired, giving rise to mutations and chromosomal rearrangements including translocations or deletions. The resulting genetic instability is believed to potentiate the accumulation of mutations that transform a normal cell into a cancer cell. Thus, BRCA2 works as a tumour suppressor indirectly through its ‘caretaker’ role in protecting chromosomal stability. BRCA2 is essential for homologous recombination because it controls the intra-cellular transport and activity of RAD51. In BRCA2-deficient cells, RAD51 fails to efficiently enter the nucleus. After exposure of BRCA2-deficient cells to DNA damaging agents, RAD51 fails to localize...
in typical nuclear foci that may represent sites for DNA damage processing. Moreover, BRCA2 controls the assembly of RAD51 into a nucleoprotein filament that coats DNA, a critical intermediate structure in recombination reactions. Unexpected and potentially informative insight into the role of BRCA1/2 genes in DNA repair in humans in vivo has come from recent studies on Fanconi anaemia (FA), a complex disorder characterized by congenital abnormalities, progressive bone marrow failure and cancer susceptibility. FA is a recessively inherited disorder which can result from mutation in at least 8 individual genes. It has recently been suggested that one of the previously unidentified FA genes, FANCD1, is in fact BRCA2 (1251). The cellular consequences of homozygosity for BRCA2 mutation, including spontaneous chromosome instability and hypersensitivity to DNA cross-linking agents, are rather similar to those observed in cells derived from FA patients. This is not the only link between FA and breast cancer susceptibility genes. Another FA gene product, FANCD2, can interact and co-localize with BRCA1 (958). Thus it seems that the pathways disrupted in FA and breast cancer susceptibility are intimately connected. Only a small proportion of FA, which in itself is rare, is caused by BRCA2 mutation but the importance of this finding is that it connects together two previously different bodies of work on DNA repair.

A current simplified model on how BRCA2 and several other genes involved in breast cancer predisposition act coordinately to repair DNA damage is indicated in Fig. 8.08. ATM and CHEK2 protein kinases signal the presence of double-stranded DNA breaks and phosphorylate (red arrows) a number of downstream effector proteins, including BRCA1. This induces their migration to sites where DNA is repaired. BRCA2 carries the DNA-recombination enzyme RAD51 to the same sites, guided there by the DNA-binding structures formed between its C-terminal domain and Dss1 protein. A complex of Fanconi anaemia proteins – termed A, C, D2, E, F, and G – triggers the ubiquitination of the D2 protein alone and its colocalization with BRCA1.

Other roles for BRCA2 have been suggested in chromatin remodelling and gene transcription [1442]. Such functions – which remain very poorly characterized – may help to explain why cancer predisposition associated with BRCA2 mutations should be specific to tissues such as the breast and ovary. However, notwithstanding these other potential functions, it seems likely that loss of BRCA2 function engenders genomic instability leading to oncogene activation and tumour suppressor loss that culminates in tumorigenic progression. A major challenge for future work will be to understand how this basic pathogenic mechanism plays out in the complex tissue environments of the breast, ovary or prostate, giving rise to site-specific epithelial malignancies.

**Mutation spectrum**

Germline mutations in BRCA2 have been detected in 5-10% of clinic-based breast cancer families, and in similar frequencies of breast-ovarian cancer families (2657,3023). Somatic mutations in sporadic breast and ovarian tumours are extremely rare. Mutations occur throughout the entire coding region, and hence the mutation spectrum did not provide immediate clues to functional gene domains. The majority of the mutations are predicted to lead to a prematurely truncated protein when translated. In conjunction with the observed loss of the wildtype allele in tumours arising in mutation carriers (560), this indicates the importance of gene inactivation for tumourigenesis to occur. Despite the strong variability in mutations detected in families, founder effects have led to some mutations being very prevalent in certain populations of defined geographical or ethnic background. Examples are the 999del5 mutation, which is present in approximately 0.6% of all Icelandic individuals (2920), and the 6174delT mutation found in an equal proportion of Ashkenazi Jews (2083). As a result, mutation spectra may vary according to ethnic background of the sampled population (2824). In recent years, an increasing number of missense changes are being detected in BRCA2 of which the clinical significance is uncertain in the absence of a functional assay. These already comprise up to 50% of all known sequence changes in BRCA2. Although many of them are expected to be rare neutral polymorphisms, some might be associated with elevated levels of breast cancer risk. An example is the arginine for histidine substitution at codon 372 (1167).

Many known deleterious BRCA1 and BRCA2 mutations affect splicing, and these typically lie near intron/exon boundaries. However, there are also potential internal exonic mutations that disrupt functional exonic splicing enhancer (ESE) sequences, resulting in exon skipping. A T2722R mutation segregated with affected individuals in a family with breast cancer and disrupted 3 potential ESE sites [816]. The mutation caused deleterious protein truncation and suggested a potentially useful method for determining the clinical significance of a subset of the many unclassified variants of BRCA1 and BRCA2. As more functional and structural information on the BRCA1 and BRCA2 proteins accumulates, our understanding of genetic variation in these genes will improve. The Breast Cancer Information Core (BIC) maintains a website providing a central repository for information regarding mutations and polymorphisms (http://research.nhgri.nih.gov/bic/).

**Genotype-phenotype correlations**

Evidence is accumulating that the risks conferred by pathogenic BRCA2 mutations are dependent on the position of the mutation in the gene, genetic variation in other genes, and environmental or lifestyle factors.

**BRCA2 mutation position**

Truncating mutations in families with the highest risk of ovarian cancer relative to breast cancer are clustered in a region of approximately 3.3 kb in exon 11 [972]. This region of BRCA2, bounded by nucleotides 3035 and 6629, was dubbed the ‘ovarian cancer cluster region,’ or OCCR. Notably, this region coincides with the BRC repeats that are critical for the functional interaction with the RAD51 protein. A much larger study of 164 families confirmed that OCCR mutations are associated with a lower risk of breast cancer and with a higher risk of ovarian cancer [2913]. The extent of risk modification is too moderate, however, to be used in genetic counseling.

**Genetic risk-modifiers**

A length-variation of the polyglutamine repeats in the estrogen receptor co-activator NCOR3 influences breast cancer risk in carriers of BRCA1 and BRCA2 [2345]. Although it should be noted that most of the carriers in these studies are BRCA1 carriers, and there was insuffi-
cient power to determine the effect in BRCA2 carriers alone. Similarly, the variant progesterone receptor allele named PROGINS was associated with an odds ratio of 2.4 for ovarian cancer among 214 BRCA1/2 carriers with no past exposure to oral contraceptives, compared to women without ovarian cancer and with no PROGINS allele [2487]. A C/G polymorphism in the 5′ untranslated region of RAD51 was found to modify both breast and ovarian cancer risk in carriers of BRCA2 [1644,3053]. These results support the hypothesis that genetic variation in the genes constituting endocrine signalling and DNA repair pathways may modify BRCA2-associated cancer risk.

Hormonal risk modifiers
As in the BRCA1 syndrome, the breast cancer risk of BRCA2 carriers is influenced by hormonal factors, including oral contraceptives and pregnancy (see page 56).

Prognosis and prevention
Life expectancy and preventive strategies are similar to those discussed for BRCA1 carriers (see page 56).

Li-Fraumeni syndrome

Definition
Li-Fraumeni syndrome (LFS) is an inherited neoplastic disease with autosomal dominant trait. It is characterized by multiple primary neoplasms in children and young adults, with a predominance of soft tissue sarcomas, osteosarcomas, breast cancer, and an increased incidence of brain tumours, leukaemia and adrenocortical carcinoma. The majority of Li-Fraumeni cases is caused by a TP53 germline mutation.

MIM Nos. (1835)
Li-Fraumeni syndrome 151623
TP53 mutations (germline and sporadic) 191170
CHEK2 mutations 604373

Synonym
Sarcoma family syndrome of Li and Fraumeni.

Incidence
From 1990 to 1998, 143 families with a TP53 germline mutations were reported [2086]. The IARC Database (www.iarc.fr/p53/germline.html) currently contains 223 families [2104a].

Diagnostic criteria
The criteria used to identify an affected individual in a Li-Fraumeni family are: (i) occurrence of sarcoma before the age of 45 and (ii) at least one first degree relative with any tumour before age 45 and (iii) a second (or first) degree relative with cancer before age 45 or a sarcoma at any age [273,957,1650].
Breast tumours

Frequency
Breast cancers are the most frequent neoplasms developed in families with a TP53 germline mutation. Thirty-seven% of these families are defined as Li-Fraumeni syndrome and 30% as Li-Fraumeni-like syndrome. In the 219 families with a TP53 germline mutation reported in 1990–2001 (IARC TP53 database: www.iarc.fr/p53), a total of 562 tumours developed in individuals with a confirmed TP53 germline mutation. Of these, 158 (28%) were breast tumours. Eighty-three (38%) families with a TP53 mutation had at least one family member with a breast tumour. Among the families in which at least one case of breast cancer developed, the mean number of breast tumours per family was 1.9.

Age and sex distribution
Breast cancers associated with a TP53 germline mutation develop earlier than their sporadic counterparts, with a mean age of 35±10 years (range 14-67 years old). The mean age of women with Li-Fraumeni-like syndrome (LFL) is approximately 8 years higher (2104a) However, breast cancers associated with TP53 germline mutations never developed in young children, suggesting that hormonal stimulation of the mammary glands constitutes an important co-factor. Sporadic breast tumours occur approximately 100 times more frequently in females than in males (1475), and none occurred in males among the 158 reported breast cancer with TP53 germline mutations.

Pathology
Of the 158 breast tumours recorded, the majority (146 cases, 92%) have not been classified histologically, but recorded as just breast cancers. Histologically classified cases included carcinoma in situ (4 cases), adenocarcinoma (1 case), Paget disease (2 cases), malignant phyllodes tumour (2 cases), comedocarcinoma (1 case), spindle cell sarcoma (1 case), and stromal sarcoma (1 case).

Prognosis and prognostic factors
The breast cancers that occur in LFS are of younger onset and so may have a poorer prognosis due to this early age at diagnosis. In mice, there is relative radioresistance in p53 mutants, however, radioresistance due to germline mutation has not been convincingly shown in man.

Other tumours
Frequency
Following breast cancer, brain tumours and sarcomas (osteosarcomas and soft tissue sarcomas) are the next most frequent manifestations. The sporadic counterparts of these tumours also show somatic TP53 mutations, suggesting that in these neoplasms, TP53 mutations are capable of initiating the process of malignant transformation (1475,2087).

Age distribution
In general, tumours associated with a TP53 germline mutation develop earlier than their sporadic counterparts, but there are marked organ-specific differences. As with sporadic brain tumours, the age of patients with nervous system neoplasms associated with TP53 germ-line mutations shows a bimodal distribution. The first peak of incidence (representing medulloblastomas and related primitive neuroectodermal tumours) is in children, and the second (mainly astrocytic brain tumours) in the third and fourth decades of life (2087). Adrenocortical carcinomas associated with a TP53 germline mutation develop almost exclusively in children, in contrast to sporadic adrenocortical carcinomas, which have a broad age distribution with a peak beyond age 40 (1475).

Genetics – TP53
Chromosomal location
The TP53 gene encompasses 20 kilobases on chromosome 17p13.1. TP53 belongs to a family of growth suppressors that also comprises two other members, TP73 and TP63. Whereas the two latter genes are mostly involved in the regulation of differentiation and development, TP53 plays specialized functions as a tumour suppressor (1643).

Gene structure
The gene contains 11 exons, the first one non-coding. The first intron is particularly large (10 kilobases). The coding sequence is concentrated over 1.3 kilobases. TP53 is ubiquitously expressed, mostly as a single mRNA species (although rare alternatively spliced variants have been reported). The promoter does not contain a classical TATA box but shows binding elements for several common transcription factors, including c-Jun and NF-kappaB (1107).

Gene expression
The p53 protein is constitutively expressed in most cell types but, in normal circumstances, does not accumulate to significant level due to rapid degradation by the proteasome machinery. In response to various types of cellular stress, the p53 protein undergoes a number of post-translational modifications that release p53 from the negative control of MDM2, a protein that binds to p53 and mediates its degradation.
These modifications result in the intranuclear accumulation of p53 and in its activation as a transcription factor. Two major signaling pathways can trigger TP53 activation. The first, and best characterized, is the pathway of response to DNA damage, including large kinases of the phosphoinositide-3 kinase family such as ATM (ataxia-telangiectasia mutated) and the cell-cycle regulatory kinase CHEK2. Both of these kinases phosphorylate p53 in the extreme N-terminus (serines 15, 20 and 37), within the region that binds to MDM2. The second is activated in response to the constitutive stimulation of growth-promoting signaling cascades. The central regulator in this pathway is p14ARF, the alternative product of the locus encoding the cyclin-kinase inhibitor p16/CDKN2a. p14ARF expression is activated by E2F transcription factors, and binds to MDM2, thus neutralizing its capacity to induce p53 degradation. This pathway may be part of a normal feedback control loop in which p53 is activated as a cell-cycle brake in cells exposed to hyperproliferative stimuli (2267).

Genetic function
After accumulation, the p53 protein acts as a transcriptional regulator for a panel of genes that differ according to the nature of the stimulus, its intensity and the cell type considered. Broadly speaking, the genes controlled by p53 fall into three main categories, including cell-cycle regulatory genes (WAF1, GADD45, 14-3-3S, CYCLING), pro-apoptotic genes (FAS, AP01/CD95, KILLER/DR5, AIF1, PUMA, BAX) and genes involved in DNA repair (O6MGMT, MLH2). The p53 protein also binds to components of the transcription, replication and repair machineries and may exert additional controls on DNA stability through the modulation of these mechanisms. Collectively, the p53 target genes mediate two type of cellular responses: cell-cycle arrest, followed by DNA repair in cells exposed to light forms of genotoxic stress, and apoptosis, in cells exposed to levels of damage that cannot be efficiently repaired. Both responses contribute to the transient or permanent suppression of cells that contain damaged, potentially oncogenic, DNA. In the mouse, inactivation of Tp53 by homologous recombination does not prevent normal growth but results in a strong predisposition to early, multiple cancers, illustrating the crucial role of this gene as a tumour suppressor (714).

Mutation spectrum
The TP53 gene is frequently mutated in most forms of sporadic cancers, with prevalences that range from a few percents in cervical cancers and in malignant melanomas to over 50% in invasive carcinomas of the aero-digestive tract. Over 75% of the mutations are single base substitutions (missense or nonsense), clustering in exons 5 to 8 that encode the DNA-binding domain of the protein. Codons 175, 245, 248, 273 and 282 are major mutation hotspots in almost all types of cancers. Together, these codons contain over 25% of all known TP53 mutations. Other codons are mutation hotspots in only specific tumour types, such as codon 249 in hepatocellular carcinoma and codon 157 in bronchial cancer. Mutation patterns can differ significantly between different types cancers or between geographic areas for the same cancer type (as for example hepatocellular carcinoma). These observations have led to the concept that mutation patterns may reveal clues on the cellular or environmental mechanisms that have caused the mutations (1107). In sporadic breast cancers, TP53 is mutated in about 25% of the cases. However, several studies have reported accumulation of the p53 protein without mutation in up to 30-40% of invasive ductal carcinoma in situ. The mutation pattern is similar to that of many other cancers and does not provide information on possible mutagenic events. There is limited evidence that the mutation prevalence is higher in BRCAl mutation carriers. Germline TP53 mutations have been identified in 223 families. Of these families, 63 match the strict LFS criteria, 67 correspond to the extended, LFL definition, 37 have a family history of cancer that does not fit within LFS or LFL definitions and 36 have germline mutations without documented familial history of cancer (IARC TP53 mutation database, www.iarc.fr/p53). The codon distribution of germline TP53 mutations show the same mutational hotspots as somatic mutations (1475). The distribution of inherited mutations that predispose to breast cancer are scattered along exons 5 to 8 with relative ‘hotspots’ at codons 245, 248 and 273, which are also commonly mutated in somatic breast cancer. In contrast, a total of 16 breast cancers have been detected in 5 families with a germline mutation at codon 132, a position which is not a common mutation hotspot in somatic breast cancer. It remains to be established whether this mutant has particular functional properties that predispose to breast cancer.

Genotype-phenotype correlations
Brain tumours appear to be associated with missense TP53 mutations in the...
DNA-binding loop that contacts the minor groove, while early onset brain tumours were associated with mutations likely to result in absence of protein or loss of function [2104a]. Adrenocortical carcinomas were associated with missense mutations in the loops opposing the protein-DNA contact surface [2104a]. 

**Genetics – CHEK2**

**Chromosomal location**

CHEK2 is on chromosome 22q12.1.

**Gene structure**

CHEK2 has 14 exons and there are several homologous loci, which encompass exons 10-14 of the gene, scattered throughout the genome. These gene fragment copies can present problems when analysing CHEK2 for germline mutations in genomic DNA, and it is important to ensure that the correct copy is being amplified [2742]. This problem can be overcome by amplifying exons 10-14 by the use of a long range PCR using primers located in the non-duplicated region of the gene [2741]. The individual exons can then be subsequently amplified using the product of the long range PCR as a template.

**Gene expression**

CHEK2 is expressed in nonproliferating and terminally differentiated cells. It is homogenously expressed in renewing cell populations such as epidermis, esophagus, rectum, bladder, stomach, intestine and colon, and heterogeneously in conditionally renewing tissues such as lung, breast kidney, salivary, thyroid, parathyroid, adrenal glands, pancreas, prostate, epididymis, sweat glands, endometrium, stomal mesenchymal cells, blood vessels, lymphoid tissues, smooth and cardiac muscle tissues and peripheral nerves. It is absent or cytoplasmic in static tissues such as muscle and brain. CHEK2 remains expressed and can be activated in all phases of the cell cycle in response to DNA damage [1714].

**Gene function**

Human CHEK2 is a homolog of the yeast G2-checkpoint kinases CDS1 and RAD53 [1791]. In response to DNA damage, CHEK2 propagates the checkpoint signal along several pathways, which eventually cause cell-cycle arrest in G1, S and G2/M phases (449,820); activation of DNA repair [1609], and in apoptotic cell death [1315]. Four of the downstream checkpoint effectors that are established as substrates of CHEK2 in vivo include p53, BRCA1 and Cdc25A and Cdc25C.

**Mutation spectrum**

Recently, heterozygous germline mutations in CHEK2 have been identified in three of a subset of individuals with the dominantly inherited Li-Fraumeni syndrome which do not harbour TP53 mutations [209]. However, one of these was found to be in a pseudogene copy of the CHEK2 gene. Another one appeared to be neutral polymorphism in the Finnish population. The third was a protein-truncating mutation, 1100delC in exon 10, which abolishes the kinase function of CHEK2. The possibility that this gene is only contributing to the breast cancer cases within LFS families rather than LFS per se has been raised [2740].

The frequency of 1100delC has been estimated in healthy control populations, and was found to vary between 0.3% and 1.7% [1840,2084,2984]. This would also suggest that the 1100delC is a polymorphism, rather than a disease-causing mutation. Yet among unselected patients with breast cancer, its prevalence was found to be approximately 1.5-fold higher than in controls. Significantly elevated frequencies were found among patients with a positive family history and among patients with bilateral breast cancer [2984].

The strongest enrichment of 1100delC carriers (approximately 5-fold) was found among familial breast cancer patients in whom the presence of BRCA1 or BRCA2 mutations were excluded [1840,2984]. However, in families with the 1100delC mutation, it appears to cosegregate poorly with breast cancer. The results suggest that CHEK2*1100delC is a low risk breast cancer susceptibility allele which may make a significant contribution to familial clustering of breast cancer, including families with smaller numbers of affected cases. As it is enriched among multiple-case families, but unable to explain all breast cancer in families with at least one carrier case, it may interact with other, as yet unknown breast cancer susceptibility alleles.

**Search for additional LFS genes**

The paucity of large LFS kindreds makes classical linkage methodology difficult. A candidate approach is therefore being used. Candidate genes are those involved in cell cycle pathways, those commonly mutated in multiple tumour types and the breast cancer genes, as this site is commonly affected in LFS kindreds. Using these approaches, the genes P16 and PTEN (379) have been analysed and no germline mutations found.
Cowden syndrome

Definition
Cowden syndrome (CS) is an autosomal dominant disorder caused by germline mutations of the PTEN gene. It is characterized by multiple hamartomas involving organs derived from all three germ cell layers and a high risk of breast, uterine and non-medullary thyroid cancer. The classic hamartoma is the trichilemmoma and is pathognomonic for CS.

MIM No. 158350 (1835)

Synonyms
Cowden disease, multiple hamartoma syndrome.

Incidence
The single most comprehensive clinical epidemiologic study before the CS susceptibility gene was identified estimated the prevalence to be 1:1,000,000 (1990,2776). Once the gene was identified (1995), a molecular-based estimate of prevalence in the same population was 1:300,000 (1989). Because of the difficulty in recognizing this syndrome, prevalence figures are likely underestimated.

Diagnostic criteria
Because of the variable and broad expression of CS and the lack of uniform diagnostic criteria prior to 1996, the International Cowden Consortium (1990) compiled operational diagnostic criteria for CS, based on the published literature and their own clinical experience (785). These criteria have been recently revised in light of new data, and have been adopted by the US-based National Comprehensive Cancer Network Practice Guidelines (786,1299). Trichilemmomas and papillomatous papules are particularly important to recognize. CS usually presents by the late 20's. It has variable expression and, probably, an age-related penetrance although the exact penetrance is unknown. By the third decade, 99% of affected individuals would have developed the mucocutaneous stigmata although any of the features could be present already. Because the clinical literature on CS consists mostly of reports of the most florid and unusual families or case reports by subspecialists interested in their respective organ systems, the spectrum of component signs is unknown. Despite this, the most commonly reported manifestations are mucocutaneous lesions, thyroid abnormalities, fibrocystic disease and carcinoma of the breast, gastrointestinal hamartomas, multiple, early-onset uterine leiomyoma, macrocephaly (specificaly, megencephaly) and mental retardation (1133, 1693,1748,2776). Recent data have suggested that endometrial carcinoma should be a component cancer of CS (657,786,1772). What its frequency is in mutation carriers is as yet unknown.

Table 8.07 International Cowden Syndrome Consortium Operational Criteria for the Diagnosis of Cowden Syndrome (Ver. 2000)*.

<table>
<thead>
<tr>
<th>Pathognomonic criteria</th>
<th>Mucocutaneous lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trichilemmomas, facial</td>
</tr>
<tr>
<td></td>
<td>Acral keratoses</td>
</tr>
<tr>
<td></td>
<td>Papillomatous papules</td>
</tr>
<tr>
<td></td>
<td>Mucosal lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Breast carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thyroid carcinoma (non-medullary), esp. follicular thyroid carcinoma</td>
</tr>
<tr>
<td></td>
<td>Macrocephaly (Megalencephaly) (say, &gt;97%ile)</td>
</tr>
<tr>
<td></td>
<td>Lhermitte-Duclos disease (LDD)</td>
</tr>
<tr>
<td></td>
<td>Endometrial carcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
<th>Other thyroid lesions (e.g. adenoma or multinodular goiter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mental retardation (say, IQ &lt; 75)</td>
</tr>
<tr>
<td></td>
<td>GI hamartomas</td>
</tr>
<tr>
<td></td>
<td>Fibrocystic disease of the breast</td>
</tr>
<tr>
<td></td>
<td>Lipomas</td>
</tr>
<tr>
<td></td>
<td>Fibromas</td>
</tr>
<tr>
<td></td>
<td>GU tumours (e.g. renal cell carcinoma, uterine fibroids) or malformation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operational diagnosis in an individual</th>
<th>1. Mucocutaneous lesions alone if:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a) there are 6 or more facial papules, of which 3 or more must be trichilemmoma, or</td>
</tr>
<tr>
<td></td>
<td>b) cutaneous facial papules and oral mucosal papillomatosis, or</td>
</tr>
<tr>
<td></td>
<td>c) oral mucosal papillomatosis and acral keratoses, or</td>
</tr>
<tr>
<td></td>
<td>d) plantar keratoses, 6 or more</td>
</tr>
<tr>
<td></td>
<td>2. Two major criteria but one must include macrocephaly or LDD</td>
</tr>
<tr>
<td></td>
<td>3. One major and 3 minor criteria</td>
</tr>
<tr>
<td></td>
<td>4. Four minor criteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operational diagnosis in a family where one individual is diagnostic for Cowden</th>
<th>1. The pathognomonic criteria/ia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Any one major criterion with or without minor criteria</td>
</tr>
<tr>
<td></td>
<td>3. Two minor criteria</td>
</tr>
</tbody>
</table>

*Operational diagnostic criteria are reviewed and revised on a continuous basis as new clinical and genetic information becomes available. The 1995 version and 2000 version have been accepted by the US-based National Comprehensive Cancer Network High Risk/Genetics Panel.
Like other inherited cancer syndromes, breast cancers, even of the breast and thyroid, have been diagnosed as early as the age of 14 years and as late as in the 60's {1693}. However, the majority of CS-related breast cancers occur after the age of 30-35 years {786,788}. A single population-based clinical study, without the benefit of genetic analysis, suggested that benign breast disease can occur in two-thirds of affected women while CS females have a 25-50% lifetime risk of developing invasive breast cancer {786,2776}. Male breast cancer can occur in CS as well but the frequency is unknown {817,1771}.

Clinical features
It is believed that the clinical presentation of breast cancer in CS is no different from that of the general population. However, no formal data is currently available.

Pathology
Like other inherited cancer syndromes, multifocality and bilateral involvement is the rule. With regard to the individual cancers, even of the breast and thyroid, as of mid 1997, there has yet to be a systematic study published. There exists, however, one study which has attempted to look at benign and malignant breast pathology in CS patients. Although these are preliminary studies, without true matched controls, it is, to date, the only study that examines breast pathology in a series of CS cases. Breast histopathology from 59 cases belonging to 19 CS women was systematically analysed {2578}. Thirty-five specimens had some form of malignant pathology. Of these, 31 (90%) had ductal adenocarcinoma, one tubular carcinoma and one lobular carcinoma-in-situ. Sixteen of the 31 had both invasive and in situ (DCIS) components of ductal carcinoma while 12 had DCIS only and two only invasive adenocarcinoma. Interestingly, it was noted that 19 of these carcinomas appeared to have arisen in the midst of densely fibrotic hamartomatous tissue. Benign breast disease is more common than malignant, with the former believed to occur in 75% of affected females. Fibrocystic disease of the breast, breast hamartomas, and fibroadenomas are commonly seen.

Breast tumours

Age distribution and penetrance
Invasive carcinomas of the breast have been diagnosed as early as the age of 14 years and as late as in the 60's {1693}. However, the majority of CS-related breast cancers occur after the age of 30-35 years {786,788}. A single population-based clinical study, without the benefit of genetic analysis, suggested that benign breast disease can occur in two-thirds of affected women while CS females have a 25-50% lifetime risk of developing invasive breast cancer {786,2776}. Male breast cancer can occur in CS as well but the frequency is unknown {817,1771}.

Clinical features
It is believed that the clinical presentation of breast cancer in CS is no different from that of the general population. However, no formal data is currently available.

Pathology
Like other inherited cancer syndromes, multifocality and bilateral involvement is the rule. With regard to the individual cancers, even of the breast and thyroid, as of mid 1997, there has yet to be a systematic study published. There exists, however, one study which has attempted to look at benign and malignant breast pathology in CS patients. Although these are preliminary studies, without true matched controls, it is, to date, the only study that examines breast pathology in a series of CS cases. Breast histopathology from 59 cases belonging to 19 CS women was systematically analysed {2578}. Thirty-five specimens had some form of malignant pathology. Of these, 31 (90%) had ductal adenocarcinoma, one tubular carcinoma and one lobular carcinoma-in-situ. Sixteen of the 31 had both invasive and in situ (DCIS) components of ductal carcinoma while 12 had DCIS only and two only invasive adenocarcinoma. Interestingly, it was noted that 19 of these carcinomas appeared to have arisen in the midst of densely fibrotic hamartomatous tissue. Benign breast disease is more common than malignant, with the former believed to occur in 75% of affected females. Fibrocystic disease of the breast, breast hamartomas, and fibroadenomas are commonly seen.

Uterine tumours

Age distribution and penetrance
Since endometrial carcinomas have only recently been suggested to be a minor component of CS {786}, it is unknown what the true frequency is among mutation carriers or what the age distribution is. Anecdotal cases suggest that the frequency could be 6-10% in affected women. Benign tumours of the uterus are common in CS. Uterine leiomyomas are believed to occur in almost half of affected women {1693}. They are usually multi-focal and occur at a young age, even in the 20’s. Other benign uterine pathologies such as polyps and hyperplasias have been found in CS patients but are of unknown frequency.

Clinical features
There have been no systematic studies of uterine tumours in CS. Clinical observation and anecdotal reports suggest that the leiomyomas can become quite symptomatic, presenting with bleeding and pain. It is unclear if the clinical presentation of the endometrial carcinomas is different from that of sporadic cases.

Pathology
There have been no systematic studies of uterine tumours in CS although it is believed that the histopathology is no different from that of typical sporadic cases.

Prognosis and prognostic factors
Whether the prognosis differs from sporadic cases is unknown.

Thyroid tumours

Age of distribution and penetrance
Apar from breast cancer, the other major component cancer in CS is non-medullary thyroid cancer. Nonmedullary thyroid carcinomas occur at a frequency of 3-10% of affected individuals, regardless of sex, in non-systematic clinical series {1693,2776}. It is unclear, however, whether the age of onset is earlier than that of sporadic cases. Benign thyroid disease occurs in approximately 70% of affected individuals. Component features include multinodular goitre and follicular adenomas. These benign tumours can occur at any age and can even manifest in teenagers.

Clinical features
Many of the benign tumours in CS individuals remain asymptomatic. However, the most common presenting sign or symptom would be a neck mass. Like many inherited syndromes, CS thyroid lesions can be multifocal and bilateral.

Pathology
No systematic studies have been performed to examine the thyroid in CS. However, clinical observations and clinical reports suggest that the histology of the nonmedullary thyroid carcinoma is predominantly of the follicular type {786,2776}.

Other tumours
Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease) is the major manifestation in the central nervous system. Peripheral lesions include verrucous skin changes, cobblestone-like papules, fibromas of the oral mucosa, multiple facial trichilemmomas and hamartomatous polyps of the colon.

Genetics
Chromosomal location and mode of transmission
CS is an autosomal dominant disorder, with age related penetrance and variable expression {787}. The CS susceptibility gene, PTEN, resides on 10q23.3 {1651,1654,1990}.

Gene structure
PTEN/MMAC1/TEP1 is comprised of 9 exons spanning 120-150 kb of genomic distance {1649,1651,1654,2777}. It is believed that intron 1 occupies much of this (approximately 100 kb). PTEN encodes a transcript of 1.2 kb.

Gene expression
PTEN is expressed almost ubiquitously in the adult human. In normal human embryonic and foetal development, PTEN protein is expressed ubiquitously as well, although levels might change throughout development {1008}. PTEN is very highly expressed in the developing central nervous system as well as neural crest and its derivatives, e.g. enteric ganglia {1008}.

Gene function
PTEN encodes a dual specificity lipid and protein phosphatase [reviewed in {3043}]. It is the major 3-phosphatase
acting in the phosphoinositol-3-kinase (PI3K)/Akt apoptotic pathway [1730, 2774]. To date, virtually all naturally occurring missense mutations tested abrogate both lipid and protein phosphatase activity, and one mutant, G129E, affects only lipid phosphatase activity [reviewed in (3043)]. Over-expression of PTEN results, for the most part, in phosphatase-dependent cell cycle arrest at G1 and/or apoptosis, depending on cell type [reviewed in (3043)]. There is also growing evidence that PTEN can mediate growth arrest independent of the PI3K/Akt pathway and perhaps independent of the lipid phosphatase activity [3096-3098] [reviewed in (3042)].

Murine models null for Pten result in early embryonic death [688,2268,2817]. Hemizygous knock-out of Pten result in various neoplasias, and the spectra are different depending on the particular model. While the neoplasias are reminiscent of the component tumours found in the human syndrome, none of the three models are similar to CS.

Mutation spectrum
As with most other tumour suppressor genes, the mutations found in PTEN are scattered throughout all 9 exons. They comprise loss-of-function mutations including missense, nonsense, frameshift and splice site mutations [309, 1771]. Approximately 30-40% of germline PTEN mutations are found in exon 5, although exon 5 represents 20% of the coding sequence. Further, approximately 65% of all mutations can be found in one of exons 5, 7 or 8 [309, 1771]. Although PTEN is the major susceptibility gene for CS, one CS family, without PTEN mutations, was found to have a germline mutation in BMPR1A, which is one of the susceptibility genes for juvenile polyposis syndrome (1256,3262). Whether BMPR1A is a minor CS susceptibility gene or whether this family with CS features actually has occult juvenile polyposis is as yet unknown.

Genotype-phenotype correlations
Approximately 70-80% of CS cases, as strictly defined by the Consortium criteria, have a germline PTEN mutation [1654,1771]. If the diagnostic criteria are relaxed, then mutation frequencies drop to 10-50% [1723,1991,2959]. A formal study which ascertained 64 unrelated CS-like cases revealed a mutation frequency of 2% if the criteria are not met, even if the diagnosis is made short of one criterion [1772]. A single research centre study involving 37 unrelated CS families, ascertained according to the strict diagnostic criteria of the Consortium, revealed a mutation frequency of 80% [1771]. Exploratory genotype-phenotype analyses revealed that the presence of a germline mutation was associated with a familial risk of developing malignant breast disease [1771]. Further, missense mutations and/or mutations 5' of the phosphatase core motif seem to be associated with a surrogate for disease severity (multi-organ involvement). One other small study comprising 13 families, with 8 PTEN mutation positive, could not find any genotype-phenotype associations [1893]. However, it should be noted that this small sample size is not suitable for statistical analyses and no conclusions should be drawn.

Previously thought to be clinically distinct, Bannayan-Riley-Ruvalcaba syndrome (BRR, MIM 153480), which is characterized by macrocephaly, lipomatosis, haemangiomatosis and speckled penis, is likely allelic to CS [1773]. Approximately 60% of BRR families and isolated cases combined carry a germline PTEN mutation [1774]. Interestingly, there were 11 cases classified as true CS-BRR overlap families in this cohort, and 10 of the 11 had a PTEN mutation. The overlapping mutation spectrum, the existence of true overlap families and the genotype-phenotype associations which suggest that the presence of germline PTEN mutation is associated with cancer strongly suggest that CS and BRR are allelic and are along a single spectrum at the molecular level. The aggregate term of PTEN hamartoma tumour syndrome (PHTS) has been suggested [1774]. Recently, the clinical spectrum of PHTS has expanded to include subsets of Proteus syndrome and Proteus-like (non-CS, non-BRR) syndromes [3260]. Germline PTEN mutations in one case of macrocephaly and autism and hydrocephaly associated with VATER association have been reported [625,2341].

Cowden syndrome 357
Inherited tumour syndromes

Endometrial tumours syndrome {595}. HNPCC (ICG-HNPCC) proposed a set of predisposed individuals from HNPCC endometrial cancer is diagnosed approx. 10 years earlier than in the general population. The mean age at diagnosis is 50 years. Patients with colorectal cancer associated with HNPCC have a better prognosis than patients with common sporadic colorectal cancer (2526,3070). In contrast, a recent study showed that the survival of endometrial cancer associated with HNPCC does not differ significantly from endometrial cancer in the general population (305).

Pathology of endometrial tumours
In patients from families with proven germline mutations in the MMR genes, MLH1, MSH2, MSH6, or from (suspected) HNPCC families, the majority of endometrial tumours were reported to be of the endometrioid type with diverse grading and staging (650,2174). Certain histopathologic features such as mucinous differentiation, solid-cribriform growth pattern, high grade and possible necrosis might suggest that a tumour is due to a mismatch repair defect (1481, 2174,2206).

Loss of MLH1 protein expression occurs in endometrial cancer associated with HNPCC (235,650,1276, 1768,2174,2264) but also in 15-30 % of sporadic cancers with somatic inactivation of MLH1 (2518,2772). Abrogation of MSH2 and/or MSH6 protein expression, especially at a young age seems to be a more specific indicator for HNPCC (235, 650). Already in the hyperplastic precursor lesions such loss of expression can be encountered (235, 650).

Other cancers
Many other cancers have been reported in HNPCC. (13,14,3009,310). The frequency of specific cancers depends on the prevalence of the cancer in the background population (2178). Cancer of the stomach for example is frequently observed in families from Finland and Japan, both countries with a high prevalence of stomach cancer in population. The ages at diagnosis of most cancers reported are earlier than their sporadic counterparts.

Table 8.08
Revised Amsterdam Criteria.
There should be at least three relatives with colorectal cancer (CRC) or with an HNPCC-associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.
-- one relative should be a first degree relative of the other two,
-- at least two successive generations should be affected,
-- at least one tumour should be diagnosed before age 50,
-- familial adenomatous polyposis should be excluded in the CRC case if any,
-- tumours should be verified by histopathologic examination.

Table 8.09
Bethesda Criteria.
1. Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extra-colonic cancers (endometrial, ovarian, gastric, hepatobiliary, small bowel cancer or transitional cell carcinoma of the renal pelvis or ureter)
2. Individuals with colorectal cancer and a first degree relative with colorectal cancer and/or HNPCC-related extra-colonic cancer and/or colorectal adenoma; one of the cancers diagnosed at age <45 y, and the adenoma diagnosed at age <40 y
3. Individuals with colorectal cancer or endometrial cancer diagnosed at age <45 y
4. Individuals with right-sided colorectal cancer with an undifferentiated pattern on histopathology diagnosed at age <45 y
5. Individuals with signet-ring-cell-type colorectal cancer diagnosed at age <45 y
6. Individuals with adenomas diagnosed at age <40 y

Hereditary non-polyposis colon cancer (HNPCC)

Definition
Hereditary non-polyposis colorectal cancer (HNPCC) is an autosomal dominant disorder characterized by the development of colorectal cancer, endometrial cancer and other cancers due to inherited mutations in one of the DNA mismatch repair (MMR) genes (1725).

MIM Nos. [1835]
Familial nonpolyposis colon cancer, type 1 120435
Familial nonpolyposis colon cancer, type 2 120436

Synonyms
Lynch syndrome, hereditary colorectal endometrial cancer syndrome (3007), hereditary defective mismatch repair syndrome (595).

Incidence
Approximately 2-5% of all cases of colorectal cancer are due to HNPCC (12).
The estimated frequency of carriers of a DNA mismatch repair gene mutation in the general population is one in 1000.

Diagnostic criteria
The International Collaborative Group on HNPCC (ICG-HNPCC) proposed a set of diagnostic criteria (Revised Amsterdam Criteria) to provide uniformity in clinical studies (2010). These criteria identify families that are very likely to represent HNPCC. Other widely used criteria are the Bethesda Criteria that can be used to identify families suspected of HNPCC that need testing for microsatellite instability (2398).

Endometrial tumours
Predisposed individuals from HNPCC families have a high risk (30-80%) of developing colorectal cancer. The most frequent extracolonic cancer is endometrial cancer. The lifetime risk of developing this cancer is 30-60% by age 70 (14,731,3009,3071). HNPCC-associated endometrial cancer is diagnosed approx. 10 years earlier than in the general population. The estimated frequency of carriers of a DNA mismatch repair gene mutation in endometrial cancer associated with HNPCC does not differ significantly from endometrial cancer in the general population (305).

Pathology of endometrial tumours
In patients from families with proven germline mutations in the MMR genes, MLH1, MSH2, MSH6, or from (suspected) HNPCC families, the majority of endometrial tumours were reported to be of the endometrioid type with diverse grading and staging (650,2174). Certain histopathologic features such as mucinous differentiation, solid-cribriform growth pattern, high grade and possible necrosis might suggest that a tumour is due to a mismatch repair defect (1481, 2174,2206).

Loss of MLH1 protein expression occurs in endometrial cancer associated with HNPCC (235,650,1276, 1768,2174,2264) but also in 15-30 % of sporadic cancers with somatic inactivation of MLH1 (2518,2772). Abrogation of MSH2 and/or MSH6 protein expression, especially at a young age seems to be a more specific indicator for HNPCC (235, 650). Already in the hyperplastic precursor lesions such loss of expression can be encountered (235, 650).

Other cancers
Many other cancers have been reported in HNPCC. (13,14,3009,310). The frequency of specific cancers depends on the prevalence of the cancer in the background population (2178). Cancer of the stomach for example is frequently observed in families from Finland and Japan, both countries with a high prevalence of stomach cancer in population. The ages at diagnosis of most cancers reported are earlier than their sporadic counterparts.
Genetics of MLH1, MSH2, MSH6
Chromosomal location and structure
HNPCC is associated with germline mutations in five genes with verified or putative DNA mismatch repair function, viz. MSH2 (MutS homologue 2), MLH1 (MutL homologue 1), PMS2 (Postmeiotic segregation 2), MSH6 (MutS homologue 6), and possibly MLH3 (MutL homologue 3). Structural characteristics of these genes are given in Table 8.11. Endometrial cancer appears to be part of the syndrome in families with mutations in any one of these genes, but is particularly associated with MSH2 and MSH6 germline mutations (236,3011,3114).

Gene product
HNPCC genes show ubiquitous, nuclear expression in adult human tissues, and the expression is particularly prominent in the epithelium of the digestive tract as well as in testis and ovary (860,1602,3132). These genes are also expressed in normal endometrium, and loss of protein expression is an early change in endometrial tumorigenesis. Studies of MSH2 or MLH1 mutation carriers have shown that these proteins may be lost already in atypical hyperplasia (precursor lesion of endometrial cancer) or even in endometrial hyperplasia without atypia in several months before the diagnosis of endometrial cancer, suggesting that immunohistochemical analysis of MSH2 and MLH1 proteins may be useful for pre-screening purposes in HNPCC patients (236,1277).

Gene function
The protein products of HNPCC genes are key players in the correction of mismatches that arise during DNA replication (1496). Two different MutS-related heterodimeric complexes are responsible for mismatch recognition: MSH2-MSH3 and MSH2-MSH6. While the presence of MSH2 in the complex is mandatory, MSH3 can replace MSH6 in the correction of insertion-deletion mismatches, but not single-base mispairs. Following mismatch binding, a heterodimeric complex of MutL-related proteins, MLH1-PMS2 or MLH1-MLH3, is recruited, and this larger complex, together with numerous other proteins, accomplishes mismatch repair. The observed functional redundancy in the DNA mismatch repair protein family may help explain why mutations in MSH2 and MLH1 are prevalent in HNPCC families, while those in MSH6, PMS2 and MLH3 are less frequent (and MSH3 mutations completely absent), although alternative hypotheses (e.g. based on the differential participation of the DNA mismatch repair proteins in apoptosis signaling (863)) have also been proposed. It is not known why some female HNPCC patients develop endometrial cancer, while others develop colon cancer. Comparison of these two tumour types originating from identical germline mutation carriers suggests the existence of some important tissue-specific differences that may indicate different pathogenetic mechanisms. For example, acquired loss of MSH2 and MSH6 appears to characterize endometrial, but not colon carcinomas developing in patients with inherited mutations of MLH1 (2589). Moreover, the general MSI patterns and target genes for MSI seem different in endometrial and colorectal cancers from HNPCC patients (1527). Early inactivation of PTEN characterizes most endometrial cancers from HNPCC patients (3361) and tumorigenesis mediated by PTEN inactivation is accelerated by mismatch repair deficiency (3052). Apart from biosynthetic errors, the DNA mismatch repair proteins also recognize and eliminate various types of endogenous and exogenous DNA damage, and differential exposure to such agents or variable capacity to correct lesions induced by them may also play a role in the organ-specific cancer susceptibility in HNPCC (665).

Gene mutations
The International Collaborative Group on HNPCC maintains a database for HNPCC-associated mutations and polymorphisms (http://www.nfdht.nl). To date (May 2002), there are 155 different MSH2 mutations (comprising 39% of all mutations) and 200 (50%) MLH1 mutations reported to the database, together with 30 (8%), 5 (1%) and 10 (3%) mutations in MSH6, PMS2, and MLH3, respectively. Most MSH2 and MLH1 mutations are truncating (2214). However, 30-40% of MLH1 and MSH6 mutations are of the missense type (leading only to an amino acid substitution), which constitutes a diagnostic problem concerning their pathogenicity. Besides commonly used theoretical predictions (evolutionary conservativeness of the amino acid change, occurrence of the variant in the normal population, co-segregation with disease phenotype) functional tests may be nec-
necessary in the evaluation of the pathogenicity of missense changes.

**Microsatellite instability**

Microsatellite instability (MSI) is the hallmark of tumours that arise in carriers of MLH1, MSH2, or MSH6 mutations. Overall, MSI is detected in approximately 15% of all colorectal cancers. It is measured as alterations in the length of simple repetitive genomic sequences, usually dinucleotide repeats, or mononucleotide runs. As these repeats have a tendency to form mismatches during DNA replication, a mismatch repair defect is expected to increase their mutation frequency. Because the definition of instability applied has been variable, in 1998 an international working group recommended the use of five markers to assess MSI [306].

Tumours are characterized as having high-frequency MSI (MSI-H) if two or more of the five markers show instability (i.e. have insertion/deletion mutations), or as having low-frequency MSI (MSI-L) if only one of the five markers shows instability. The distinction between microsatellite stable (MSS) and low-frequency MSI (MSI-L) can only be accomplished if a greater number of markers is utilized. MSI analysis, in conjunction with immunohistochemistry, can greatly improve the efficacy of the molecular screening for HNPCC.

In one study, all 12 endometrial carcinomas from carriers of MLH1 and MSH2 germline mutations demonstrated an MSI-high phenotype involving all types of repeat markers, while this was found in only 4 out of 11 (36%) endometrial carcinomas from MSH6 mutation carriers [650]. In another study, MSI-patterns in endometrial cancers differed from those in colorectal cancers, even though the patients had identical predisposing mutations in the MMR genes MLH1 or MSH2 [1527]. In endometrial cancers, the pattern was more heterogeneous and involved a lower proportion of unstable markers per tumour and shorter allelic shifts for BAT markers. These results might point to gene-specific and/or organ-specific differences that may be important determinants of the HNPCC tumour spectrum.

**Mutation spectrum**

Hereditary non-polyposis colorectal cancer (HNPCC) is caused by germline mutations in one of 5 DNA mismatch repair genes (MMR): MSH2 [864], MLH1 [353], PMS1 [2010], PMS2 [2010], and MSH6 (formerly GTBP) [53,1884]. Other genes like EXO1 [3161], MLH3 [1674,3162] and TGFBR1 [1705] have been reported to possibly cause HNPCC-like syndromes, although no definitive evidence has been delivered yet, both in terms of pathogenicity and/or cosegregation with the disease of the alleged germline mutations in affected families. To date, more than 300 different predisposing mutations have been identified, most in MSH2 and MLH1 and in families complying with the clinical Amsterdam criteria (AMS+) [2214]. Many HNPCC families, however, do not fully comply with these criteria, and in most of these cases the disease-causing mutations are yet unknown. Mutations in MSH6 have been found in atypical HNPCC families (see below).

In general, MMR mutations are scattered along the coding sequence of MSH2 and MLH1 and predict either the truncation of the corresponding protein products, or a subter amino acid substitutions. These mutations appear evenly distributed throughout the coding regions of the main MMR genes, with some clustering in MSH2 exon 12 [2214] and MLH1 exon 16 [3115]. While most of the MSH2 mutations consist of frameshift or nonsense changes, MLH1 is mainly affected by frameshift or missense alterations. Most of the mutations found to date are unique, with a few common recurring ones [2214]. Genomic deletions have also been found at both loci [442,2070,3116]. MSH2 deletions appear to be a very frequent cause of HNPCC, contributing for up to a quarter of the families selected by Amsterdam criteria [3116]. MLH1 deletions are less frequent than in MSH2 [1793,2070]. Southern analysis and/or PCR-based methods to detect larger rearrangements at the genomic level [443] should be routinely employed when approaching the mutation analyses of these major mismatch repair genes.

**Genotype-phenotype correlations**

The combination of clinical (number and type of tumours, age of onset, clinical course of the disease, etc.) and genetic (different mismatch repair genes, truncating and missense mutations) heterogeneity in HNPCC represents an ideal opportunity to attempt the establishment of genotype-phenotype correlations. Unfortunately, and notwithstanding the large number of mutations and clinical data collected to date, no clear-cut correlations have been observed between specific MMR gene mutations and their clinical outcome. For example, the identification of identical mutations both in HNPCC and in Muir-Torre or Turcot syndrome does not support the existence of consistent genotype-phenotype correlations [179,1115,1494].

The most reliable correlation found to date is the association between clear-cut pathogenic mutations at MSH2, MLH1 and MSH6, and the resulting spectrum of colorectal and extracolonic tumours. HNPCC kindreds due to MSH2 or MLH1 germline mutations are characterized by high penetrance and early onset of colorectal and endometrial cancer. The diagnostic criteria, Amsterdam I and II, established by the International Collaborative Group on HNPCC [3008,3010] well serve the purpose of selecting families with a high likelihood to carry MSH2 and MLH1 mutations [3117]. In addition to the fulfillment of the above criteria, other factors represent valid predictors of the presence of germline MSH2 and MLH1 mutations in HNPCC families. These include: 1) young age at diagnosis of colorectal cancer, and 2) the occurrence of at least one patient with an extra-colonic cancer, such as those of the endometrium, small intestine, brain, and stomach, within an AMS+ HNPCC kindred. The frequency of mutations identified in these families increased to about 70% [3117]. Moreover, the occurrence of at least one patient with multiple synchronous or metachronous colorectal cancers, and the combined occurrence of colorectal cancer with endometrial cancer in one patient are very good predictors of MSH2 or MLH1 mutations [3117].

The first reports on MSH6 germline mutations already indicated that the clinical phenotype differed from the “classical” HNPCC caused by MSH2 and MLH1 mutations [53,1884]. More recently, MSH6 germline mutations have been demonstrated in a considerable number of the atypical HNPCC families, i.e. not complying with the Amsterdam criteria (ACI and II) [1497,3039,3114,3160]. In general, the penetrance of colorectal
cancer seemed to be reduced while endometrial cancer seems to represent a more important clinical manifestation among female MSH6 mutation carriers. Also, the mean age of onset of colorectal and endometrial cancer appeared to be delayed in families with MSH6 germline mutations \([3011,3039,3114]\). Notably, MSI analysis of tumours from MSH6 mutation carriers suggests a reduced penetrance of the MSI-H phenotype and preferential instability at mononucleotide repeats \((650,1497,3114,3160)\). An additional MSH6-associated clinical phenotype is the papillary transitional cell carcinoma of the ureter and renal pelvis, observed in approx. 10% of the carriers from an extended MSH6 kindred \[3039]\. Notably, the lifetime cumulative risk of this tumour type in MLH1 or MSH2 mutation carriers is only 2.6% \[2673]\.

**Ataxia telangiectasia syndrome**

**Definition**
Ataxia telangiectasia syndrome (A-T) is a rare, progressive neurological disorder that manifests at the toddler stage. The disease is characterized by cerebellar degeneration (ataxia), dilated blood vessels in the eyes and skin (telangiectasia), immunodeficiency, chromosomal instability, increased sensitivity to ionizing radiation and a predisposition to cancer, in particular leukaeamias and lymphomas. Germline mutations in the ATM gene (ataxia telangiectasia mutated), homozygous or compound heterozygous, are the cause of this autosomal recessive disorder. Heterozygous carriers are phenotypically unaffected but exhibit an increased risk to develop breast cancer and often display a variety of age related disorders which may result in reduced life expectancy \(2808\).

**MIM No.** 208900 \[1835\]

**Synonyms**
Louis-Bar Syndrome, A-T complementation group A (ATA), group C (ATC), group D (ATD) and group E (ATE). The different complementation groups are all linked to the ATM gene.

**Incidence**
The rare A-T disease occurs in both genders and world wide among all races. The disease has an estimated incidence of one per 40,000 to one per 300,000 live births. Approximately 0.2-1% of the general population has been estimated to be heterozygous carriers of a type of germline mutation in the ATM gene that in homozygous state causes the A-T syndrome.

**Tumours in A-T patients**
Individuals with A-T have a 50 to 150 fold excess risk of cancer, with approximately 70% being lymphomas and T cell leukaeamias. In younger patients, an acute lymphoblastic leukaemia is most often of T-cell origin, although the pre-B common ALL of childhood has also been seen in A-T patients. When leukaemia develops in older A-T patients it is usually an aggressive T-cell leukaemia (T-PLL, T cell prolymphocytic leukaemia). Lymphomas are usually B cell types. A wide range of solid tumours makes up the remainder of the tumours seen in A-T patients and includes cancers of the breast, stomach, ovary and melanoma. The presence of missense mutations in A-T patients has been associated with a milder clinical phenotype and altered cancer predisposition. In two British A-T families a T>G transversion at base pair 7271 was found to be associated with a milder clinical phenotype, lower radiosensitivity but an increased risk of breast cancer. This increased risk was observed in both the homozygote and heterozygote carriers of this modification \((RR \ 12.7 \ p=0.0025)\ \[2775\]\. This sequence alteration has subsequently been found in multiple-case breast cancer families. The expression and activity analyses of the ATM protein in homozygous cell lines carrying this sequence change indicated that this mutation was dominant negative \[462\].

**Breast cancer in ATM heterozygotes**
Heterozygous carriers of ATM mutations have a higher mortality rate and an earlier age at death from cancer and ischemic heart disease than non-carriers \(2808\). A-T heterozygotes have been reported to have a 3 to 8 fold increased risk of breast cancer. The association between ATM heterozygosity and breast cancer risk was initially found among blood relatives of A-T patients \[2820\] and in almost every study of A-T relatives since an increased breast cancer risk has been detected \((318,741,981,1291,1334,2105,2257,2819)\). Paradoxically, in the years following the cloning of the ATM gene \[2546\], several studies investigating large breast cancer cohorts failed to find an increased incidence of ATM mutations of the type found in A-T patients, and a controversy arose regarding the role of ATM in breast cancer susceptibility \[194,281,884\]. However, a number of recent studies, analysing the frequency of all type of ATM mutations, did confirm previous findings of an elevated breast cancer risk in ATM mutation carriers \[129,351,462,2592,2775\].
Age distribution and penetrance
Most of the studies finding an increased risk of breast cancer in A-T relatives point to an early onset of the disease. The penetrance has been difficult to estimate since most of the studies are small, and different mutations may have different effects. In several studies of A-T relatives, the elevated risk is restricted to obligate carriers (mothers), and is not increased in other relatives according to their probability of being a mutation carrier. This may point to an interaction with environmental and/or other genetic factors contributing to the elevated breast cancer risk.

Clinical and pathological features
No typical clinical or pathological features are so far known for ATM heterozygous breast cancer patients, other than early age at onset (before age 50) and frequent bilateral occurrence [351].

Response to therapy and prognosis
ATM heterozygotes with breast cancer do not seem to exhibit acute radiation sensitivity as A-T patients do, and excessive toxicity has not been observed after radiotherapy [115,2331,3088]. It has however been speculated whether ATM heterozygous breast cancer patients have an increased risk of developing a second breast cancer after radiation treatment, and large multi-center studies are ongoing to answer this question. There are only few studies evaluating the prognosis of A-T carriers with breast cancer, pointing to a long-term survival. This may be due to their tumours being more susceptible to cell killing by ionizing radiation than tumour cells in non-carriers [2809].

ATM expression in breast cancer
Normal breast tissue shows a distinct pattern of ATM expression, the protein being found in the nucleus of the ductal epithelial cells and to a lesser extent in the surrounding myoepithelial cells. Decreased ATM expression is often observed in breast carcinomas [102, 1384] and ATM mRNA levels have also been found to be lower in invasive breast carcinomas than in normal tissues or benign lesions [3041]. Significant loss of heterozygosity in sporadic breast tumours across chromosome 11q22-23 where the ATM gene is located has been reported [1118,1439, 1553,1754,2375].

Table 8.12
Proposed ATM genotype / phenotype relationships [971].

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM WT/WT</td>
<td>Normal</td>
</tr>
<tr>
<td>ATM WT/Int</td>
<td>Ataxia telangiectasia, High cancer risk</td>
</tr>
<tr>
<td>ATM Int/Int</td>
<td>Ataxia telangiectasia, Variant A-T, High cancer risk?</td>
</tr>
<tr>
<td>ATM Int/Trun</td>
<td>Ataxia telangiectasia? Variant A-T, High cancer risk?</td>
</tr>
<tr>
<td>ATM Trun/Trun</td>
<td>A-T relatives, Elevated breast cancer risk, Increased age related disorders?</td>
</tr>
<tr>
<td>ATM Trun/Int</td>
<td>Few A-T relatives, Moderate breast cancer risk? Increased age related disorders?</td>
</tr>
</tbody>
</table>

Genetics
Chromosomal location
The ATM gene is located on human chromosome 11q22-23.

Gene structure
The ATM gene has 66 exons scanning 150 kilobase of genomic DNA and is expressed in a wide range of tissues as an approximately 12-kilobase messenger RNA encoding a 350 kD serine/threonine protein kinase. The initiation codon falls with exon 4. The last exon is 3.8kb and contains the stop codon and a 3’ untranslated region of about 3600 nucleotides [2983].

Gene expression
The major 13 kb ATM transcript is observed in every tissue tested to date. Northern blots and RT-PCR products from various tissues failed to disclose any evidence of alternative forms within the coding region. However the first four exons, which fall within the 5’-untranslated region (UTR), undergo extensive alternative splicing. Differential polyadenylation results in 3’UTRs of varying lengths. These structural features suggest that ATM expression might be subject to complex post-transcriptional regulation [2547].

Gene function
The ATM protein plays a central role in sensing and signalling the presence of DNA double-strand breaks (DSB) or damage caused by external agents. The kinase domain in the carboxy-terminal region of the protein contains the signature motifs of phosphatidylinositol 3-kinases. ATM’s kinase activity is itself enhanced in response to DNA double-strand breaks resulting in a phosphorylation cascade activating many proteins each of which in turn affects a specific signalling pathway. These substrates include the protein products of a number of well characterized tumour-suppressor genes including TP53, BRCA1 and CHEK2 which play important roles in triggering cell cycle arrest, DNA repair or apoptosis (reviewed in Shiloh et al. [2660]). Additional DSB-induced responses that are ATM dependent include the activation of transcription factors such as AP-1, p73 and NFKB, and deacetylation of chromatin proteins (reviewed in Barzilai et al. [189]).

Mutation spectrum in A-T patients
Since the ATM gene was cloned [2546] more than 300 different A-T disease-causing mutations have been reported. The profile of these has revealed that most are unique and uniformly distributed along the length of the gene, no muta-
tional hotspots have been detected. The majority of A-T patients are compound heterozygotes having two different ATM mutations and patients homozygous for the same ATM mutation are rare. The pre-dominant type of mutation found in the ATM gene in A-T patients results in a truncated and unstable ATM protein. Some A-T patients have a milder phenotype (variant A-T) that may be related to the presence of missense mutations or mutations producing an ATM protein retaining some normal function [1825,2592].

Genotype-phenotype correlations
Gatti et al. [971], in distinguishing between truncating mutations where no
ATM protein is detected and missense substitutions where mutant protein of variable stability is observed, have suggested that this mutant protein could produce a dominant negative effect in heterozygotes, resulting in an altered phenotype and an increased breast cancer susceptibility. The expected phenotypes that might arise from having two types of A-T carriers in the general population are shown in Table 8.12. The genotype $\text{ATM}^{\text{trun/trun}}$ with two truncating mutations causes the classical A-T disorder. The genotype $\text{ATM}^{\text{mis/mis}}$ with two missense mutations is also found in some children with the classical form of the disease, in particular when these are located within the ATM kinase domain (for instance Belzen et al. [2087], Angele et al. [101]) but may also be associated with a variant A-T phenotype with some neurological features and cancer susceptibility. Two types of ATM heterozygotes exist and the phenotypes differ, i.e. those with truncating mutations that make no protein and those with missense mutations that make reduced amount or partly defective protein [115,462,971, 1825,2331,2592,2775,2809,3088], and these two groups may have different breast cancer risks. If this proposed model is correct it necessitates a re-analyses of the epidemiological data stratifying for the two types of heterozygotes. The literature to date suggests that germline ATM missense mutations are more frequent than the 0.2-1% frequency of A-T causing mutations and hence contribute to a larger fraction of breast cancer patients [351,462,2592].
Contributors

Dr Vera M. ABELER**
Department of Pathology
The Norwegian Radium Hospital
3071 Oslo
NORWAY
Tel. +47 22 93 40 00
Fax. +47 22 93 54 24
v.m.abeler@klatmed.uio.no

Dr Jorge ALBARES-SAAVEDRA
Department of Pathology
LSU Health Sciences Center
1831 Kings Highway
Shreveport, LA 71130
U.S.A
Tel. +1 318 675 7732
Fax. +1 318 675 7662
jalbor@lsuhsc.edu

Dr Isabel ALVARADO-CABRERO
Vicente Suarez 42-201
Colonia Condesa
Tel. +52-56-27-69-00
Fax. +52-56-27-69-01
isa98@prodigy.net.mx

Dr Alan ASHWORTH
The Breakthrough Breast Cancer Centre
The Institute of Cancer Research
233 Fulham Road
London SW3 6JJ
UNITED KINGDOM
Tel. +44 207 153 5303
Fax. +44 207 153 5340
alan.ashworth@icr.ac.uk

Dr Jean-Pierre BELLICOTI*
Service d’Anatomie Pathologique
Hôpitaux Universitaires de Strasbourg
84 rue de Courlancy
67098  Strasbourg
U.S.A
Tel. +33 71 527 6117
Fax. +33 71 527 6075
p.deveaux@llumc.fr

Dr Maria Luisa CARCAGNI
Department of Pathology
National Cancer Institute
Via G. Venezian 1
20133 Milano
ITALY
Tel. +39 02 239 02756
carcangiu@istitutotumorimilanese.it

Dr Silvestro CARINELLI
Department of Pathology
Istituti Clinici di Perfezionamento
Villa della Commenda 12
20122 Milano
ITALY
Tel. +39 02 5799 2415
Fax. +39 02 5799 2860
silvestro.carinelli@icp.mi.it

Dr Arnne Lise BIRKRESEN-DALE
Department of Genetics
The Norwegian Radium Hospital
0810 Oslo
NORWAY
Tel. +47 22 93 44 19
Fax. +47 22 93 44 40
alb@radium.uio.no

Dr Werner BÖCKER*
Gerhard Domagk Institute of Pathology
University of Minster
Domagkstrasse 17
D-46219 Münster
GERMANY
Tel. +49 251 835 54 40
Fax. +49 251 835 54 40
werner.boecker@uni-muenster.de

Dr Annegien BROEKS
Department of Pathology
Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam
THE NETHERLANDS
Tel. +31 20 5122754
Fax. +31 20 5122759
a.broeks@lknl.nl

Dr Robert BUCKLEY
Department of Gynecologic Pathology
Manchester M13 0JH
UNITED KINGDOM
Tel. +44 161 445 7132
Fax. +44 161 276 6488
cbh@chmpath.fsunet.co.uk

Dr Gianni BUSSOLATI*
Istituto di Anatomia e Istologia Patologica
University of Turin
Vienna 42-201
10117 Turin
ITALY
Tel. +39 011 663 52 67
Fax. +39 011 663 52 68
gianni.bussolati@unito.it

Dr Drs. B. Cutuli
Département de Radiothérapie
Poly clinique de Courlancy
38 rue de Courlancy
51100 Reims
FRANCE
Tel. +33 3 22 94 02 84
Fax. +33 3 22 94 70 20
b.cutuli@wanadoo.fr

Dr Peter DEVELLE*
Department of Human and Clinical Genetics and Pathology
Leiden University Medical Center
2333 AL Leiden
THE NETHERLANDS
Tel. +31 71 527 6075
Fax. +31 71 527 6075
p.deveaux@llumc.nl

Dr Stephen DDBBS
Department of Gynaecological Oncology
Belfast City Hospital
Lidum Road
Belfast BT9 7AG
UNITED KINGDOM
Tel. +44 28 90 26 38 94
Fax. +44 28 90 26 38 95
stephen.dobbs@bch.n-i.nhs.uk

Dr Maria DRUKJONINGEN**
Department of Pathology
University of Hong Kong
St. Paul's Hospital
Shaunmunstraat 20/21
10117 Berlin
GERMANY
Tel. +49 30 4905 3601
Fax. +49 30 4905 3690
manfred.dietel@charite.de

Dr Christopher P. CRUM
Department of Pathology
Brigham and Women’s Hospital
75 Francis Street
Boston MA 02115
U.S.A
Tel. +1 617 732 75 30
Fax. +1 617 732 8843
crum@partners.org

Dr Ross S. BERKOWITZ
Department of Pathology
Brigham and Women’s Hospital
75 Francis Street
Boston, MA 02115
U.S.A
Tel. +1 617 738 5124
Fax. +1 617 732 8843
rberkowitz@partners.org

* One asterisk indicates participation in the Editorial and Consensus Conference on the WHO classification of Tumours of the Breast during January 12-16 in Lyon, France. ** Two asterisks indicate participation in the conference on the WHO classification of Tumours of Female Genital Organs during March 16-20, 2002.
Contributors 369
02.100 Dr. A. Ostor
02.101 Dr. F.A. Tavassoli
02.102 Dr. M. Devouassoux-Shishboran
02.103 Dr. S. Lax
02.104-02.106 Dr. M. Devouassoux-Shishboran
02.107-02.109B Dr. F.A. Tavassoli
02.110-02.112 Dr. A. Taleman
02.114-02.116B Dr. F. Nogales
02.117-02.118B Dr. L. Roth
02.119A, B Dr. H. Senzaki/ Dr. A. Tsuura
02.120-02.121 Dr. L. Roth
02.122A, B Dr. M. Devouassoux-Shishboran
02.123-02.128 Dr. L. Roth
02.127 Dr. F.A. Tavassoli
02.128A-02.129B Dr. R. Vang
02.130A-02.131A Dr. J. Prat
02.130B Dr. L. Roth
02.131C-02.134 Dr. J. Prat
02.135 Dr. L. Roth
02.136-02.137C Dr. J. Prat
02.138A Dr. R. Vang
02.138B Dr. F. Nogales
02.139A-B Dr. L. Roth
02.140A-C Dr. F.A. Tavassoli
02.141 Dr. M.R. Hendrickson
02.142A Dr. F.A. Tavassoli
02.142B Dr. L. Roth
02.143A-02.144 Dr. M.R. Hendrickson
02.145 Dr. F.A. Tavassoli

3.
03.01 Dr. R. Caduff
03.02A-03.04C Dr. I. Alvarado-Cabero
03.05A-03.06 Dr. L. Roth
03.07 Dr. A. Cheung
03.08 Dr. L. Roth
03.09 Dr. A. Cheung
03.10 Dr. L. Roth
03.11A, B Dr. F.A. Tavassoli
03.12-03.13 Dr. L. Roth
03.14A Dr. M. Devouassoux-Shishboran
03.14B Dr. L. Roth
03.15A, B Dr. F.A. Tavassoli
03.16 Dr. R. Vang
03.17A, B Dr. L. Roth

4.
04.01 IARC
04.02B Dr. F.A. Tavassoli
04.03-04.04 Dr. S. G. Silverberg
04.05 Dr. S. Lax
04.06 Dr. F.A. Tavassoli
04.07 Dr. S. G. Silverberg
04.08 Dr. F. Nogales
04.09-04.12 Dr. S. G. Silverberg
04.13 Dr. F.A. Tavassoli
04.14 Dr. S. G. Silverberg
04.15A Dr. M. Márquez
04.15B Hospital Clinic
04.16A Barcelona, Spain
04.16B-04.16A Dr. F.A. Tavassoli
04.18B Dr. F. Nogales
04.19-04.21 Dr. S. Lax
04.22 Dr. G. L. Mutter
04.23-04.24 Dr. M.R. Hendrickson
04.25A-C Dr. S. G. Silverberg
04.26A Dr. F.A. Tavassoli
04.26B-04.26B Dr. F.A. Tavassoli
04.28C, D Dr. S. G. Silverberg
04.29 Dr. M.R. Hendrickson
04.30A Dr. S. G. Silverberg
04.30B-C Dr. M.R. Hendrickson
04.30D-04.32B Dr. S. G. Silverberg
04.32C Dr. R.A. Kubik-Huch
04.33 Dr. M.R. Hendrickson
04.34 Dr. S. G. Silverberg
04.35-04.36 Dr. M.R. Hendrickson
04.37-04.38C Dr. S. G. Silverberg
04.39 Dr. R. Vang
04.40A-C Dr. W.G. McCluggage
04.41 Dr. F.A. Tavassoli
04.41A Dr. R. Vang
04.41B Dr. A. Ostor
04.41C Dr. L. Roth
04.42B Dr. D. Giemst
04.43A Dr. M. Wells
04.43B Dr. D. Giemst
04.44A Dr. M. Wells
04.44B-04.45 Dr. D. Giemst
04.45B Dr. M. Wells
04.46A Dr. D. Giemst
04.46B Dr. D. Giemst
04.47A Dr. D. Giemst
04.47B Dr. D. Giemst
04.48A Dr. A. Ostor
04.48B Dr. A. Ostor
04.49A Dr. M. Wells
04.49B Dr. A. Ostor

5.
05.01-05.02 Dr. F.A. Tavassoli
05.03 Dr. M. Tommasino
05.03A, B Dr. A. Tommasino
05.04 Dr. D. Giemst
05.05 Dr. D. Giemst
05.06 Dr. D. Giemst
05.07 Dr. D. Giemst
05.08-05.09 Dr. D. Giemst
05.10 Dr. D. Giemst
05.15B-05.16A Dr. L. Roth
05.20A, B Dr. R. Vang
05.20B Dr. R. Vang
05.21 Dr. L. Roth
05.22A, B Dr. R. Vang
05.22B A, C Dr. L. Roth
05.24-05.27 Dr. R. Vang
05.28 Dr. R. Vang
05.31-05.30 Dr. L. Roth
05.31-05.32A Dr. R. Vang
05.32B Dr. R. Vang
05.33-05.34 Dr. R. Vang
05.35A, B Dr. R. Vang

6.
06.01A, B Dr. E. Andersen
06.02-06.09 Dr. E. Andersen
06.10 Dr. D. Giemst
06.11A Dr. F.A. Tavassoli
06.11B Dr. R. Vang
06.12A-06.15 Dr. A. Ostor

7.
07.01-07.02 Dr. E.J. Wilkinson
07.03A Dr. F.A. Tavassoli
07.03B-07.05A Dr. E.J. Wilkinson
07.06 Dr. L. Roth
07.07C Dr. R.L. Kempson
07.10A, B Dr. E.J. Wilkinson
07.11 Dr. L. Roth
07.12A Dr. E.J. Wilkinson
07.12C Dr. F.A. Tavassoli
07.13A-07.14 Dr. E.J. Wilkinson
07.15 Dr. R.L. Kempson
07.16A-07.17C Dr. L. Roth
07.18A-07.19 Dr. R.L. Kempson
07.20A-07.22 Dr. E.J. Wilkinson
07.23A, B Dr. M. Wells

8.
08.01-08.02 Dr. D. Easton
08.03-08.05 Dr. J. Piek
08.06 Dr. P. Devilee
08.07 Dr. S. Narod
08.08 Dr. A.R. Venkitaraman (4116)
08.09 Dr. P. Devilee
08.10 Dr. A.R. Venkitaraman
08.11A-08.12 Dr. H. Ohgaki
08.13-08.14 Dr. P. Hainaut

Source of charts and photographs 371


References

375
376 References


References


References 381


References 383
References


ErbB-2 and EGF receptor genes in inflammatory ependymoma of the ovary. A case report


uterus.

MR imaging in the management of Cancer


tern of infiltrating lobular carcinoma and lymphoma and granulocytic sarcoma of hematological malignancies report of the Analytical Cellular Pathology.


Hartman J, Magee HM, O'Loughlin J, 2281-2286.

Hardesty LA, Sumkin JH, Nath ME, 1140. Use of preoperative inducible expression of BRCA1.


Healea Y, Faulx A, Serres, F, Dufour, 228-231.


not serve as direct precursors of human endometrium and ovary and atypical poly-
Clinicopathologic analysis.

1451.

1454.

malignant transformation: MR appear-
Clin Pathol

1457.

1452.

1453.

1469.

1475.

1476.

1481.

1482.

1483.

1484.

1485.

1486.

1487.

1488.

1489.

1490.

1491.

1492.

1493.

1494.

1495.

1496.

1497.

1498.

1499.

1500.

1501.

1502.

1503.

1504.

1505.

1506.

1507.

1508.

1509.

1510.

1511.

1512.

1513.

1514.

1515.

1516.

1517.

1518.

1519.

1520.

1521.

1522.

1523.

1524.

1525.

1526.

1527.

1528.

1529.

1530.

1531.

1532.

1533.

1534.

1535.

1536.

1537.

1538.

1539.

1540.

1541.

1542.

1543.

1544.

1545.

1546.

1547.

1548.

1549.

1550.

1551.

1552.

1553.

1554.

1555.

1556.

1557.

1558.

1559.

1560.

1561.

1562.

1563.

1564.

1565.

1566.

1567.

1568.

1569.

1570.

1571.

1572.

1573.

1574.

1575.

1576.

1577.

1578.

1579.

1580.

1581.

1582.

1583.

1584.

1585.

1586.

1587.

1588.

1589.

1590.

1591.

1592.

1593.

1594.

1595.

1596.

1597.

1598.

1599.

1600.

1601.

1602.

1603.

1604.

1605.

1606.

1607.

1608.

1609.

1610.

1611.

1612.

1613.

1614.

1615.

1616.

1617.

1618.

1619.

1620.

1621.

1622.

1623.

1624.

1625.

1626.

1627.

1628.

1629.

1630.

1631.

1632.

1633.

1634.

1635.

1636.

1637.

1638.

1639.

1640.

1641.

1642.

1643.

1644.

1645.

1646.

1647.

1648.

1649.

1650.

1651.

1652.

1653.

1654.

1655.

1656.

1657.

1658.

1659.

1660.

1661.

1662.

1663.

1664.

1665.

1666.

1667.

1668.

1669.

1670.

1671.

1672.

1673.

1674.

1675.

1676.

1677.

1678.

1679.

1680.

1681.

1682.

1683.

1684.

1685.

1686.

1687.

1688.

1689.

1690.

1691.

1692.

1693.

1694.

1695.

1696.

1697.

1698.

1699.

1700.

1701.

1702.

1703.

1704.

1705.

1706.

1707.

1708.

1709.

1710.

1711.

1712.

1713.

1714.

1715.

1716.

1717.

1718.

1719.

1720.

1721.

1722.

1723.

1724.

1725.

1726.

1727.

1728.

1729.

1730.

1731.

1732.

1733.

1734.

1735.

1736.

1737.

1738.

1739.

1740.

1741.

1742.

1743.

1744.

1745.

1746.

1747.

1748.

1749.

1750.

1751.

1752.

1753.

1754.

1755.

1756.

1757.

1758.

1759.

1760.

1761.

1762.

1763.

1764.

1765.

1766.

1767.

1768.

1769.

1770.

1771.

1772.

1773.

1774.

1775.

1776.

1777.

1778.

1779.

1780.

1781.

1782.

1783.

1784.

1785.

1786.

1787.

1788.

1789.

1790.

1791.

1792.

1793.

1794.

1795.

1796.

1797.

1798.

1799.

1800.

1801.

1802.

1803.

1804.

1805.

1806.

1807.

1808.

1809.

1810.

1811.

1812.

1813.

1814.

1815.

1816.

1817.

1818.

1819.

1820.

1821.

1822.

1823.

1824.

1552. Kouelis S, Kaprinos N, Kouri E, Coppola D, Papadaki H, Jones MW (2000). Immunohistochemical profile of endome-


mary carcinoma of the vagina: management and results of different therapy schemes. Gynecol Oncol 27: 87-93.


cecal tumors from patients with hered-
tary nonpolyposis colon cancer display diver-


396 References
References 397
398 References


399

References
stromal sarcoma with smooth muscle and for true sex cord differentiation. Pathol. of ovarian granulosa cell tumors with monotypic glandular lesions. DD, Toner PG (1998). Malignant fibrothecoma. Histopathology of two cases including one of the spindle article).”. Histopathology of two cases including one of the spindle article).”. Histopathology of two cases including one of the spindle article).”. Histopathology of two cases including one of the spindle article).”.

References

401


406 References
Correlation studies with human gonads.


different treatment policy?


A multicenter study of its diagnostic con-

References

Tavassoli FA (1997). Use of monoclonal

non- 

Ridolfi RL, Rosen PP, Port A, Kinne D, 

Blackwell

2371.

2370.

2369.

2368.

2367.

2366.

2365.

2364.

2363.

2362.

2361.

2360.

2359.

2358.

2357.

2356.

2355.

2354.

2353.

2352.

2351.

2350.

2349.

2348.

2347.

2346.

2345.

2344.

2343.

2342.

2341.

2340.

2339.

2338.

2337.

2336.

2335.

2334.

2333.

2332.

2331.

2330.

2329.

2328.

2327.

2326.

2325.

2324.

2323.

2322.

2321.

2320.

2319.

2318.

2317.

2316.

2315.

2314.

2313.

2312.

2311.

2310.

2309.

2308.

2307.

2306.

2305.

2304.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.

2302.

2301.

2300.

2303.


377-379.

metaplasia.


Schmidt-Kittler O, Ragg T, Daskalakis
(2000). Prospective management of stage
with literature review.

factors for local recurrence in patients
femoral region alone to preserve fertility: a prelimi-

378. Schorge JD, Miller VB, Gi Li, Muto MG,
Welch WR, Berkowitz RS, Mok SC (2000).
Genetic alterations of the WT1 gene in papillary serous carcinoma of the peri-
neum. Gynecol Oncol 76: 369-372.

379. Schorge JD, Muto MG, Lee SJ, Huang LW, Welch WR, Bell DA, Keong EZ,
Berkowitz RS, Mok SC (2000). BRCA1-relat-
ed papillary serous carcinoma of the peri-
nneum has a unique molecular pathogen-

380. Schorge JD, Muto MG, Welch WR,
Bander CA, Rubin SC, Bell DA, Berkowitz
RS, Mok SC (1998). Molecular evidence for
multifollicular papillary serous carcinoma of
the peritoneum in patients with germline
BRCA1 mutations. J Natl Cancer Inst 90:
841-845.

381. Schottenfeld D, Lilienfeld AM,
Diamond H (1963). Some observations on
the epidemiology of breast cancer among

382. Schragger CA, Schneider D, Grauer
and pathological features of breast cancer
in Cowden's syndrome: an underrec-
ned papillary serous carcinoma of the peri-
nneum: a distinctive ovarian tumor.

383. Schuh ME, Benda R, Chen P, Clark R,
Dori T, Lavin MF (2002). Missense muta-
tions but not allelic variants after the gen-
derisking study of patterns of cer-
nerneum. In: FOGG stage II endome-
trial carcinoma. Int J Gynecol Cancer 10:
497-502.

Combined ovarian serous papillary and
epithelial carcinoma. Gynecol Oncol 71:
132-140.

385. Seidall BA (1994). Cavernous heman-
gioma of the female breast. Cleve Clin Q 21:
419-474.

386. Seckel MJ, Mulholland PJ, Bishop AE,
Teale JD, Hales CN, Glaser M, Watkins S,
Seckl JR (1999). Hypoglycemia due to an
insulin-secreting small-cell carcinoma of

production of androgens in women with breast
cancer. Anticancer Res 14: 2133-
2137.

388. Sedlis A (1961). Primary carcinoma of
the fallopian tube. Obstet Gynecol Surv 16:
219-221.

cancer of low malignant potential (serous borderline tumors). The relation-
ship of exophytic surface tumor to peri-
toneal 'implants'. Am J Surg Pathol 16:
577-582.

390. Seckel MJ, Mulholland PJ, Bishop AE,
Teale JD, Hales CN, Glaser M, Watkins S,
Seckl JR (1999). Hypoglycemia due to an
insulin-secreting small-cell carcinoma of

production of androgens in women with breast
cancer. Anticancer Res 14: 2133-
2137.

392. Sedlis A (1961). Primary carcinoma of
the fallopian tube. Obstet Gynecol Surv 16:
219-221.

cancer of low malignant potential (serous borderline tumors). The relation-
ship of exophytic surface tumor to peri-
toneal 'implants'. Am J Surg Pathol 16:
577-582.

394. Seckel MJ, Mulholland PJ, Bishop AE,
Teale JD, Hales CN, Glaser M, Watkins S,
Seckl JR (1999). Hypoglycemia due to an
insulin-secreting small-cell carcinoma of

production of androgens in women with breast
ancer. Anticancer Res 14: 2133-
2137.

396. Sedlis A (1961). Primary carcinoma of
the fallopian tube. Obstet Gynecol Surv 16:
219-221.

cancer of low malignant potential (serous borderline tumors). The relation-
ship of exophytic surface tumor to peri-
toneal 'implants'. Am J Surg Pathol 16:
577-582.

398. Seckel MJ, Mulholland PJ, Bishop AE,
Teale JD, Hales CN, Glaser M, Watkins S,
Seckl JR (1999). Hypoglycemia due to an
insulin-secreting small-cell carcinoma of

production of androgens in women with breast
ancer. Anticancer Res 14: 2133-
2137.

400. Sedlis A (1961). Primary carcinoma of
the fallopian tube. Obstet Gynecol Surv 16:
219-221.
References

416 References


Metaplastic carcinoma with osteoclastic
among hereditary nonpolyposis colorectal
Ashkenazi Jewish women with breast can-
breast. A clinical and pathological study of
(1998). Colorectal carcinoma survival
3077.
3078.
3064.
3068.
3063.
3071.
3073.
3079.
3092.
Waxman M, Vuletin JC, Urcuyo R,
3082.
3084.
3091.
3105.
3104.
3103.
3108.
3106.
3109.
3103.
3107.
3113.
3114.
3115.
3116.
3117.
3118.
3123.
3124.
3125.
3126.
3127.
3128.
3129.
3130.
3131.
3132.
3133.
3134.
3135.
3136.
3137.
3138.
3139.
3140.
3141.
3142.
3143.
3144.
3145.
3146.
3147.
3148.
3149.
3150.
3151.
3152.
3153.
3154.
3155.
3156.
3157.
3158.
3159.
3160.
3161.
3162.
3163.
3164.
3165.
3166.
3167.
3168.
3169.
3170.
3171.
3172.
3173.
3174.
3175.
3176.
3177.
3178.
3179.
3180.
3181.
3182.
3183.
3184.
3185.
3186.
3187.
3188.
3189.
3190.
3191.
3192.
3193.
3194.
3195.
3196.
3197.
3198.
3199.
3200.
3201.
3202.
3203.
3204.
3205.
3206.
3207.
3208.
3209.
3210.
3211.
3212.
3213.
3214.
3215.
3216.
3217.
3218.
3219.
3220.
3221.
3222.
3223.
3224.
3225.
3226.
3227.
3228.
3229.
3230.
3231.
3232.
3233.
3234.
3235.
3236.
3237.
3238.
3239.
3240.
3241.
3242.
3243.
3244.
3245.
3246.
3247.
3248.
3249.
3250.
3251.
3252.
3253.
3254.
3255.
3256.
3257.
3258.
3259.
3260.
3261.
3262.
3263.
3264.
3265.
3266.
3267.
3268.
3269.
3270.
3271.
3272.
3273.
3274.
3275.
3276.
3277.
3278.
3279.
3280.
3281.
3282.
3283.
3284.
3285.
3286.
3287.
3288.
3289.
3290.
3291.
3292.
3293.
3294.
3295.
3296.
3297.
3298.
3299.
3300.
3301.
3302.
3303.
3304.
3305.
3306.
3307.
3308.
3309.
3310.
3311.
3312.
3313.
3314.
3315.
3316.
3317.
3318.
3319.
3320.
3321.
3322.
3323.
3324.
3325.
3326.
3327.
3328.
3329.
3330.
3331.
3332.
3333.
3334.
3335.
3336.
3337.
3338.
3339.
3340.
3341.
3342.
3343.
3344.
3345.
3346.
3347.
3348.
3349.
3350.
3351.
3352.
3353.
3354.
3355.
3356.
3357.
3358.
3359.
3360.
3361.


Acantholytic variant, squamous cell carcinoma, 38, 40, 41
Acanthosis nigricans, 189
Acinic cell carcinoma, 45
Acquired melanocytic naevus, 331, 332
Adenocarcinoma in situ, 232, 272, 273, 275, 276
Adenocarcinoma of Skene gland origin, 324
Adenocarcinoma of the rete ovarii, 180
Adenocarcinoma with spindle cell metaplasia, 38
Adenocystic basal cell carcinoma, 44
Adenofibroma, 122, 124, 125, 127, 130, 196, 209, 245, 248, 284, 285
Adenohibernoma, 103
Adenoid basal carcinoma, 267, 277-279, 301
Adenoid cystic carcinoma, 28, 44, 57, 86, 182, 184, 185, 228, 267, 277-279, 301, 321-323
Adenolipoma, 94, 103
Adenoma malignum, 273
Adenoma of minor vestibular glands, 324
Adenoma of the rete ovarii, 181
Adenomatoid tumour, 197, 199, 211, 243, 244, 310
Adenomatous hyperplasia of the rete ovarii, 181
Adenomyoepithelial adenosis, 82, 86, 87
Adenomyoepithelioma, 44, 46, 82, 86, 87
Adenomyoma, 134, 188, 215, 235, 245, 249, 273, 284-286, 301, 323
Adenosarcoma, 130, 133, 210, 212, 215, 244-248, 281, 282, 284-286, 306, 307
Adenosis, 78, 81-83, 85, 87, 104, 295, 297, 299, 300
Adenosis with apocrine metaplasia, 82
Adenosquamous carcinoma, 39-41, 130, 174, 266, 272, 277, 278, 301, 322, 321
Adrenocortical carcinoma, 351, 352, 354
Adult granulosa cell tumour, 131, 146
AFP, see alpha-fetoprotein
Aggressive angiomyxoma, 305, 329
Aggressive T-cell leukaemia, 361
Akt, 231, 357
Alpha lactalbumin, 41, 43
Alpha-fetoprotein, 138, 155, 156, 165-168, 184, 207, 246, 309
Alveolar rhabdomyosarcoma, 215, 244, 282
Alveolar soft part sarcoma, 215, 244, 280-282, 304, 326, 327
Alveolar variant, lobular carcinoma, 24, 32
Amenorrhea, 154, 157, 175, 190
Amylase, 45
Androblastoma, 153
Androgen insensitivity syndrome, 157
Androgen receptor gene, 112, 154
Angiogenesis, 22
Angiolipoma, 93
Angiomyoepithelial adenosis, 82, 86, 87
Angiomyoepithelioma, 44, 46, 82, 86, 87
Angiosarcoma, 40, 89, 91, 94-96, 175, 188, 244, 280, 282, 304
Apocrine adenoma, 85
Apocrine adenosis, 82
Apocrine carcinoma, 36, 37, 47, 71
Apocrine cell, 36, 37, 47, 65
APPBP2, 51
Argyrophilia, 33, 80
A-T complementation, 361
Ataxia telangiectasia, 27, 342, 350, 353, 361-363
ATM see Ataxia telangiectasia
Atypical adenosis, 299, 300
Atypical carcinoid, 277, 279
Atypical columnar change, 66
Atypical cystic lobules, 66
Atypical ductal hyperplasia, 20, 63, 64, 66, 78
Atypical hyperplasia, 63, 84, 136, 210, 221, 222, 228, 229, 232, 359
Atypical intraductal hyperplasia, 66, 78
Atypical leiomyoma, 236, 241
Atypical lobular hyperplasia, 60
Atypical lobules, type A, 66
Atypical medullary carcinoma, 28, 338
Atypical melanocytic naevus of the genital type, 332
Atypical papilloma, 78
Atypical polyoid adenomyoma, 249, 285, 286
Atypical proliferative serous tumour, 121
Atypical vulvar naevus, 332
Aurora-A, 51
B
B72.3 (TAG-72) antibody, 119, 131, 138, 187
Bannayan-Riley-Ruvalcaba syndrome, 357
BARD1, 342
Barr bodies, 171
Bartholin gland adenoma, 323
Bartholin gland carcinoma, 322
Bartholin gland nodular hyperplasia, 323
Bartholin gland tumour, 321, 322
Basal cell carcinoma, 151, 174, 175, 184, 185, 316, 318, 319
Basal cell tumour, 182, 184, 185
Basaloid carcinoma, 267, 316
Basaloid squamous cell carcinoma, 267, 278, 279, 317
BASC, see BRCA1-associated surveillance complex
Bcl-2, 58, 92, 108, 109, 250
BEK, 51
Benign mesothelioma, 199
Benign metastasizing leiomyoma, 237, 242
Benign mixed epithelial tumour, 144
Benign mixed tumour, 85, 306, 307
Benign peripheral nerve sheath tumour, 92, 94
Benign sclerosing ductal proliferation, 83
Beta-catenin, 131
Bethesda Criteria, 358
ß-hCG, 22, 164, 165, 167, 168, 207, 250, 251, 252
Bilateral breast carcinoma, 23, 48
Biphasic teratomas, 168
BLM, 341, 342
Bloom syndrome, 349
Blue naevus, 287, 288, 308, 309, 331, 332
Blunt duct adenosis, 82
BMRF1A, type 1A receptor of bone morphogenetic proteins (BMP) 357
Body mass index, 111
Borderline Brenner tumour, 140, 142
Borderline clear cell adenofibromas with intraepithelial carcinoma, 139
Borderline clear cell adenofibromatous tumour, 139
Borderline mixed epithelial tumour, 144
Bowenoid papulosis, 319, 320
BRAF, 120
BRCA1, 14, 20, 29, 53-56, 118, 120, 202, 207, 208, 347-351, 353, 354, 362
BRCA1-associated genome surveillance complex, 341, 342
BRCA2, 20, 29, 53-56, 112, 118, 133, 207, 208, 337-351, 354
Brenner tumour, 140-145, 172, 190, 196, 212
Brenner tumour of low malignant potential, 142
BRUSH-1, 112
BTAK /aurora2 /STK15, centrosome-associated serine/threonine kinase, 51
Burkitt lymphoma, 107, 108, 191, 196
C
CA125, 109, 119, 130, 138, 141, 180, 181, 184, 202, 272, 322, 340, 341, 347, 348
CA19-9, 108, 109, 130, 138, 141, 180, 181, 184, 202, 272, 322, 340, 341, 347, 348
CA19-9, carbohydrate antigen 19-9, 109
Call-Exner bodies, 131, 145, 147, 177
Calponin, 45, 75, 86, 91, 243
Calretinin, 119, 147, 157, 180, 185, 198, 213, 244, 255, 275
Cambium layer, 230, 283, 297, 302, 303
Carcinoembryonic antigen, 106, 138, 164, 187, 224, 272, 276, 322, 332
Carcinofibroma, 245, 248
Carcinoid, 171, 172, 196, 277, 279, 301
Carcinoid syndrome, 172
Carcinoma adenoides cysticum, 44
Carcinoma of the male breast, 110
Carcinoma with choriocarcinomatous features, 22
Carcinoma with melanotic features, 22
Carcinoma with osteoclastic giant cells, 21
CCND1, 51, 59, 72, 73
CD117, 164
Cdc25A, 354
Cdc25C, 354
CDH1, 53
CDKN2A, 52
CEA, 164, 341, 348
Cellular angiofibroma, 327, 329, 330
Cellular fibroma, 149-151
Cellular leiomyoma, 235, 236, 239, 240
Cellular variant, blue naevus, 308, 309
Central papillom, 76-78
C-erbB, 250, 266
Cervical intraepithelial neoplasia, 63, 262, 264-273, 276, 279, 294, 295, 319
Cervical intraepithelial neoplasia
C-erbB, 250, 266
Cervical intraepithelial neoplasia
C-my, 72, 266
Cg-ase 1, 112
CTNNB1 (beta-catenin), 131
Cushing syndrome, 160, 175
Cyclin D1, 51, 73, 338
Cytokeratin 7, 25, 33, 45, 106, 109, 119, 129, 141, 147, 156, 195, 226, 268, 275
Cytokeratin 4, 45
Cytokeratin 20, 33, 119, 143, 187, 213, 226, 341, 348
Cytokeratin 34betaE12, 38, 61, 65
Cytokeratin 5, 38
Cytokeratin 6, 38
Cytokeratin 7, 38, 226, 227
C-kit, 164
Clear cell adenocarcinoma, 137-139, 188, 195, 206, 207, 212, 221, 223-226, 272, 274, 276, 297-300
Clear cell adenofibroma, 137, 139
Clear cell adenofibromatous tumour of borderline malignancy, 139
Clear cell carcinoma, 46, 137, 138, 160, 166, 196, 212, 228, 339
Clear cell cystadenofibroma, 137
Clear cell cystadenoma, 137
Clear cell hidradenoma, 46, 325
Clear cell leiomyoma, 241
Clinging carcinoma, 63, 66
CML, 72, 266
Coagulative necrosis, 164
Cobblestone-like papules, 356
COL1A1/PDGFB, 327
Collagenous spherulosis, 44, 60, 78
Colloid carcinoma, 30, 272
Columnar cell mucinous carcinoma, 30, 31
Complete hydatidiform mole, 252-254
Complex (adenomatous) hyperplasia of the endometrium, 229
Complex sclerosing lesion, 27, 81-83
Condylomatous squamous cell carcinoma, 267
Conegenital melanocytic naevus, 331, 332
Cowden syndrome, 232, 355
CSE1L/CAS, 51
CTNNB1 (beta-catenin), 131
Cushing syndrome, 160, 175
Cyclin D1, 51, 73, 338
Cylindromatous carcinoma, 44
CYP24, 51
Cystadenocarcinoma, 145
Cystic lymphangioma, 199
Cytokeratin 7, 25, 33, 45, 106, 109, 119, 129, 141, 147, 156, 195, 226, 268, 275
Cytokeratin 14, 45
Cytokeratin 20, 33, 119, 143, 187, 213, 226, 341, 348
Cytokeratin 34betaE12, 86, 187, 213
Cytokeratin AE1/AE3, 21, 47, 119, 161
Cytokeratin CAM5.2, 21, 119, 187
Cytotrophoblast, 164, 167, 168, 186, 251, 252
DAM1, 50
DAM1, 50
Subject Index

DCIS, see Ductal carcinoma in situ 20, 25, 26, 28, 32, 33, 35, 60, 61, 63-73, 75, 77-81, 101, 106, 112, 338, 346, 347, 356
Deciduoid mesothelioma, 197
Deep angiomyxoma, 304, 305, 327, 329, 330
Dermatofibrosarcoma protuberans, 327
Dermoid cyst, 127, 129, 143, 169-175, 186, 196, 215, 287, 288, 310
DES, 274, 297, 298, 299
Desmoplastic small round cell tumour, 197, 200
Diethylstilbestrol, 274, 297
Diffuse angioma, 89
Diffuse large B-cell lymphoma, 108
Diffuse leiomyomatosis, 237, 241
Diffuse malignant mesothelioma, 197, 198
Diffuse peritoneal leiomyomatosis, 200
DIN, 63, 64, 66, 67
Dissecting leiomyoma, 241
Disseminated peritoneal adenomucinosis, 128
DNA ploidy, 53, 54
Ductal adenoma, 77, 85
Dysgerminoma, 138, 163-166, 168, 176-179, 191, 196, 340
Dyskeratinosis, 270
Dysplasia, 254, 269, 284, 294, 295, 319, 345
Dysplasia/carcinoma-in-situ, 269
Dysplastic melanocytic naevus, 331, 333
Embryoid bodies, 167
Embryonal carcinoma, 163, 166-168
Embryonal rhabdomyosarcoma, 97, 191, 215, 248, 281, 302, 303, 326
EMK, 112
Encrusted papillary carcinoma, 79
Endocervical polyp, 276, 277
Endocervical-like borderline tumour, 126, 127
Endocrine carcinoma, 32
Endodermal sinus tumour, 165, 175
Endometrial hyperplasia, 131, 132, 137, 146, 152, 187, 221, 222, 225, 228, 229, 231, 232, 239
Endometrial polyp, 209, 230, 245, 246, 249
Endometrial stromal nodule, 233-236
Endometrial stromal sarcoma, 149, 190, 196, 216, 233, 234, 245, 247, 281, 309
Endometrioid adenocarcinoma, 130, 143, 206, 207, 212, 221-226, 230, 232, 249, 272-275, 297, 300
Endometrioid borderline tumour, 130, 135, 136
Endometrioid polyp, 209
Endometrioid stromal sarcoma, 130, 134, 135, 147, 215, 236, 280, 281, 302, 303
Endometrioid tumour of borderline malignancy, 135
Endometrioid tumour of low malignant potential, 135
Endometriosis, 127, 130-137, 143, 145, 180, 190, 195, 200, 210, 212, 215, 235, 281, 300, 303, 324
Endometriosis with smooth muscle metaplasia, 215
Endometrioid yolk sac tumour, 186
Endomyometriosis, 215
Endosalpingiosis, 123, 210
Endosalpinx, 340, 347
Ependymoma, 171, 174, 212, 213
Epidermoid cyst, 144, 175
Epithelial membrane antigen, 21, 22, 43, 45, 91, 119, 131, 138, 147, 154, 156, 157, 161, 180, 182, 187, 200, 213, 255, 275, 322
Epithelial leiomyoma, 236, 241
Epithelioid leiomyosarcoma, 238, 241, 252, 280, 281
Epithelioid trophoblastic tumour, 251, 252
Epitheliosis, 65, 104
Epstein-Barr virus, 17, 29, 108, 268, 311
ERß receptor, 58
ERBB3, 51, 202
ERBB4, 51, 202
Erosive adenomatosis, 104
Ewing tumour, 174, 200, 211, 244, 255, 309, 333, 334
EWS/FL1, 174, 309, 334
EWS-WT1, 200, 201
Exaggerated placental site, 254
Exonic splicing enhancer, 350
Extranodal marginal-zone B-cell lymphoma, 108

F
Factor VIII protein, 91
FANCA, 52
FANCD2, 346, 350
Fanconi anaemia, 342, 349, 350
Fanconi anaemia D2 protein, 342
Fetiform teratoma, 163, 170
FGFR1, 50, 59
FGFR2, 51
FHIT, 27, 52, 265
Fibroadenoma, 30, 81, 84, 90, 98, 99, 253
Fibrocystic disease, 355, 356
Fibroepithelial polyp, 271, 297, 302, 303, 321, 329, 330
Fibroma, 134, 135, 149-153, 158, 187, 190, 216, 325
Fibromas of the oral mucosa, 356
Fibromatosis, 39, 40, 88, 92, 190
Fibrosarcoma, 40, 101, 135, 151, 175, 188, 304
Fibrosis mammae virilis, 110
Fibrothecomatous stroma, 147, 148
Flat epithelial atypia, 26, 63, 65, 66
FLG, 50
Florid papillomatosis, 104
Follicular lymphoma, 107, 109, 191
Folliculome lipidique, 157
Fragile histidine triad, 265
Subject Index

G
GADD45, 343, 353
GCDFP-15, 25, 33, 36, 37, 44, 45
Gelatinous carcinoma, 30
Genital rhabdomyoma, 282, 304
Gestational choriocarcinoma, 168, 182, 186, 210, 251, 334
Gestational trophoblastic disease, 210, 250
GFAP, 86, 174
Glandular dysplasia, 265, 276
Glassy cell carcinoma, 228, 277, 279
Glioblastoma, 171, 174
Gliomatosis peritonei, 170
Glomus tumour, 171, 175, 283, 330
Glycogen-rich carcinoma, 46
Goblet cell, 124-127, 156, 173, 195, 206, 224, 272
Goldenhar syndrome, 149
Gonadoblastoma, 163, 164, 167, 176-179
Grading of invasive carcinoma, 18
Granular cell tumour, 36, 37, 94, 283, 327, 330
Granulocytic sarcoma, 109, 191, 192, 196, 215
Granulosa cell tumour, 131, 134, 145-151, 159, 160, 183, 186
Granulosa-stromal cell tumours, 160
GRB7, 52
Gynaecomastia, 90, 91, 110, 111
Gynandroblastoma, 158, 159

H
5-HIAA, 5-hydroxyindoleacetic acid, 173
Haemangioblastoma, 94
Haemangioma, 89, 94, 244, 283, 330
Haemangiomatosis, 149, 357
Haemangiopericytoma, 90, 244
Haemangiosarcoma, 94
Haematopoietic, 186
Haematosalpinx, 206
Haemorrhagic cellular leiomyoma, 240
HAIR-AN syndrome, 189
Hamartoma, 98, 100, 355, 357
Hamartomatous polyps of the colon, 356
HBME1, 244
H-caldesmon, 234, 235, 240, 243
Hepatocellular carcinoma, 184, 353
Hepatoid carcinoma, 182, 184
Hepatoid yolk sac tumour, 165, 184
HER2, 51, 58
Herceptin, 58, 73
Hereditary breast-ovarian cancer syndrome, 208
Hereditary colorectal endometrial cancer syndrome, 358
Hereditary defective mismatch repair syndrome, 358
Hereditary fallopian tube carcinoma, 340, 347
Hereditary non-polyposis colon cancer syndrome, 53, 118, 132, 232, 337, 358-360
Hibernoma, 94
HIC1, 52
HILC1, 244
Hirsutism, 154, 157, 190
Histiocytoid carcinoma, 46
HIV, 262, 269, 319, 320
HMB45, 106, 109
HMGI, 230, 242
HMGIY, 230, 242
HNPPC, see Hereditary non-polyposis colon cancer
Homunculus, 170
HPV, see Human papilloma virus
hRad50-hMre11-NBS1p95 (R/M/N) complex, 342
HRAS1, 343
Human papillomavirus, 226, 227, 262, 265-271, 293, 296, 311, 316-321
Hydatidiform mole, 182, 186, 210, 250-252, 254
Hydrosalpinx, 206
Hypercalcaemia, 137, 138, 148, 182
Hyperestrinism, 146, 221, 222, 225
Hyperplasia of the usual type, 65
Hyperplasias without atypia of the endometrium 229
Hyperreactio luteinalis, 189

I
IGF2R, 52
IGF-binding proteins, 16
Immature teratoma, 166, 169-171, 174, 188
Infiltrating ductal carcinoma, 19, 20, 22, 23, 28, 31
Infiltrating epitheliosis, 83
Infiltrating myoepithelioma, 88
Infiltrating syringomatous adenoma, 39, 105
Inflammatory carcinoma, 47
Inflammatory myofibroblastic tumour, 92, 93
Inflammatory pseudotumour, 93
Inhibin, 131, 135, 138, 147, 148, 150, 151, 154, 156, 157, 159-161, 174, 180, 182, 187, 188, 213, 234, 243, 255
Insulin-growth factor-I, 16
Intercellular adhesion molecule-1, 29
Intracellular trophoblastic disease, 210, 127, 129
Intracystic papillary carcinoma, 34, 79, 80
Intraductal carcinoma, 27, 46, 67, 105, 106
Intraductal hyperplasia, 65
Intraductal papillary carcinoma, 76, 78, 79, 80
Intraductal papillary neoplasms, 76
Intraductal papilloma, 76, 78, 81, 85
Intraductal proliferative lesions, 63, 64, 77
Intravenous leiomyomatosis, 216, 235, 237, 241, 242
Invasive breast carcinoma, 13, 18, 58, 63, 64, 71, 78, 96, 112, 362
Invasive cribriform carcinoma, 22, 27, 28
Invasive ductal carcinoma, 18-20, 35, 57, 64, 72, 73, 353
Invasive ductal carcinoma, no specific type, 19
Invasive ductal carcinoma, not otherwise specified, 19
Invasive hydatidiform mole, 254
Invasive lobular carcinoma, 20, 23, 32, 36, 42, 49, 51, 61, 62, 338, 346
Invasive micropapillary carcinoma, 35
Invasive papillary carcinoma, 34, 35
Inverted follicular keratosis, 321

J
JAZF1, JJAZ1, 234
Juvenile carcinoma, 42
Juvenile fibroadenoma, 99
Juvenile granulosa cell tumour, 146, 148, 174, 182

K
Keratinizing type squamous cell carcinoma, 266, 267, 316, 317
Keratoacanthoma, 317, 321
Ki-67, 57, 270, 272
Koilicytosis, 267, 270, 271, 294, 295, 296, 320, 321
KRAS, 120, 125, 129, 145, 202, 231, 281
Krukenberg tumour, 153, 190, 193-196

L

Lactating adenoma, 84
Laminin, 27, 28, 44, 53, 81, 82, 278
Large cell keratinizing squamous cell carcinoma, 38
Large cell neuroendocrine carcinoma, 33, 184, 279
Large duct papilloma, 76
LCIS, see Lobular carcinoma in situ
Leiomyoblastoma, 238, 241
Leiomyoma, 98, 215, 216, 233-237, 239-242, 244, 256, 281, 282, 304, 327, 330, 355
Leiomyomatosis peritonealis disseminata, 200
Leiomyosarcoma, 98, 175, 196, 211, 215, 233, 236-240, 245, 280, 281, 283, 302, 303, 326, 330
Leukaemia, 49, 109, 191, 192, 196, 211, 289, 311, 334, 351, 361
Leukoplakia, 264
Leuprolide, 238
Leydig cell tumour, 131, 154, 158, 160, 161
Leydig cell tumour, non-hilar type, 161
Lichen sclerosus, 316
Li-Fraumeni syndrome, 65, 67, 351, 352, 354
LIN, see Lobular intraepithelial neoplasia
Lipid cell tumour, 160
Lipid secreting carcinoma, 41
Lipid-rich carcinoma, 41
Lipofuscin, 22, 154, 160, 161
Lipoleiomyoma, 237, 241, 244
Lipoma, 93, 94, 103, 175, 244, 283, 330
Lipomatosis, 357
Liposarcoma, 40, 96, 97, 101, 215, 216, 233-237, 244, 246, 282, 326, 327, 330
Lobular carcinoma in situ, 23-25, 53, 60, 61, 74, 338, 346
Lobular intraepithelial neoplasia, 60-62, 81, 101, 106, 112
Lobular neoplasia, 20, 26, 60, 71, 75, 338
Louis-Bar Syndrome, 361
Low grade adenosquamous carcinoma, 39, 105
Luteinized thecoma, 149, 150, 158
Luteoma of pregnancy, 160, 188, 189, 196
Lymphangiosarcoma, 94, 188
Lymphoblastic lymphoma, 107
Lymphoedema, 95, 96, 263
Lymphoepithelioma, 29, 207, 266-268
Lymphoepithelioma-like carcinoma, 207, 268
Lymphoma, 108, 191, 289, 310
Lynch syndrome, 358
Lysozyme, 45, 196, 311

M

M6P/IGF2R, 52
Macrocephaly, 355, 357
Maffucci syndrome, 149, 150, 158
Major duct papilloma, 76
Malignant Brenner tumour, 140, 142
Malignant fibrous histiocytoma, 96, 175, 244, 282, 304
Malignant lymphoma, 107, 109, 112, 183, 191, 192, 211, 256, 311, 334
Malignant mesodermal mixed tumour, 153, 245, 306
Malignant mesothelioma, 182, 185, 197-199
Malignant mixed epithelial tumour, 144
Malignant müllerian mixed tumour, 130, 133, 149, 156, 188, 210, 245, 284, 306
Malignant myoepithelioma, 86, 88
Malignant peripheral nerve sheath tumour, 188, 244, 280-282, 304
Malignant pigmentary neuroectodermal tumour of infancy, 244
Malignant rhabdoid tumour, 244, 327
Malignant struma, 171, 172
Malignant thymoma, 175, 176
MALT lymphoma, 108, 109
Mammary hamartoma, 103
Mammary osteogenic sarcoma, 97
Masculization, 189
Maspin, 86
Massive ovarian oedema, 190
Matrix producing carcinoma, 37, 40
Microinvasive squamous cell carcinoma, 268, 269
Microsatellite instability, 26, 70, 123
Microviridin, 257, 262, 300
Microscopic papilloma, 77
Minimal deviation adenocarcinoma, 265, 272, 273, 285, 286
Mispread repair, 53, 132, 232, 337, 358, 360
Mitotically active leiomysarcoma, 240
Mixed ductal-lobular carcinoma, 25
Mixed endometrial stromal and smooth muscle tumour, 235, 242
Mixed epithelial tumour, 143, 144
Mixed germ cell-sex cord-stromal tumour, 176, 178, 179
Mixed gonadal dysgenesis, 177
Mixed type carcinoma, 21, 24, 27
MLH1, 53, 118, 131, 132, 337, 342, 358-361
MLH3, 359, 360
MMR, 358, 360
Monoclonality, 265
Monodermal teratoma, 171, 175

References 429
Placental site nodule, 211, 252, 254
Placental site trophoblastic tumour, 210, 251
Placental-like alkaline phosphatase (PLAP) 164, 168, 191, 252
Plasma cell granuloma, 93
Plasmacytoma, 192
Pleomorphic adenoma, 41, 85, 86, 88, 307, 324
Pleomorphic carcinoma, 21, 41
Pleomorphic lobular carcinoma, 24, 25
Plexiform leiomyoma, 241
PMS1, 53, 360
PMS2, 53, 359, 360
PNET, see Primitive neuroectodermal tumour
Polycystic ovary syndrome, 163
Polypoid adenofibroma, 209
Polyvesicular vitelline tumour, 165
Postmeiotic segregation 2, 359
Postoperative spindle cell nodule, 244, 281, 283, 305, 326
Post-radiotherapy angiosarcoma, 96
Potter syndrome, 149
Primary peritoneal borderline tumour, 197, 202
Primary peritoneal carcinoma, 197, 201
Primary peritoneal oval cell tumour, 171, 174, 309, 310
Proliferating trichilemmal tumour, 325
Prophylactic bilateral mastectomy, 345
Prophylactic bilateral salpingo-oophorectomy, 345
Proteus syndrome, 357
Protocadherin 9, 112
Protocadherin 10, 112
Rad50, 341
RAD51, 341-343, 348-351
Radial scar, 26, 27, 39, 60, 78, 81-83
Radial sclerosing lesion, 83
Radial scar, 26, 27, 39, 60, 78, 81-83
RASSF1A (Ras association domain family 1A gene), 52
RB1CC1 (RB1-inducible Coiled-Coil 1), 52
Reichert membrane, 165
Reifenstein syndrome, 112
Reinke crystals, 154, 158, 160, 161, 176, 177
Renin, 157, 207
Rete cyst, 124
Rete ovarii adenocarcinoma, 180
Rete ovarii adenoma, 180
Reitform Sertoli-Leydig cell tumour, 156
Reitform wolffian adenocarcinoma, 212
Reitform wolffian adenoma, 212
Reitform wolffian tumour, 186
Rhabdoid tumour, 244
Rhabdomyoma, 244, 282, 305, 330
Rhabdomyosarcoma, 40, 97, 101, 109, 135, 155, 175, 189, 244, 302, 309, 311, 326
RING domain, 342
Rokitansky protuberance, 163, 171
RPS6KB1, 51
Salpingitis isthmica nodosa, 210
Sarcoma botryoides, 155, 248, 280, 281, 283, 297, 302, 303, 305, 309, 326
Sarcoma family syndrome of Li and Fraumeni, 351
Schiller-Duval bodies, 165
Schwannoma, 94, 283, 304, 330
Sclerosing trichoepithelioma, 83
Sclerosing adenosis, 27, 39, 60, 61, 78, 81-83, 86, 98, 99, 104
Sclerosing papillary lesion, 39, 83
Sclerosing papilloma, 77, 85, 104
Sclerosing papillomatosis, 104
Sclerosing peritonitis, 149, 150
Sclerosing stromal tumour, 149, 152
Sema3A, 33
Seminoma, 163, 164, 176, 177
Serotonin, 143, 173, 272, 279
Serous adenocarcinoma, 119, 141, 201, 206, 212, 221, 224-226, 272, 274, 339
Serous adenofibroma, 119
Serous borderline adenofibroma, 122
Serous borderline tumour, 119, 120, 121, 127, 144, 202, 209
Serous borderline tumour with microinvasion, 120
Serous cystadenoma, 119, 124, 209, 212
Serous cystadenocarcinoma, 119, 120
Serous papillary cystadenocarcinoma, 119, 120
Serous surface borderline tumour, 122
Serous tumour of borderline malignancy, 120, 121
Serous tumour of borderline malignancy with microinvasion, 120
Serous tumour of low malignant potential with microinvasion, 120
Serous tumour of low malignant potential,, 121
Sertoli cell tumour, 153, 156-159, 179, 196, 213
Sertoli cell tumour, annular tubular variant, 158
Sertoli-Leydig cell tumour, 131, 153, 157, 159, 172, 180, 188, 196, 213
Sertoli-Leydig tumour with heterologous elements, 155
Sex cord tumour with annular tubules, 157-159, 179, 273
Sex hormone-binding globulin, 16
Signet ring cell adenocarcinoma, 30, 32, 42
Signet-ring cell, 138, 272, 273
Signet-ring cell adenocarcinoma, 193, 273
Signet-ring stromal tumour, 153
Simple atypical hyperplasia of the endometrium, 229
Simple hyperplasia of the endometrium, 229
Site specific early onset breast cancer syndrome, 346
SIX1 homeobox gene, 72
Sebaceous adenoma, 171, 175
Sebaceous carcinoma, 37, 46, 47, 171, 175, 324
Sebocrine cell, 47
Seborrheic keratosis, 321
Secretory carcinoma, 42
Secretory variant, endometrioid adenocarcinoma, 130, 221, 223
Seminoma, 163, 164, 176, 177
Serotonin, 143, 173, 272, 279
Serous adenocarcinoma, 119, 141, 201, 206, 212, 221, 224-226, 272, 274, 339
Serous adenofibroma, 119
Sebaceous adenoma, 171, 175
Sebaceous carcinoma, 37, 46, 47, 171, 175, 324
Sebocrine cell, 47
Seborrheic keratosis, 321
Secretory carcinoma, 42
Secretory variant, endometrioid adenocarcinoma, 130, 221, 223
Seminoma, 163, 164, 176, 177
Serotonin, 143, 173, 272, 279
Serous adenocarcinoma, 119, 141, 201, 206, 212, 221, 224-226, 272, 274, 339
Serous adenofibroma, 119
Sebaceous adenoma, 171, 175
Sebaceous carcinoma, 37, 46, 47, 171, 175, 324
Sebocrine cell, 47
Seborrheic keratosis, 321
Secretory carcinoma, 42
Secretory variant, endometrioid adenocarcinoma, 130, 221, 223
Seminoma, 163, 164, 176, 177
Serotonin, 143, 173, 272, 279
Serous adenocarcinoma, 119, 141, 201, 206, 212, 221, 224-226, 272, 274, 339
Serous adenofibroma, 119
Sebaceous adenoma, 171, 175
Sebaceous carcinoma, 37, 46, 47, 171, 175, 324
Sebocrine cell, 47
Seborrheic keratosis, 321
Secretory carcinoma, 42
Secretory variant, endometrioid adenocarcinoma, 130, 221, 223
Seminoma, 163, 164, 176, 177
Serotonin, 143, 173, 272, 279
Serous adenocarcinoma, 119, 141, 201, 206, 212, 221, 224-226, 272, 274, 339
Serous adenofibroma, 119
Sebaceous adenoma, 171, 175
Sebaceous carcinoma, 37, 46, 47, 171, 175, 324
Sebocrine cell, 47
Seborrheic keratosis, 321
Small cell / oat cell carcinoma, 32
Small cell carcinoma, 32-34, 145, 148, 174, 182, 196, 207, 221, 227, 266, 267, 277-279, 301, 309, 321, 323
Small cell carcinoma of neuroendocrine type, 183, 227
Small cell carcinoma hypercalcaemic type, 145, 182
Small cell carcinoma, pulmonary type, 183
Smooth muscle myosin, 75, 86
Smooth muscle tumour of uncertain malignant potential, 238
Solid neuroendocrine carcinoma, 32
Spangaro bodies, 157
Speckled penis, 357
Spindle cell carcinoma, 37, 88, 92
Spindle cell epithelioma, 307
Spindle cell lipoma, 93
Spindle cell variant, adenomyoepithelioma, 87
Spindle cell variant, squamous cell carcinoma, 38
Squamotransitional carcinoma, 268
Squamous intraepithelial lesion, 269, 270, 294
Squamous papilloma, 266, 271, 272, 293, 296
S-T syndrome, 95, 96
ST7, 52
Stellate scar, 83
Sternberg tumour, 216
Steroid cell tumour, 138, 160, 188, 196, 216
Stewart Treves syndrome, 95
STK11, 273
STK15, 51
Stromal hyperplasia, 189, 190
Stromal hyperthecosis, 161, 189, 190
Stromal luteoma, 160, 161
Stromal polyp, 271, 297
Stromal tumour with minor sex cord elements, 152
Stromal-Leydig cell tumour, 158
Subareolar duct papillomatosis, 104
Superficial angiomyxoma, 327, 329
Superficial spreading melanoma, 331
Supernumerary ring chromosome, 327
Sustentacular cell, 187
Sympathetic leiomyoma, 241
Synaptophysin, 30, 33, 34, 173, 279, 334
Synovial sarcoma, 280, 281
Undifferentiated endodermal sarcoma, 233, 234, 236
Undifferentiated endometrial sarcoma, 233, 234, 236
Undifferentiated ovarian sarcoma, 134, 135
Undifferentiated uterine sarcoma, 236
Undifferentiated vaginal sarcoma, 302, 303
Uterus-like mass, 215
V
Vaginal intraepithelial neoplasia (VAIN), 293-296
Vaginal micropapillomatosis, 296
VATER, 357
Verrucous carcinoma, 267, 294, 316, 317
Vestibular micropapillomatosis, 320
Vestibular papilloma, 316, 320
VHL, see von-Hippel Lindau disease, 214, 215
Villoglandular variant, adenocarcinoma, 221, 223, 273
Villus adenoma, 300
VIN, see Vulvar intraepithelial neoplasia
Virilization, 152, 156, 188-190
von Hippel-Lindau disease, 212, 214, 215
Vulvar intraepithelial neoplasia (VIN), 316, 318-320, 324
W
Walthard cell nests, 144
Warty type, squamous cell carcinoma, 266, 267, 294, 316, 317
Well differentiated papillary mesothelioma, 197, 198
Wilms tumour, 169, 182, 187, 200, 256, 284, 285
Wolfian adrenal tumour, 207, 212, 213, 215
WT1, 200, 202
Y
Z
ZNF217, 51
Zymogen-like granule, 45