CHAPTER 3

Tumours of the Prostate

Prostate cancer contributes significantly to the overall cancer burden, being the most frequent malignant neoplasia in men. The number of cases has continuously increased over the past decades, partly due to the higher life expectancy. An additional factor is the Western lifestyle, characterized by a highly caloric diet and lack of physical exercise. Epidemiological data indicates that black people are most susceptible, followed by white people, while Asian people have the lowest risk.

The extent to which prostate cancer mortality can be reduced by PSA screening, is currently being evaluated. Histopathological diagnosis and grading play a major role in the management of prostate cancer.
## WHO histological classification of tumours of the prostate

### Epithelial tumours

**Glandular neoplasms**

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma (acinar)</td>
<td>8140/3</td>
</tr>
<tr>
<td>Atrophic</td>
<td>8480/3</td>
</tr>
<tr>
<td>Pseudohyperplastic</td>
<td>8490/3</td>
</tr>
<tr>
<td>Foamy</td>
<td>8290/3</td>
</tr>
<tr>
<td>Lymphoepithelioma-like</td>
<td>8082/3</td>
</tr>
<tr>
<td>Carcinoma with spindle cell differentiation (carcinosarcoma, sarcomatoid carcinoma)</td>
<td>8572/3</td>
</tr>
</tbody>
</table>

**Prostatic intraepithelial neoplasia (PIN)**

<table>
<thead>
<tr>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>8148/2</td>
</tr>
</tbody>
</table>

**Ductal adenocarcinoma**

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cribriform</td>
<td>8201/3</td>
</tr>
<tr>
<td>Papillary</td>
<td>8260/3</td>
</tr>
<tr>
<td>Solid</td>
<td>8230/3</td>
</tr>
</tbody>
</table>

**Prostatic intraepithelial neoplasia, grade III (PIN III)**

<table>
<thead>
<tr>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>8148/2</td>
</tr>
</tbody>
</table>

**Basal cell tumours**

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell adenoma</td>
<td>8147/0</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>8147/3</td>
</tr>
</tbody>
</table>

**Neuroendocrine tumours**

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine differentiation within adenocarcinoma</td>
<td>8574/3</td>
</tr>
<tr>
<td>Carcinoid tumour</td>
<td>8240/3</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>8041/3</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>8680/1</td>
</tr>
<tr>
<td>Neuroblasticoma</td>
<td>9500/3</td>
</tr>
</tbody>
</table>

**Prostatic stromal tumours**

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stromal tumour of uncertain malignant potential</td>
<td>8935/1</td>
</tr>
<tr>
<td>Stromal sarcoma</td>
<td>8935/3</td>
</tr>
</tbody>
</table>

**Mesenchymal tumours**

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyosarcoma</td>
<td>8890/3</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>8900/3</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>9220/3</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>9120/3</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>8830/3</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour</td>
<td>9540/3</td>
</tr>
</tbody>
</table>

### Urothelial tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial carcinoma</td>
<td>8120/3</td>
</tr>
</tbody>
</table>

### Squamous tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
</tbody>
</table>

### Basal cell tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell adenoma</td>
<td>8147/0</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>8147/3</td>
</tr>
</tbody>
</table>

### Miscellaneous tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male adnexal tumour of probable Wolffian origin</td>
<td>9100/3</td>
</tr>
</tbody>
</table>

### Metastatic tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choriocarcinoma</td>
<td>9100/3</td>
</tr>
</tbody>
</table>

### Urothelial carcinomas

<table>
<thead>
<tr>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>8120/3</td>
</tr>
</tbody>
</table>

---

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O-3) (808) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade III intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
### TNM classification of carcinomas of the prostate

#### T – Primary tumour
- **TX**: Primary tumour cannot be assessed
- **T0**: No evidence of primary tumour
- **T1**: Clinically inapparent tumour not palpable or visible by imaging
  - **T1a**: Tumour incidental histological finding in 5% or less of tissue resected
  - **T1b**: Tumour incidental histological finding in more than 5% of tissue resected
  - **T1c**: Tumour identified by needle biopsy (e.g., because of elevated PSA)
- **T2**: Tumour confined within prostate
  - **T2a**: Tumour involves one half of one lobe or less
  - **T2b**: Tumour involves more than half of one lobe, but not both lobes
  - **T2c**: Tumour involves both lobes
- **T3**: Tumour extends beyond the prostate
  - **T3a**: Extracapsular extension (unilateral or bilateral)
  - **T3b**: Tumour invades seminal vesicle(s)
- **T4**: Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall

#### N – Regional lymph nodes
- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

**Note:** Metastasis no larger than 0.2cm can be designated pN1mi

#### M – Distant metastasis
- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis
  - **M1a**: Non-regional lymph node(s)
  - **M1b**: Bone(s)
  - **M1c**: Other site(s)

#### G – Histopathological grading
- **GX**: Grade cannot be assessed
- **G1**: Well differentiated (Gleason 2-4)
- **G2**: Moderately differentiated (Gleason 5-6)
- **G3-4**: Poorly differentiated/undifferentiated (Gleason 7-10)

#### Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G1</td>
</tr>
<tr>
<td>II</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G2, 3-4</td>
</tr>
<tr>
<td></td>
<td>T1b, c</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>T1, T2</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any G</td>
</tr>
</tbody>
</table>

1. [944,2662].
2. A help desk for specific questions about the TNM classification is available at [http://www.uicc.org/tnm/](http://www.uicc.org/tnm/)
Acinar adenocarcinoma

Definition
An invasive malignant epithelial tumour consisting of secretory cells.

ICD-O code  8140/3

Epidemiology

Geographical distribution
Prostate cancer is now the sixth most common cancer in the world (in terms of number of new cases), and third in importance in men [2012]. The estimated number of cases was 513,000 in the year 2000. This represents 9.7% of cancers in men (15.3 % in developed countries and 4.3% in developing countries). It is a less prominent cause of death from cancer, with 201,000 deaths (5.6% of cancer deaths in men, 3.2% of all cancer deaths). The low fatality means that many men are alive following a diagnosis of prostate cancer – an estimated 1.5 million at 5 years, in 2000, making this the most prevalent form of cancer in men. In recent years, incidence rates reflect not only differences in risk of the disease, but also the extent of diagnosis of latent cancers both by screening of asymptomatic individuals, and by detection of latent cancer in tissue removed during prostatectomy operations, or at autopsy. Thus, especially where screening is widespread, recorded ‘incidence’ may be very high (in the United States, for example, where it is now by far the most commonly diagnosed cancer in men). Incidence is very high also in Australia and the Scandinavian countries (probably also due to screening). Incidence rates in Europe are quite variable, but tend to be higher in the countries of northern and western Europe, and lower in the East and South. Prostate cancer remains relatively rare in Asian populations. Mortality is less affected by the effects of early diagnosis of asymptomatic cancers, but depends upon survival as well as incidence; survival is significantly greater in high-incidence countries (80% in the USA vs. 40% in developing countries). However, this more favourable prognosis could well be due to more latent cancer being detected by screening procedures [310]. Mortality rates are high in North America, North and West Europe, Australia/New Zealand, parts of South America (Brazil) and the Caribbean, and in much of sub-Saharan Africa. Mortality rates are low in Asian populations, and in North Africa. The difference in mortality between China and the U.S.A is 26 fold (while it is almost 90 fold for incidence).

Fig. 3.01 Mortality from prostate cancer. Age adjusted rates (ASR), world standard population, all ages. From Globocan 2000 (748).

These international differences are clearly reflected within the United States, where the Black population has the highest incidence (and mortality) rates; some 70% higher than in Whites, who in turn have rates considerably higher than populations of Asian origin (e.g. Chinese, Japanese and Korean males). Similarly, in São Paulo, Brazil, the risk of prostate cancer in Black males was 1.8 (95% CI 1.4–2.3) times that of White men [297]. Latent cancers are frequent in older men, and the prevalence greatly exceeds the cumulative incidence in the same population. Two international studies of latent prostate cancer [316,2874] observed that prevalence increases steeply with age, but varies much less between populations than the incidence of clinical cancer. The country/ethnic-specific ranking was much the same. The frequency of latent carcinoma of prostate in Japan is increasing (as with clinical prostate cancer) and may eventually approach the prevalence for U.S. Whites.

Migrants
Migrants from West Africa to England & Wales have mortality rates 3.5 times (95% CI 2.4–5.1) those of the local-born population, and mortality is significantly higher also among migrants from the Caribbean (RR 1.7; 95% CI 1.5–2.0);
contrast, mortality among migrants from East Africa, of predominantly Asian (Indian) ethnicity, are not high [966]. Migrants from low-risk countries to areas of higher risk show quite marked increases in incidence (for example, Japanese living in the United States). Some of this change reflects an elimination of the ‘diagnostic bias’ influencing the international incidence rates. Localized prostate cancer forms a small proportion of cases in Japan (24%) compared with 66-70% in the U.S.A; incidence in Japan could be 3-4 times that actually recorded if, for example, all transurethral prostatectomy (TURP) sections were carefully examined (2392). However, rates in Japanese migrants remain well below those in the U.S. White populations, even in Japanese born in the United States, which suggests that genetic factors are responsible for at least some of the differences between ethnic groups.

**Age distribution**

The risk of prostate cancer rises very steeply with age. Incidence of clinical disease is low until after age 50, and then increases at approximately the 9-10th power of age, compared with the 5-6th power for other epithelial cancers [488]. Worldwide, about three-quarters of all cases occur in men aged 65 or more.

**Time trends**

Time trends in prostate cancer incidence and mortality have been greatly affected by the advent of screening for raised levels of serum Prostate-Specific Antigen (PSA), allowing increasing detection of preclinical (asymptomatic) disease [2100]. In the USA, prostate cancer incidence rates were increasing slowly up to the 1980’s, probably due to a genuine increase in risk, coupled with increasing diagnosis of latent, asymptomatic cancers in prostatectomy specimens, due to the increasing use of TURP (2099). Beginning in 1986, and accelerating after 1988, there was a rapid increase in incidence. The recorded incidence of prostate cancer doubled between 1984 and 1992, with the increase being mainly in younger men (under 65) and confined to localized and regional disease. The incidence rates began to fall again in 1992 (1993 in Black males), probably because most of the prevalent latent cancers in the subset of the population reached by screening had already been detected [1467]. With the introduction of PSA screening, there was also an increase in the rate of increase in mortality, but this was very much less marked than the change in incidence. More recently, (since 1992 in White men, 1994 in Black men), mortality rates have decreased. The contribution that PSA screening and/or improved treatment has made to this decline has been the subject of considerable debate [728, 763, 1015]. The increased mortality was probably partly due to mis-certification of cause of death among the large number of men who had been diagnosed with latent prostate cancer in the late 80’s and early 90’s. The later decline may be partly due to a reversal of this effect; it seems unlikely that screening was entirely responsible. International trends in mortality have been reviewed by Oliver et al. [1956], and in incidence and mortality by Hsing et al. [1130]. The largest increases in incidence, especially in younger men,
have been seen in high-risk countries, probably partly the effect of increasing detection following TURP, and, more recently, due to use of PSA. But there have been large increases also in low risk countries; 3.5 x in Shanghai, China, 3.0 x in Singapore Chinese, 2.6 x in Miyagi, Japan, 1.7 x in Hong Kong, between 1975 and 1995 (2016,2788). Only in India (Bombay) does there seem to have been little change (+13%) in incidence. Some of this increase may be due to greater awareness of the disease, and diagnosis of small and latent cancers. But it is also probable that there is a genuine increase in risk occurring. This is confirmed by studying changes in mortality. The increases in rates in the “high risk” countries were much less than for incidence, but quite substantial nevertheless (15-25%). In low risk countries, the increase in mortality rates is large, and not much inferior to the changes observed in incidence. As in the USA, there have been declines in mortality from prostate cancer since around 1988-1991, in several high-risk populations, rather more marked in older than in younger men. In some of the countries concerned (Canada, Australia), there has been considerable screening activity, but this is not the case in others where the falls in mortality are just as marked (France, Germany, Italy, UK) (1956). There may be a contribution from improvements in treatment which is difficult to evaluate from survival data because of lead-time bias introduced by earlier diagnosis.

**Etiology**

The marked differences in risk by ethnicity suggest that genetic factors are responsible for at least some of the differences between ethnic groups. Nevertheless, the changes in rates with time, and on migration, also imply that differences in environment or lifestyle are also important. Despite extensive research, the environmental risk factors for prostate cancer are not well understood.

Evidence from ecological, case–control and cohort studies implicates dietary fat in the etiology of prostate cancer, although few studies have adjusted the results for caloric intake, and no particular fat component has been consistently implicated. There is a strong positive association with intake of animal products, especially red meat. The evidence from these studies for a protective effect of fruits and vegetables on prostate cancer, unlike many other cancer sites, is not convincing. There is little evidence for anthropometric associations with prostate cancer, or for a link with obesity (1348,2842).

A cohort study of health professionals in the United States, found that differences in the distribution of possible dietary and lifestyle risk factors did not explain the higher risk (RR 1.81) of prostate cancer in Blacks versus Whites (2091). Genetic factors appear therefore to play a major role in explaining the observed racial differences, and findings of elevated risk in men with a family history of the disease support this. There is a 5–11 fold increased risk among men with two or more affected first-degree relatives (2499). A similar study involving a population-based case–control study of prostate cancer among Blacks, Whites and Asians in the United States and Canada found the prevalence of positive family histories somewhat lower among the Asian Americans than among Blacks or Whites (2815).

It is clear that male sex hormones play an important role in the development and growth of prostate cancers. Testosterone diffuses into the gland, where it is converted by the enzyme steroid 5-alpha reductase type II (SRD5A2) to the more metabolically active form dihydrotestosterone (DHT). DHT and testosterone bind to the androgen receptor (AR), and the receptor/ligand complex translocates to the nucleus for DNA binding and trans-activation of genes which have androgen-responsive elements, including those controlling cell division. Much research has concentrated on the role of polymorphisms of the genes regulating this process and how inter-ethnic variations in such polymorphisms might explain the higher risk of prostate cancer in men of African descent (2246). Polymorphisms in the SRD5A2 genes may provide at least part of the explanation (2389), but more interest is focused on the AR gene, located on the long arm of chromosome X. The AR gene contains a highly polymorphic region of CAG repeats in exon 1, the normal range being 6–39 repeats. Several studies suggest that men with a lower number of AR CAG repeat lengths are at higher risk of prostate cancer (404). Blacks in the United States have fewer CAG repeats than Whites, which has been postulated to partly explain their susceptibility to prostate cancer (2091,2246). Other genetic mechanisms possible related to prostate cancer risk are polymorphisms in the vitamin D receptor gene (1169,1170) or in the insulin-like growth factor (IGF) signalling pathway (403), but there is no evidence for significant inter-ethnic differences in these systems. Other environmental factors (occupational exposures) or behavioural factors (sexual life) have been investigated, but do not seem to play a clear role.

**Localization**

Most clinically palpable prostate cancers diagnosed on needle biopsy are predominantly located posteriorly and posterolaterally (354,1682). In a few cases, large transition zone tumours may extend into the peripheral zone and become palpable. Cancers detected on TURP are predominantly within the transition zone. Nonpalpable cancers detected on needle biopsy are predominantly located peripherally, although 15-25% have tumour predominantly within the transition zone (716). Large tumours may extend into the central zone, yet cancers uncommonly arise in this zone. Multifocal adenocarcinoma of the prostate is present in more than 85% of prostate (354).
Clinical features
Signs and symptoms
Even before the serum prostate specific antigen test came into common usage over a decade ago, most prostate cancer was asymptomatic, detected by digital rectal examination. PSA screening has decreased the average tumour volume, and hence further lowered the percentage of cancers that present with symptoms today. Most cancers arise in the peripheral zone, so that transition zone enlargement sufficient to cause bladder outlet obstruction usually indicates hyperplasia. However, 8.0% of contemporary transurethral resection specimens disclose carcinoma (1605), and rarely, urinary obstruction results from large-volume periurethral tumour. Locally extensive cancer is seen less often than in the past but may present with pelvic pain, rectal bleeding or obstruction (2348).

Metastatic prostatic adenocarcinoma can present as bone pain, mainly in the pelvic bones and spinal cord, where it can cause cord compression (1138). However, when bone scan discloses metastasis after diagnosis of a primary prostatic carcinoma, the metastasis is most often asymptomatic (2487). Enlarged lymph nodes, usually pelvic, but rarely supraclavicular or axillary (typically left-sided), can sometimes be a presenting symptom. Ascites and pleural effusion are rare initial presentations of prostate cancer.

Imaging
Ultrasound imaging
Transrectal ultrasound imaging (TRUS) with high frequency transducers is a useful tool for the work-up of patients with a prostate problem. It enables the operator to evaluate gland volume, as well as delineate and measure focal lesions. Its primary application, however, remains in image guidance of transrectal prostate biopsies. It has proven to be of limited value for the detection of prostate cancer and the assessment of extraglandular spread due to lack of specificity. While the majority of early prostate cancers present as hypoechoic lesions in the peripheral zone on TRUS, this sono-graphic appearance is non-specific, because not all cancers are hypoechoic and not all hypoechoic lesions are malignant (1012). Sonographic-pathologic correlation studies have shown that approximately 70-75% of cancers are hypoechoic and 25-30% of cancers are isoechoic and blend with surrounding tissues (539,2285). These cancers cannot be detected by TRUS. A small number of cancers are echogenic or contain echogenic foci within hypoechoic lesions (1010). The positive predictive value of a hypoechoic lesion to be cancer increases with the size of the lesion, a palpable abnormality in this region and an elevated PSA level (689). Overall the incidence of malignancy in a sonographically suspicious lesion is approximately 20-25% (2193). Even with high-resolution equipment many potentially clinically significant cancers are not visualized by TRUS. A large multicentre study demonstrated that up to 40% of significant cancers were missed by TRUS. In addition, the sensitivity to detect neurovascular bundle invasion has been reported to only be about 66% with a specificity of 78% (1011,2196).

To improve lesion detection the use of colour Doppler US (CDUS) has been advocated particularly for isoechoic lesions or to initiate a TRUS guided biopsy which may not have been performed, thus tailoring the biopsy to target isoechoic yet hypervascular areas of the gland (56,1885,2195). Results from these studies are however conflicting due to a problematic overlap in flow detected in cancers, inflammatory conditions or benign lesions. Newer colour flow techniques such as power Doppler US may be helpful as they may allow detection of slow flow in even smaller tumour vessels. Other recent developments such as intravenous contrast agents, harmonic imaging and 3-D US have shown a potential role for these US techniques to delineate subtle prostate cancers, assess extraglandular spread or monitor patients with prostate cancer undergoing hormonal treatment (364,658,1013).

Computed tomography and magnetic resonance imaging
Cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have
not proven valuable because of low sensitivities to detect and stage prostate cancer (1011, 2149, 2594, 2910). MRI is sometimes reserved for staging of patients with biopsy proven prostate cancer (2605). The combined use of MRI and proton MRI-spectroscopy imaging (MRSI) is currently being evaluated for staging of prostate cancer. These techniques however, also appear to have limitations for imaging of microscopic disease (1412, 2911). Knowledge obtained from MRSI may provide insight into the biological behaviour of prostate cancer, such as tumour aggressiveness and extra-prostatic extension (2911).

Plain film radiography and nuclear medicine

Skeletal radiography (bone survey) is an insensitive method to screen for bony metastases and should be reserved to confirm skeletal abnormalities in patients with positive bone scintigraphy. Bone scintigraphy (radionuclide bone scans) provides the most sensitive method for detecting bone metastases. Upper urinary tract obstruction may also be identified on bone scintigraphy obviating the need for intravenous urography. Monoclonal antibody radioimmuno-scintigraphy (prostate specific membrane antigen-PMSA) chelated to Indium111 (Prostacint®, Cytogen Corporation, Princeton, N.J.) has shown promise to detect microscopic metastatic deposits in regional and distant sites. However, due to limited positive predictive values reported (50-62%) its use in combination with PSA, histologic grade and clinical staging is recommended to provide increased predictive information (147, 1621). Another new development in the field of nuclear medicine is positron emission tomography (PET), which allows in vivo-characterization of tumours and may have implications for the evaluation of patients with prostate cancer in the future.

Laboratory tests

Prostate specific antigen (PSA)

PSA is produced by the epithelial cells lining the prostatic ducts and acini and is secreted directly into the prostatic ductal system. The PSA gene is located on chromosome 19 (2211, 2558). Its androgen-regulated transcription results in the biosynthesis of a 261 amino acid PSA precursor. This precursor, is believed to be activated by the proteolytic liberation of a small amino-terminal fragment (2098). Conversion from inactive proPSA to active PSA requires action of exogenous prostatic proteases, e.g. hK2, prostin (hK15), prostate (hK4) or trypsin. Different molecular forms of PSA exist in serum (392, 1498, 1499, 2504). These result from complex formation between free PSA and two major extracellular protease inhibitors that are synthesized in the liver. As PSA is a serine protease, its normal mode of existence in the serum is in a complex with α1-anti-chymotrypsin (ACT), a 67 kDa single chain glycoprotein, and α2-macroglobulin (AMG), a 720 kDa glycoprotein. Only a small percentage of the PSA found in the serum is free. Because this free form does not bind to ACT or AMG, it is thought to be either the enzymatically inactive precursor (i.e., zymogen) for PSA or an inactive nicked or damaged form of the native molecule. Subfractions of free PSA include: mature single-chain, and multi-chain, nicked free PSA forms.

Serum total PSA and age specific reference ranges

Serum PSA is determined with immunoassay techniques. No PSA epitopes that interact with anti-PSA antibodies are exposed on the PSA-AMG complex. This is thought to result from the 25-fold larger AMG molecule "engulfing" PSA and hindering recognition of PSA epitopes. Therefore, conventional assays do not measure PSA-AMG. In contrast, only one major PSA epitope is completely shielded by complex formation with ACT: PSA-ACT can therefore be readily measured in serum (1498, 1667). Monoclonal antibodies have been designed to detect the free form of PSA (29kDa), the complex of PSA and ACT (90 kDa) and the total PSA. It has been found that total PSA correlates well with advancing age (92, 483, 546, 576, 1937, 2022, 2185). Based on the 95th percentile values in a regression model, white men under age 50 have PSA values <2.5 ng/ml, under age 60 have PSA values <3.5 ng/ml, under age 70 have PSA values <4.5 ng/ml, and under age 80 PSA levels were <6.5 ng/ml. It has been suggested that these age-related values be used as the upper limit of normal in

Fig. 3.08 Bone scanning showing multiple metastases of a prostate carcinoma.

Fig. 3.07 A Pelvic metastases of prostate carcinoma. B Spinal osteoblastic metastases from prostate cancer. Radioscopic photograph. C Radiography of the same case.
PSA-related diagnostic strategies. 

PSA is elevated beyond the arbitrary cut-off point of 4.0 ng/ml in the majority of patients with prostate cancer. It may also be greater than 4.0 ng/ml in some benign conditions, including benign prostatic hyperplasia (BPH). Prostate cancer may also be present in men with serum PSA values lower than the above quoted cut-off points. This may be specifically true for men considered at higher risk (i.e., family history; men with faster doubling time; and in the United States African American men). Therefore, serum PSA lacks high sensitivity and specificity for prostate cancer. This problem has been partially overcome by calculating several PSA-related indices and/or evaluating other serum markers (1660,1775). PSA tests are also useful to detect recurrence and response of cancer following therapy. The exact value used to define recurrence varies depending on the treatment modality.

**Free PSA.** The free form of PSA occurs to a greater proportion in men without cancer (2607) and, by contrast, the α1- chymotrypsin complex PSA comprises a greater proportion of the total PSA in men with malignancy. The median values of total PSA and of the free-to-total PSA ratio are 7.8 ng/ml and 10.5% in prostate cancer patients, 4.3 ng/ml and 20.8% in patients with BPH, and 1.4 ng/ml and 23.6% in a control group of men without BPH (2506). There is a significant difference in free-to-total PSA ratio between prostate cancer and BPH patients with prostate volumes smaller than 40 cm³, but not between patients in these two groups with prostate volumes exceeding 40 cm³ (2506).

**Complex PSA.** Problems associated with the free-to-total PSA ratio, particularly assay variability, and the increased magnitude of error when the quotient is derived, are obviated by assays for complex PSA. Complex PSA value may offer better specificity than total and free-to-total PSA ratio (308).

**PSA density**

This is the ratio of the serum PSA concentration to the volume of the gland, which can be measured by transrectal ultrasound (total PSA/prostatic volume = PSA density, PSAD). The PSAD values are divided into three categories: normal (values equal or lower than 0.050 ng/ml/cm³), intermediate (from 0.051 to 0.099 ng/ml/cm³) and pathological (equal to or greater than 0.1 ng/ml/cm³). The production of PSA per volume of prostatic tissue is related to the presence of BPH and prostate cancer and to the proportion of epithelial cells and the histological grade of the carcinoma (1476).

**PSA density of the transition zone.** Nodular hyperplasia is the main determinant of serum PSA levels in patients with BPH (139,109,1521). Therefore, it seems logical that nodular hyperplasia volume rather than total volume should be used when trying to interpret elevated levels of serum PSA. PSA density of the transition zone (PSA TZD) is more accurate in predicting prostate cancer than PSA density for PSA levels of less than 10 ng/ml (625).

**Prostate-specific antigen epithelial density.** The serum PSA level is most strongly correlated with the volume of epithelium in the transition zone. The prostate-specific antigen epithelial density (PSAED, equal to serum PSA divided by prostate epithelial volume as determined morphometrically in biopsies) should be superior to PSAD. However, the amount of PSA produced by individual epithelial cells is variable and serum levels of PSA may be related to additional factors such as hormonal milieu, vascularity, presence of inflammation, and other unrecognized phenomena (2696, 2941).

**PSA velocity and PSA doubling time**

PSA velocity (or PSA slope) refers to the rate of change in total PSA levels over time. It has been demonstrated that the rate of increase over time is greater in men who have carcinoma as compared to those who do not (380,381). This is linked to the fact that the doubling time of prostate cancer is estimated to be 100 times faster than BPH. Given the short-term variability of serum PSA values, serum PSA velocity should be calculated over an 18-month period with at least three measurements. PSA doubling time (PSA DT) is closely related to PSA velocity (1470). Patients with BPH have PSA doubling times of 12 ± 5 and 17 ± 5 years at years 60 and 85, respectively. In patients with prostate cancer, PSA change has both a linear and exponential phase. During the exponential phase, the doubling time for patients with local/regional and advanced/metastatic disease ranges from 1.5-6.6 years (median, 3 years) and 0.9-8.5 years (median, 2 years), respectively (1470,1775).

**Prostate markers other than PSA**

**Prostatic acid phosphatase (PAP)**

PAP is produced by the epithelial cells lining the prostatic ducts and acini and is secreted directly into the prostatic ductal system. PAP was the first serum marker for prostate cancer. Serum PAP may be significantly elevated in patients with BPH, prostatitis, prostatic infection or prostate cancer. Serum PAP currently plays a limited role in the diagnosis and management of prostate cancer. The sensitivity and specificity of this tumour marker are far too low for it to be used as a screening test for prostate cancer (1660).

**Human glandular kallikrein 2 (hk2)**

The gene for hk2 has a close sequence homology to the PSA gene. hk2 messenger RNA is localized predominately to the prostate in the same manner as PSA. hk2 and PSA exhibit different proteolytic specificities, but show similar patterns of complex formation with serum protease inhibitors. In particular, hk2 is found to form a covalent complex with ACT at rates comparable to PSA. Therefore, serum hk2 is detected in its free form, as well as in a complex with ACT (2074). The serum level of hk2 is relatively high, especially in men with diagnosed prostate cancer and not proportional to total PSA or free PSA concentrations. This difference in serum expression between hk2 and PSA allows additional clinical information to be derived from the measurement of hk2.

**Prostate specific membrane antigen (PSMA)**

Although it is not a secretory protein, PSMA is a membrane-bound glycoprotein with high specificity for benign or malignant prostatic epithelial cells (142, 1125,1839,1842,2412,2846,2847). This is a novel prognostic marker that is present in the serum of healthy men, according to studies with monoclonal antibody 7E11.C5. An elevated concentration is associated with the presence of prostate cancer. PSMA levels correlate best with advanced stage, or with a hormone-refractory state. However, studies of the
Methods of tissue diagnosis

Needle biopsies

The current standard method for detection of prostate cancer is by transrectal ultrasound-guided core biopsies. Directed biopsies to either lesions detected on digital rectal examination or on ultrasound should be combined with systematic biopsies taken according to a standardized protocol [1008, 1703]. The sextant protocol samples the apex, mid and base region bilaterally [1099]. Sextant biopsies aim at the centre of each half of the prostate equidistant from the midline and the lateral edge while the most common location of prostate cancer is in the dorsolateral region of the prostate. Several modifications of the sextant protocol have been proposed. Recent studies have shown that protocols with 10 to 13 systematic biopsies have a cancer detection rate up to 35% superior to the traditional sextant protocol [1057, 724, 2151]. This increased yield relates to the addition of biopsies sampling the more lateral part of the peripheral zone, where a significant number of cancers are located. Approximately 15-22% of prostate cancers arise in the transition zone, while sextant biopsies mainly sample the peripheral zone. Most studies have found few additional cancers by adding transition zone biopsies to the sextant protocol (1.8-4.3% of all cancers detected) and transition zone biopsies are usually not taken in the initial biopsy session [778, 2598].

Handling of needle biopsies. Prostate biopsies from different regions of the gland should be identified separately. If two cores are taken from the same region, they can be placed into the same block. However, blocking more than two biopsy specimens together increases the loss of tissue at sectioning [1272]. When atypia suspicious for cancer is found, a repeat biopsy should concentrate on the initial atypical site in addition to sampling the rest of the prostate. This cannot be performed unless biopsies have been specifically designated as to their location. The normal histology of the prostate and its adjacent structures differs between base and apex and knowledge about biopsy location is helpful for the pathologist. The location and extent of cancer may be critical for the clinician when selecting treatment option [2151]. The most common fixative used for needle biopsies is formalin, although alternative fixatives, which enhance nuclear details are also in use. A potential problem with these alternative fixatives is that lesions such as high-grade prostatic intraepithelial neoplasia may be over-diagnosed.

Immunohistochemistry for high molecular weight cytokeratins provides considerable help in decreasing the number of inconclusive cases from 6-2% [1923]. It has therefore been suggested that intervening unstained sections suitable for immunohistochemistry are retained in case immunohistochemistry would be necessary. Intervening slides are critical to establish a conclusive diagnosis in 2.8% of prostate biopsies, hence, sparing a repeat biopsy [939].

Transurethral resection of the prostate

When transurethral resection of the prostate (TURP) is done without clinical suspicion of cancer, prostate cancer is incidentally detected in approximately 8-10% of the specimens. Cancers detected at TURP are often transition zone tumours, but they may also be of peripheral zone origin, particularly when they are large [941, 1685, 1686]. It is recommended that the extent of tumour is reported as percentage of the total specimen area. If the tumour occupies less than 5% of the specimen it is stage T1a, and otherwise stage T1b. However, in the uncommon situation of less than 5% of cancer with Gleason score 7 or higher, patients are treated as if they had stage T1b disease. Most men who undergo total prostatectomy for T1a cancer have no or minimal residual disease, but in a minority there is substantial tumour located in the periphery of the prostate [711]. Handling of TURP specimens. A TURP specimen may contain more than a hundred grams of tissue and it is often necessary to select a limited amount of tissue for histological examination. Submission should be random to ensure that the percentage of the specimen area involved with cancer is representative for the entire specimen. Several strategies for selection have been evaluated. Submission of 8 cassettes will identify almost all stage T1b cancers and approximately 90% of stage T1a tumours [1847, 2223]. In young men, submission of the entire specimen may be considered to ensure detection of all T1a tumours. Guidelines have been developed for whether additional sampling is needed following the initial detection of cancer in a TURP specimen [1673].

Fine needle aspiration cytology

Before the era of transrectal core biopsies, prostate cancer was traditionally diagnosed by fine needle aspiration (FNA). FNA is still used in some countries and has some advantages. The technique is cheap, quick, usually relatively painless and has low risk of complications. In early studies comparing FNA and limited core biopsy protocols, the sensitivity of FNA was usually found to be comparable with that of core biopsies [2765]. However, the use of FNA for diagnosing prostate cancer has disadvan-
and in posterolateral sites for the more common peripheral zone carcinomas (1684). The peripheral zone carcinomas often grow into periprostatic soft tissue by invading along nerves (2735) or by direct penetration out of the prostate. The term "capsule" has been used to denote the outer boundary of the prostate. However, as there is no well-defined capsule surrounding the entire prostate this term is no longer recommended. Extraprostatic invasion superiorly into the bladder neck can occur with larger tumours, and in advanced cases, this can lead to bladder neck and ureteral obstruction. Extension into the seminal vesicles can occur by several pathways, including direct extension from carcinoma in adjacent soft tissue, spread along the ejaculatory duct complex, and via lymphvascular space channels (1944). Posteriorly, Denovillier’s fascia constitutes an effective physical barrier (2734), and direct prostatic carcinoma spread into the rectum is a rare event. Metastatic spread of prostatic carcinoma begins when carcinoma invades into lymphvascular spaces. The most common sites of metastatic spread of prostatic carcinoma are the regional lymph nodes and bones of the pelvis and axial skeleton. The obturator and hypogastric nodes are usually the first ones to be involved, followed by external iliac, common iliac, presacral, and presciatic nodes. In a few patients, periprostatic/periseminal vesicle lymph nodes may be the first ones to harbour metastatic carcinoma, but these nodes are found in less than 5% of radical prostatectomy specimens (1364). Metastasis to bone marrow, with an osteoblastic response, is a hallmark of disseminated prostate cancer (835). The bones most frequently infiltrated by metastatic disease are, in descending order, pelvic bones, dorsal and lumbar spine, ribs, cervical spine, femur, skull, sacrum, and humerus. Visceral metastatic deposits in the lung and liver are not often clinically apparent, but are common in end-stage disease. The TNM classification scheme (944, 2662) is the currently preferred system for clinical and pathologic staging of prostatic carcinoma.

Histopathology
Adenocarcinomas of the prostate range from well-differentiated gland forming cancers, where it is often difficult to dis-
Distinguish them from benign prostatic glands, to poorly differentiated tumours, difficult to identify as being of prostatic origin. A feature common to virtually all prostate cancers is the presence of only a single cell type without a basal cell layer. Benign prostate glands, in contrast, contain a basal cell layer beneath the secretory cells. The recognition of basal cells on hematoxylin and eosin stained sections is not straightforward. In cases of obvious carcinoma, there may be cells that closely mimic basal cells. These cells when labeled with basal cell specific antibodies are negative and represent fibroblasts closely apposed to the neoplastic glands. Conversely, basal cells may not be readily recognized in benign glands without the use of special studies. The histopathology of prostate cancer, and its distinction from benign glands, rests on a constellation of architectural, nuclear, cytoplasmic, and intraluminal features. With the exception of three malignant specific features listed at the end of this section, all of the features listed below, while more commonly seen in cancer, can also be seen in benign mimickers of cancer.

Architectural features
Benign prostatic glands tend to grow either as circumscribed nodules within benign prostatic hyperplasia, radiate in columns out from the urethra in a linear fashion, or are evenly dispersed in the peripheral zone (1685). In contrast, gland-forming prostate cancers typically contain glands that are more crowded than in benign prostatic tissue, although there is overlap with certain benign mimickers of prostate cancer. Glands of adenocarcinoma of the prostate typically grow in a haphazard fashion. Glands oriented perpendicular to each other and glands irregularly separated by bundles of smooth muscle are indicative of an infiltrative process. Another pattern characteristic of an infiltrative process is the presence of small atypical glands situated in between larger benign glands. With the loss of glandular differentiation and the formation of cribriform structures, fused glands, and poorly formed glands, the distinction between benign glands based on the architectural pattern becomes more apparent. Tumours composed of solid sheets, cords of cells, or isolated individual cells characterize undifferentiated prostate cancer. These architectural patterns are key components to the grading of prostate cancer (see Gleason grading system).
Nuclear features
Nuclei in prostate cancer range from those indistinguishable from benign prostatic epithelium to those with overt malignancy. Typically, the extent of nuclear atypia correlates with the architectural degree of differentiation, although exceptions occur. In most prostate cancers, there are cytological differences in the malignant glands when compared to the surrounding benign glands. Nuclear enlargement with prominent nucleoli is a frequent finding, although not every cancer cell will display these features. Some neoplastic nuclei lack prominent nucleoli, yet are enlarged and hyperchromatic. Prostate cancer nuclei, even in cancers which lack glandular differentiation, show little variability in nuclear shape or size from one nucleus to another. Rarely, high-grade prostate cancer, typically seen in the terminal disseminated phase of the disease, reveals marked nuclear pleomorphism. Mitotic figures may be relatively common in high-grade cancer, yet are infrequent in lower grade tumours.

Cytoplasmic features
Glands of adenocarcinoma of the prostate tend to have a discrete crisp, sharp luminal border without undulations or ruffling of the cytoplasm. In contrast, equivalently sized benign glands have an irregular luminal surface with small papillary infoldings and a convoluted appearance. The finding of apical snouts is not helpful in distinguishing benign versus malignant glands as they can be seen in both. Cytoplasmic features of low grade prostate cancer are also often not very distinctive, since they are often pale-clear, similar to benign glands. Neoplastic glands may have amphophilic cytoplasm, which may be a useful diagnostic criterion of malignancy. Prostate cancer cytoplasm of all grades typically lacks lipofuscin, in contrast to its presence in some benign prostatic glands (314).

Intraluminal features
A feature more commonly seen in low grade prostate cancer, as opposed to higher grade cancer is prostatic crystalloids (1111,2204). These are dense eosinophilic crystal-like structures that appear in various geometric shapes such as rectangular, hexagonal, triangular and rod-like structures. Crystalloids, although not diagnostic of carcinoma, are more frequently found in cancer than in benign glands. The one condition that mimics cancer where crystalloids are frequently seen is adenosis (atypical adenomatous hyperplasia) (843). Intraluminal pink acellular dense secretions or blue-tinged mucinous secretions seen in hematoxylin and eosin stained sections are additional findings seen preferentially in cancer, especially low-grade cancer (703). In contrast, corpora amyloidea, which consists of well-circumscribed round to oval structures with concentric lamellar rings, are common in benign glands and only rarely seen in prostate cancer (2204).

Malignant specific features
Short of seeing prostatic glands in an extra-prostatic site, there are only three features that are in and of themselves diagnostic of cancer, as they have not been described in benign prostatic glands.

**Fig. 3.16** Adenocarcinoma with amphophilic cytoplasm and enlarged nuclei containing prominent nucleoli.

**Fig. 3.17** A Well differentiated carcinoma with mild nuclear atypia. B Apocrine-like cytoplasmic blebbing in prostatic adenocarcinoma glands.
glands. These are perineural invasion, mucinous fibroplasia (collagenous micronodules), and glomerulations. Although perineural indentation by benign prostatic glands has been reported, the glands in these cases appear totally benign and are present at only one edge of the nerve rather than circumferentially involving the perineural space, as can be seen in carcinoma (379,1676). The second specific feature for prostate cancer is known as either mucinous fibroplasia or collagenous micronodules. It is typified by very delicate loose fibrous tissue with an ingrowth of fibroblasts, sometimes reflecting organization of intraluminal mucin. The final malignant specific feature is glomerulations, consisting of glands with a cribriform proliferation that is not transluminal. Rather, these cribriform formations are attached to only one edge of the gland resulting in a structure superficially resembling a glomerulus.

**Stromal features**

Ordinary acinar adenocarcinoma lacks a desmoplastic or myxoid stromal response, such that evaluation of the stroma is typically not useful in the diagnosis of prostate cancer. Typically adenocarcinoma of the prostate does not elicit a stromal inflammatory response.

**Immunoprofile**

**Prostate specific antigen (PSA)**

Following PSA's discovery in 1979, it has become a useful immunohistochemical marker of prostatic differentiation in formalin-fixed, paraffin-embedded tissue, with both polyclonal and monoclonal antibodies available (702). PSA is localized to the cytoplasm of non-neoplastic prostatic glandular cells in all prostatic zones, but is neither expressed by basal cells, seminal vesicle/ejaculatory duct glandular cells, nor urothelial cells. Because of its relatively high specificity for prostatic glandular cells, PSA is a useful tissue marker expressed by most prostatic adenocarcinomas (66, 702,1863,2905). There is frequently intratumoural and intertumoural heterogeneity, with most studies indicating decreasing PSA expression with increasing tumour grade (702, 906). PSA is diagnostically helpful in distinguishing prostatic adenocarcinomas from other neoplasms secondarily involving the prostate and establishing prostatic origin in metastatic carcinomas of unknown primary (702,1863). PSA is also helpful in excluding benign mimics of prostatic carcinoma, such as seminal vesicle/ejaculatory duct epithelium, nephrogenic adenoma, mesonephric duct remnants, Cowper’s glands, granulomatous prostatitis and malakoplakia (66,309,2905). Whereas monoclonal antibodies to PSA do not label seminal vesicle tissue, polyclonal antibodies have been shown to occasionally label seminal vesicle epithelium (2714). PSA in conjunction with a basal cell marker is useful in distinguishing intraglandular proliferations of basal cells from acinar cells, helping to separate prostatic intraepithelial neoplasia from basal cell hyperplasia and transitional cell metaplasia in equivocal cases (66, 2374,2905).

A minority of higher grade prostatic adenocarcinomas are PSA negative, although some of these tumours have been shown to express PSA mRNA. Some prostatic adenocarcinomas lose PSA immunoreactivity following androgen deprivation or radiation therapy. Prostate specific membrane antigen (PSMA) (membrane bound antigen expressed in benign and malignant prostatic acinar cells) and androgen receptor may be immunoreactive in some high grade, PSA immunonegative prostatic adenocarcinomas. Extraprostatic tissues which are variably immunoreactive for PSA, include urethral and periurethral glands (male and female), urothelial glandular metaplasia (cystitis cystica and glandularis), anal glands (male), urachal remnants and neutrophils. Extraprostatic neoplasms and tumour-like conditions occasionally immunoreactive for PSA include urethral/periurethral adenocarcinoma (female), bladder adenocarcinoma, extramammary Paget disease of the penis, salivary gland neoplasms in males (pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, salivary duct carcinoma), mammary carcinoma, mature teratoma, and some nephrogenic adenomas (66,702,2905).

**Prostate specific acid phosphatase (PAP)**

Immunohistochemistry for PAP is active in formalin-fixed, paraffin-embedded tissues (26,66,702,1771,1862,2905). The polyclonal antibody is more sensitive, but less specific than the monoclonal antibody (309). PAP and PSA have similar diagnostic utility; since a small number of prostatic adenocarcinomas are immunoreactive for only one of the two markers, PAP is primarily reserved for cases of suspected prostatic carcinoma in which the PSA stain is negative (849). Extraprostatic tissues reported to be immunoreactive for PAP include pancreatic islet cells, hepatocytes, gastric parietal cells, some renal tubular epithelial cells and neutrophils. Reported PAP immunoreactive neoplasms include some neuroendocrine tumours (pancreatic islet cell tumours, gastrointestinal carcinoids), mammary carcinoma, urothelial adenocarcinoma, anal cloacogenic carcinoma, salivary gland neoplasms (males) and mature teratoma (66,702,2905).

**High molecular weight cytokeratins detected by 34BE12 (Cytokeratin-903)**

Prostatic secretory and basal cells are immunoreactive for antibodies to broad
Acinar adenocarcinoma

Fig. 3.20 A, B Adenocarcinoma with mucinous fibroplasia (collagenous micronodules).

Fig. 3.21 A Adenocarcinoma with perineural invasion. B Prostate cancer with glomerulations.

spectrum and low molecular weight cytokeratins. However, only basal cells express high molecular weight cytokeratins (309). One high molecular monoclonal cytokeratin antibody, clone 34βE12, recognizes 57 and 66 kilodalton cytokeratins in stratum corneum corresponding to Moll numbers 1, 5, 10 and 14, and is widely used as a basal cell specific marker active in paraffin-embedded tissue following proteolytic digestion (66,309,918,1048,1765,2374,2905). 34βE12 is also immunoreactive against squamous, urothelial, bronchial/pneumocyte, thymic, some intestinal and ductal epithelium (breast, pancreas, bile duct, salivary gland, sweat duct, renal collecting duct), and mesothelium (918). An immunoperoxidase cocktail containing monoclonal antibodies to cytokeratins 5 and 6 is also an effective basal cell stain (1286). Since uniform absence of a basal cell layer in prostatic acinar proliferations is one important diagnostic feature of invasive carcinoma and basal cells may be inapparent by H&E stain, basal cell specific immunostains may help to distinguish invasive prostatic adenocarcinoma from benign small acinar cancer - mimics which retain their basal cell layer, e.g. glandular atrophy, post-atrophic hyperplasia, adenosis (atypical adenomatous hyperplasia), sclerosing adenosis and radiation induced atypia (66,1048,2905). Because the basal cell layer may be interrupted or not demonstrable in small numbers of benign glands, the complete absence of a basal cell layer in a small focus of acini cannot be used alone as a definitive criterion for malignancy; rather, absence of a basal cell layer is supportive of invasive carcinoma only in acinar proliferations which exhibit suspicious cytologic and / or architectural features on H&E stain (1048). Conversely, some early invasive prostatic carcinomas, e.g. microinvasive carcinomas arising in association with or independent of high grade prostatic intraepithelial neoplasia, may have residual basal cells (1952). Intraductal spread of invasive carcinoma and entrapped benign glands are other proposed explanations for residual basal cells (66,2905). Rare prostatic adenocarcinomas contain sparse neoplastic glandular cells, which are immunoreactive for 34βE12, yet these are not in a basal cell distribution (66,2374). The use of antibodies for 34βE12 is especially helpful for the diagnosis for of deceptively benign appearing variants of prostate cancer. Immunohistochemistry for cytokeratins 7 and 20 have a limited diagnostic use in prostate pathology with the exception that negative staining for both markers, which can occur in prostate
adenocarcinoma, would be unusual for transitional cell carcinoma [849].

p63

p63, a nuclear protein encoded by a gene on chromosome 3q27-29 with homology to p53 (a tumour suppressor gene), has been shown to regulate growth and development in epithelium of the skin, cervix, breast and urogenital tract. Specific isotypes are expressed in basal cells of pseudostratified epithelia (prostate, bronchial), reserve cells of simple columnar epithelia (endocervical, pancreatic ductal), myoepithelial cells (breast, salivary glands, cutaneous apocrine/eccrine glands), urothelium and squamous epithelium [1286]. A monoclonal antibody is active in paraffin-embedded tissue following antigen retrieval. p63 has similar applications to those of high molecular weight cytokeratins in the diagnosis of prostatic adenocarcinoma, but with the advantages that p63: 1) stains a subset of 34βE12 negative basal cells, 2) is less susceptible to the staining variability of 34βE12 (particularly in TURP specimens with cautery artefact), and 3) is easier to interpret because of its strong nuclear staining intensity and low background. Interpretative limitations related to presence or absence of basal cells in small numbers of glands for 34βE12 apply to p63, requiring correlation with morphology [2374]. Prostatic adenocarcinomas have occasional p63 immunoreactive cells, most representing entrapped benign glands or intraductal spread of carcinoma with residual basal cells [1286].

α-Methyl-CoA racemase (AMACR)

AMACR mRNA was recently identified as being overexpressed in prostatic adenocarcinoma by cDNA library subtraction utilizing high throughput RNA microarray analysis [2856]. This mRNA was found to encode a racemase protein, for which polyclonal and monoclonal antibodies have been produced which are active in formalin-fixed, paraffin-embedded tissue [187,1220,2856,2935]. Immunohistochemical studies on biopsy material with an antibody directed against AMACR (P504S) demonstrate that over 80% of prostatic adenocarcinomas are labeled [1221,1593]. Certain subtypes of prostate cancer, such as foamy gland carcinoma, atrophic carcinoma, pseudo-hyperplastic, and treated carcinoma show lower AMACR expression [2936]. However, AMACR is not specific for prostate cancer and is present in nodular hyperplasia (12%), atrophic glands, high grade PIN (>90%) [2935], and adenosis (atypical adenomatous hyperplasia) (17.5%) [2869]. AMACR may be used as a confirmatory stain for prostatic adenocarcinoma, in conjunction with H&E morphology and a basal cell specific marker [2935]. AMACR is expressed in other non-prostatic neoplasms including urothelial and colon cancer.

Androgen receptor (AR)

AR is a nuclear localized, androgen binding protein complex occurring in prostatic glandular, basal, stromal cells. The activated protein serves as a transcription factor, mediating androgen dependent cellular functions, e.g. PSA transcription in secretory cells and promoting cellular proliferation. AR monoclonal and polyclonal antibodies are active in formalin-fixed, paraffin-embedded tissue following antigen retrieval [1592,2559]. Positive nuclear staining indicates immunoreactive protein, but does not distinguish active from inactive forms of the protein. AR immunoreactivity was demonstrated in a minority (42.5%) cases of high grade prostatic intraepithelial neoplasia. Most invasive prostatic adenocarcinomas are immunoreactive for AR; one study demonstrated that 85% of untreated
prostate adenocarcinomas exhibit AR immunoreactivity in greater than 50% of tumour cells, with increasing heterogeneity occurring with increasing histologic grade and pathologic stage (1592). Some studies have shown AR heterogeneity or loss in a subset of AR independent tumours, suggesting one mechanism of androgen resistance may be AR loss (1592,2559). Because androgen insensitivity may occur without loss of AR immunoreactivity, positive AR immunophenotype may not reliably distinguish androgen dependent from independent tumours (1592). Immunostaining for AR is not in routine clinical use.

**Histologic variants**

The following histologic variants of prostate adenocarcinoma are typically seen in association with ordinary acinar adenocarcinoma. However, on limited biopsy material, the entire sampled tumour may demonstrate only the variant morphology.

**Atrophic variant**

As described under histopathology, most prostate cancers have abundant cytoplasm. An unusual variant of prostate cancer resembles benign atrophy owing to its scant cytoplasm. Although ordinary prostate cancers may develop atrophic cytology as a result of treatment (see carcinoma affected by hormone therapy), atrophic prostate cancers are usually unassociated with such a prior history (467,664). The diagnosis of carcinoma in these cases may be based on several features. First, atrophic prostate cancer may demonstrate a truly infiltrative process with individual small atrophic glands situated between larger benign glands. In contrast, benign atrophy has a lobular configuration. A characteristic finding in some benign cases of atrophy is the presence of a centrally dilated atrophic gland surrounding by clustered smaller glands, which has been termed "post-atrophic hyperplasia (PAH)" (83). Although the glands of benign atrophy may appear infiltrative on needle biopsy, they are not truly infiltrative, as individual benign atrophic glands are not seen infiltrating in between larger benign glands. Whereas some forms of atrophy, are associated with fibrosis, atrophic prostate cancer lack such a desmoplastic stromal response. Atrophic prostate cancer may also be differentiated from benign atrophy by the presence of marked cytologic atypia. Atrophy may show enlarged nuclei and prominent nucleoli, although not the huge eosinophilic nucleoli seen in some atrophic prostate cancers. Finally, the concomitant presence of ordinary less atrophic carcinoma can help in recognizing the malignant nature of the adjacent atrophic cancer glands.

**Pseudohyperplastic variant**

Pseudohyperplastic prostate cancer resembles benign prostate glands in that the neoplastic glands are large with branching and papillary infolding (1146, 1485). The recognition of cancer with this pattern is based on the architectural pattern of numerous closely packed glands as well as nuclear features more typical of carcinoma. One pattern of pseudohyperplastic adenocarcinoma consists of numerous large glands that are almost back-to-back with straight even luminal borders, and abundant cytoplasm. Comparably sized benign glands either have papillary infoldings or are atrophic. The presence of cytologic atypia in some of these glands further distinguishes them from benign glands. It is almost always helpful to verify pseudohyperplastic cancer with the use of immunohistochemistry to verify the absence of basal cells. Pseudohyperplastic cancer, despite its benign appearance, may be associated with typical intermediate grade cancer and can exhibit aggressive behaviour (i.e., extraprostatic extension).

**Foamy gland variant**

Foamy gland cancer is a variant of acinar adenocarcinoma of the prostate that is characterized by having abundant foamy appearing cytoplasm with a very low nuclear to cytoplasmic ratio. Although the cytoplasm has a xanthomatous appearance, it does not contain lipid, but rather empty vacuoles (2637). More typical cytological features of adenocarcinoma such as nuclear enlargement and prominent nucleoli are frequently absent, which makes this lesion difficult to recognize as carcinoma especially on biopsy material. Characteristically, the nuclei in foamy gland carcinoma are small and densely hyperchromatic. Nuclei in foamy gland cancer are round, more so than those of benign prostatic secretory cells. In addition to the unique nature of its cytoplasm, it is recognized as carcinoma by its architectural pattern of crowded and/or infiltrative glands, and frequently present dense pink acellular secretions (1880). In most cases, foamy gland cancer is seen in association with ordinary

Fig. 3.24 Atrophic adenocarcinoma. A Note the microcystic pattern and B the prominent nucleoli.
adenocarcinoma of the prostate. In almost all such cases, despite foamy glands cancer's benign cytology, the ordinary adenocarcinoma component is not low grade. Consequently, foamy gland carcinoma appears best classified as intermediate grade carcinoma.

**Colloid & signet ring variant**

Using criteria developed for mucinous carcinomas of other organs, the diagnosis of mucinous adenocarcinoma of the prostate gland should be made when at least 25% of the tumour resected contains lakes of extracellular mucin. On biopsy material, cancers with abundant extracellular mucin should be diagnosed as carcinoma with mucinous features, rather than colloid carcinoma, as the biopsy material may not be reflective of the entire tumour. Mucinous (colloid) adenocarcinoma of the prostate gland is one of the least common morphologic variants of prostatic carcinoma (710,2207,2274). A cribriform pattern tends to predominate in the mucinous areas. In contrast to bladder adenocarcinomas, mucinous adenocarcinoma of the prostate rarely contain mucin positive signet cells. Some carcinomas of the prostate will have a signet-ring-cell appearance, yet the vacuoles do not contain intracytoplasmic mucin (2206). These vacuolated cells may be present as singly invasive cells, in single glands, and in sheets of cells. Only a few cases of prostate cancer have been reported with mucin positive signet cells (1057,2660). One should exclude other mucinous tumours of non-prostatic origin based on morphology and immunohistochemistry and if necessary using clinical information.

Even more rare are cases of in-situ and infiltrating mucinous adenocarcinoma arising from glandular metaplasia of the prostatic urethra with invasion into the prostate (2636). The histologic growth pattern found in these tumours were identical to mucinous adenocarcinoma of the bladder consisting of lakes of mucin lined by tall columnar epithelium with goblet cells showing varying degrees of nuclear atypia and in some of these cases, mucin-containing signet cells. These tumours have been negative immunohistochemically for PSA and PAP.

---

**Fig. 3.25** A Pseudohyperplastic adenocarcinoma. Branding and papillary type of and growth is typical. B Perineural invasion. C Higher magnification, showing prominent nucleoli.

---

**Fig. 3.26** A Cancer of pseudohyperplastic type. Crowded glands with too little stroma to be a BPH. B Pseudohyperplastic adenocarcinoma with prominent nucleoli (arrow).
Mucinous prostate adenocarcinomas behave aggressively (710, 2207, 2274). In the largest reported series, 7 of 12 patients died of tumour (mean 5 years) and 5 were alive with disease (mean 3 years). Although these tumours are not as hormonally responsive as their non-mucinous counterparts, some respond to androgen withdrawal. Mucinous prostate adenocarcinomas have a propensity to develop bone metastases and increased serum PSA levels with advanced disease.

**Oncocytic variant**
Prostatic adenocarcinoma rarely is composed of large cells with granular eosinophilic cytoplasm. Tumour cells have round to ovoid hyperchromatic nuclei, and are strongly positive for PSA. Numerous mitochondria are seen on ultrastructural examination. A high Gleason grade (1972, 2080), elevated serum PSA (2080) and metastasis of similar morphology (1972) have been reported.

**Lymphoepithelioma-like variant**
This undifferentiated carcinoma is characterized by a syncytial pattern of malignant cells associated with a heavy lymphocytic infiltrate. Malignant cells are...
PSA positive. Associated acinar adenocarcinoma has been noted [34,2145]. In situ hybridization has been negative for Epstein-Barr virus [34]. Clinical significance is uncertain.

**Sarcomatoid variant (carcinosarcoma)**

There is considerable controversy in the literature regarding nomenclature and histogenesis of these tumours. In some series, carcinosarcoma and sarcomatoid carcinoma are considered as separate entities based on the presence of specific mesenchymal elements in the former. However, given their otherwise similar clinico-pathologic features and identically poor prognosis, these two lesions are best considered as one entity. Sarcomatoid carcinoma of the prostate is a rare neoplasm composed of both malignant epithelial and malignant spindle-cell and/or mesenchymal elements [207,588,644,1555,2175,2376]. Sarcomatoid carcinoma may be present in the initial pathologic material (synchronous presentation) or there may be a previous history of adenocarcinoma treated by radiation and/or hormonal therapy [1578]. The gross appearance often resembles sarcomas. Microscopically, sarcomatoid carcinoma is composed of a glandular component showing variable Gleason score [644,2093]. The sarcomatoid component often consists of a non-specific malignant spindle-cell proliferation. Amongst the specific mesenchymal elements are osteosarcoma, chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma or multiple types of heterologous differentiation [644,1578]. Sarcomatoid carcinoma should be distinguished from the rare carcinoma with metaplastic, benign-appearing bone or cartilage in the stroma. By immunohistochemistry, epithelial elements react with antibodies against PSA and/or pan-cytokeratins, whereas spindle-cell elements react with markers of soft tissue tumours and variably express cytokeratins. Serum PSA is within normal limits in most cases. Nodal and distant organ metastases at diagnosis are common [644,1578,2093]. There is less than a 40% five-year survival [644].

**Treatment effects**

**Radiation therapy**

Radiation therapy can be given as either external beam or interstitial seed implants or as a combination of the two. After radiation therapy the prostate gland is usually small and hard. Radiation therapy affects prostate cancer variably with some glands showing marked radiation effect and others showing no evidence of radiation damage. Architecturally, carcinoma showing treatment effect typically loses their glandular pattern, resulting in clustered cells or individual cells. Cytologically, the cytoplasm of the tumour cells is pale, increased in volume and often vacuolated. There is often a greater variation of nuclear size than in non-irradiated prostate cancer and the nuclei may be pyknotic or large with clumped chromatin. Nucleoli are often lost [607,842,1060,1061,1086,1584]. Paradoxically the nuclear atypia in prostate carcinoma showing radiation effect is less than that seen in radiation atypia of benign glands. By immunohistochemistry, tumour cells with treatment effect are usually positive for PAP and PSA. These antibodies along with pan-cytokeratins are very helpful to detect isolated residual tumour cells, which can be overlooked in H&E stained sections. The stroma is often sclerosed, particularly following radioactive seed implantation. In the latter the stromal hyalinization is often sharply delineated. Following radiation therapy, prostatic biopsy should be diagnosed as no evidence of cancer, cancer showing no or minimal radiation effect, or cancer showing significant radiation effect, or a combination of the above. Although there exists various systems to grade radiation effects, these are not recommended for routine clinical practice. Biopsy findings predict prognosis with positive biopsies showing no treatment effect having a worse outcome than negative biopsies, and cancer with treatment effect having an intermediate prognosis [511].

**Hormone therapy**

The histology of prostate cancer may be significantly altered following its treatment with hormonal therapy (2358). One pattern is that neoplastic glands develop pyknotic nuclei and abundant xanthomatous cytoplasm. These cells then desquamate into the lumen of the malignant glands where they resemble histiocytes and lymphocytes, sometimes resulting in empty clefts. In some areas, there may be only scattered cells within the stroma resembling foamy histiocytes with pyknotic nuclei and xanthomatous cytoplasm. A related pattern is the presence of individual tumour cells resembling inflammatory cells. At low power, these areas may be difficult to identify, and often the only clue to areas of hormonally treated carcinoma is a fibrotic background with scattered larger cells.
Immunohistochemistry for PSA or pancytokeratin can aid in the diagnosis of carcinoma in these cases by identifying the individual cells as epithelial cells of prostatic origin. Cancer cells following hormonal therapy demonstrate a lack of high molecular weight cytokeratin staining, identical to untreated prostate cancer. Following a response to combination endocrine therapy, the grade of the tumour appears artefactually higher, when compared to the grade of the pretreated tumour. As with radiation, the response to hormonal therapy may be variable, with areas of the cancer appearing unaffected [117,340,470,1059,1852,2176,2447,2681].

**Gleason grading system**
Numerous grading systems have been designed for histopathological grading of prostate cancer. The main controversies have been whether grading should be based on glandular differentiation alone or a combination of glandular differentiation and nuclear atypia, and also whether prostate cancer should be graded according to its least differentiated or dominant pattern. The Gleason grading system named after Donald F. Gleason is now the predominant grading system, and in 1993, it was recommended by a WHO consensus conference [1840]. The Gleason grading system is based on glandular architecture; nuclear atypia is not evaluated [894,895]. Nuclear atypia as adopted in some grading systems, correlates with prognosis of prostate cancer but there is no convincing evidence that it adds independent prognostic information to that obtained by grading glandular differentiation alone [1801].

The Gleason grading system defines five histological patterns or grades with decreasing differentiation. Normal prostate epithelial cells are arranged around a lumen. In patterns 1 to 3, there is retained epithelial polarity with luminal differentiation in virtually all glands. In pattern 4, there is partial loss of normal polarity and in pattern 5, there is an almost total loss of polarity with only occasional luminal differentiation. Prostate cancer has a pronounced morphological heterogeneity and usually more than one histological pattern is present. The primary and secondary pattern, i.e. the most prevalent and the second most prevalent pattern are added to obtain a Gleason score or sum. It is recommended that the primary and secondary pattern as well as the score be reported, e.g. Gleason score 3+4=7. If the tumour only has one pattern, Gleason score is obtained by doubling that pattern, e.g. Gleason score 3+3=6. Gleason scores 2 and 3 are only exceptionally
Gleason pattern 1

Gleason pattern 1 is composed of a very well circumscribed nodule of separate, closely packed glands, which do not infiltrate into adjacent benign prostatic tissue. The glands are of intermediate size and approximately equal in size and shape. This pattern is usually seen in transition zone cancers. Gleason pattern 1 is exceedingly rare. When present, it is usually only a minor component of the tumour and not included in the Gleason score.

Gleason pattern 2

Gleason pattern 2 is composed of round or oval glands with smooth ends. The glands are more loosely arranged and not quite as uniform in size and shape as those of Gleason pattern 1. There may be minimal invasion by neoplastic glands into the surrounding non-neoplastic prostatic tissue. The glands are of intermediate size and larger than in Gleason pattern 3. The variation in glandular size and separation between glands is less than that seen in pattern 3. Although not evaluated in Gleason grading, the cytoplasm of Gleason pattern 1 and 2 cancers is abundant and pale-staining. Gleason pattern 2 is usually seen in transition zone cancers but may occasionally be found in the peripheral zone.

Gleason pattern 3

Gleason pattern 3 is the most common pattern. The glands are more infiltrative and the distance between them is more variable than in patterns 1 and 2. Malignant glands often infiltrate between adjacent non-neoplastic glands. The glands of pattern 3 vary in size and shape and are often angular. Small glands are typical for pattern 3, but there may also be large, irregular glands. Each gland has an open lumen and is circumscribed by stroma. Cribriform pattern 3 is rare and difficult to distinguish from cribriform high-grade PIN.

Gleason pattern 4

In Gleason pattern 4, the glands appear fused, cribriform or they may be poorly defined. Fused glands are composed of a group of glands that are no longer completely separated by stroma. The edge of a group of fused glands is scalloped and there are occasional thin strands of connective tissue within this group. Cribriform pattern 4 glands are large or they may be irregular with jagged edges. As opposed to fused glands, there are no strands of stroma within a cribriform gland. Most cribriform invasive cancers should be assigned a pattern 4 rather than pattern 3. Poorly defined glands do not have a lumen that is completely encircled by epithelium.
The hypernephromatoid pattern described by Gleason is a rare variant of fused glands with clear or very pale-staining cytoplasm.

Gleason pattern 5
In Gleason pattern 5, there is an almost complete loss of glandular lumina. Only occasional lumina may be seen. The epithelium forms solid sheets, solid strands or single cells invading the stroma. Care must be applied when assigning a Gleason pattern 4 or 5 to limited cancer on needle biopsy to exclude an artefact of tangential sectioning of lower grade cancer. Comedonecrosis may be present.

Grade progression
The frequency and rate of grade progression is unknown. Tumour grade is on average higher in larger tumours [1688]. However, this may be due to more rapid growth of high grade cancers. It has been demonstrated that some tumours are high grade when they are small [707]. Many studies addressing the issue of grade progression have a selection bias, because the patients have undergone a repeat transurethral resection or repeat biopsy due to symptoms of tumour progression [526]. The observed grade progression may be explained by a growth advantage of a tumour clone of higher grade that was present from the beginning but undersampled. In patients followed expectantly there is no evidence of grade progression within 1-2 years [717].

Grading minimal cancer on biopsy. It is recommended that a Gleason score be reported even when a minimal focus of cancer is present. The correlation between biopsy and prostatectomy Gleason score is equivalent or only marginally worse with minimal cancer on biopsy [668,2257,2498]. It is recommended that even in small cancers with one Gleason pattern that the Gleason score be reported. If only the pattern is reported, the clinician may misconstrue this as the Gleason score.

Tertiary Gleason patterns
The original Gleason grading system does not account for patterns occupying less than 5% of the tumour or for tertiary patterns. In radical prostatectomy specimens, the presence of a tertiary high grade component adversely affects prognosis. However, the prognosis is not necessarily equated to the addition of the primary Gleason pattern and the tertiary highest Gleason pattern. For example, the presence of a tertiary Gleason pattern 5 in a Gleason score 4+3=7 tumour worsens the prognosis compared to the same tumour without a tertiary high grade component. However, it is not
associated with an adverse prognosis as a Gleason score 4+5=9 (2005). When this tertiary pattern is pattern 4 or 5, it should be reported in addition to the Gleason score, even when it is less than 5% of the tumour. Although comparable data do not currently exist for needle biopsy material, in the setting of three grades on biopsy where the highest grade is the least common, the highest grade is incorporated as the secondary pattern. An alternative option is in the situation with a tertiary high grade pattern (i.e. 3+4+5 or 4+3+5) is to diagnose the case as Gleason score 8 with patterns 3, 4 and 5 also present. The assumption is that a small focus of high grade cancer on biopsy will correlate with a significant amount of high grade cancer in the prostate such that the case overall should be considered high grade, and that sampling artefact accounts for its limited nature on biopsy.

Reporting Gleason scores in cases with multiple positive biopsies
In cases where different positive cores have divergent Gleason scores, it is controversial whether to assign an averaged (composite) Gleason score or whether the highest Gleason score should be considered as the patient’s grade (1407). In practice, most clinicians take the highest Gleason score when planning treatment options.

Grading of variants of prostate cancer
Several morphological variants of prostate adenocarcinoma have been described (e.g. mucinous and ductal cancer). They are almost always combined with conventional prostate cancer and their effect on prognosis is difficult to estimate. In cases with a minor component of a prostate cancer variant, Gleason grading should be based on the conventional prostate cancer present in the specimen. In the rare case where the variant form represents the major component, it is controversial whether to assign a Gleason grade.

Grading of specimens with artefacts and treatment effect
Crush artefacts. Crush artefacts are common at the margins of prostatectomy specimens and in core biopsies. Crush artefacts cause disruption of the glandular units and consequently may lead to overgrading of prostate cancer. These artefacts are recognized by the presence of noncohesive epithelial cells with fragmented cytoplasm and dark, pyknotic nuclei adjacent to preserved cells. Crushed areas should not be Gleason graded.

Hormonal and radiation treatment. Prostate cancer showing either hormonal or radiation effects can appear artefactu-
ally to be of higher Gleason score. Consequently, Gleason grading of these cancers should not be performed. If there is cancer that does not show treatment effect, a Gleason score can be assigned to these components.

**Correlation of needle biopsy and prostatectomy grade.** Prostate cancer displays a remarkable degree of intratumoural grade heterogeneity. Over 50% of total prostatectomy specimens contain cancer of at least three different Gleason grades [41], and cancer of a single grade is present in only 16% of the specimens [2261]. Of individual tumour foci, 58% have a single grade, but most of these foci are very small [2261]. Several studies have compared biopsy
and prostatectomy Gleason score (375,668,2498). Exact correlation has been observed in 28.2-67.9% of the cases. The biopsies undergraded in 24.5-60.0% and overgraded in 5.2-32.2%. Causes for biopsy grading discrepancies are undersampling of higher or lower grades, tumours borderline between two grade patterns, and misinterpretation of patterns (2498). The concordance between biopsy and prostatectomy Gleason score is within one Gleason score in more than 90% of cases (668).

Reproducibility
Pathologists tend to undergrade (665,2498). The vast majority of tumours graded as Gleason score 2 to 4 on core biopsy are graded as Gleason score 5 to 6 or higher when reviewed by experts in urological pathology (2498). In a recent study of interobserver reproducibility amongst general pathologists, the overall agreement for Gleason score groups 2-4, 5-6, 7, and 8-10 was just into the moderate range (67). Undergrading is decreased with teaching efforts and a substantial interobserver reproducibility can be obtained (665,1400).

Prognosis
Multiple studies have confirmed that Gleason score is a very powerful prognostic factor on all prostatic samples. This includes the prediction of the natural history of prostate cancer (54,667) and the assessment of the risk of recurrence after total prostatectomy (713,1144) or radiotherapy (937). Several schedules for grouping of Gleason scores in prognostic categories have been proposed. Gleason scores 2 to 4 behave similarly and may be grouped. Likewise, Gleason scores 8 to 10 are usually grouped together, although they could be stratified with regard to disease progression in a large prostatectomy study (1446). There is evidence that Gleason score 7 is a distinct entity with prognosis intermediate between that of Gleason scores 5-6 and 8 to 10, respectively (667,2590). Although the presence and amount of high grade cancer (patterns 4 to 5) correlates with tumour prognosis, reporting the percentage pattern 4/5 is not routine clinical practice (666,2479). Gleason score 7 cancers with a primary pattern 4 have worse prognosis than those with a primary pattern 3 (406,1447,2282).

Genetics
In developed countries, prostate cancer is the most commonly diagnosed non-skin malignancy in males. It is estimated that 1 in 9 males will be diagnosed with prostate cancer during their lifetime. Multiple factors contribute to the high incidence and prevalence of prostate cancer. Risk factors include age, family history, and race. Environmental exposures are clearly involved as well. Although the exact exposures that increase prostate cancer risk are unclear, diet (especially those high in animal fat such as red meat, as well as those with low levels of antioxidants such as selenium and vitamin E), job/industrial chemicals, sexually transmitted infections, and chronic prostatitis have been implicated to varying degrees. The marked increase in incidence in prostate cancer that occurred in the mid 1980s, which subsequently leveled off in the mid to late 1990s, indicates that wide spread awareness and serum prostate specific antigen screening can produce a transient marked increase in prostate cancer incidence.

Hereditary prostate cancer
Currently the evidence for a strong genetic component is compelling. Observations made in the 1950s by Morganti and colleagues suggested a strong familial predisposition for prostate cancer (1784). Strengthening the genetic evidence is a high frequency for prostate cancer in monozygotic as compared to dizygotic twins in a study of twins from Sweden, Denmark, and Finland (1496). Work over the past decade using genome wide scans in prostate cancer families has identified high risk alleles, displaying either an autosomal dominant or X-linked mode of inheritance for a hereditary prostate cancer gene, from at least 7 candidate genetic loci. Of these loci, three candidate genes have been identified HPC2/ELAC2 on 17p (2584), RNASEL on 1q25 (377), and MSR1 on 8p22-23 (2857). These 3 genes do not account for the majority of hereditary prostate cancer cases. In addition, more than 10 other loci have been implicated by at least some groups. The discovery of highly penetrant prostate cancer genes has been particularly difficult for at least 2 main reasons. First, due to the advanced age of onset (median 60 years), identification of more than two generations to perform molecular studies on is difficult. Second, given the high frequency of prostate cancer, it is likely that cases considered to be hereditary during segregation studies actually repre-
sent phenocopies; currently it is not possible to distinguish sporadic (phenocopies) from hereditary cases in families with high rates of prostate cancer. In addition, hereditary prostate cancer does not occur in any of the known cancer syndromes and does not have any clinical (other than a somewhat early age of onset at times) or pathologic characteristics to allow researchers to distinguish it from sporadic cases (302). Perhaps even more important in terms of inherited susceptibility for prostate cancer are common polymorphisms in a number of low penetrance alleles of other genes - the so-called genetic modifier alleles. The list of these variants is long, but the major pathways currently under examination include those involved in androgen action, DNA repair, carcinogen metabolism, and inflammation pathways (2246,2858). It is widely assumed that the specific combinations of these variants, in the proper environmental setting, can profoundly affect the risk of developing prostate cancer.

**Molecular alterations in sporadic prostate cancer**

While mutations in any of the classic oncogenes and tumour suppressor genes are not found in high frequency in primary prostate cancers, a large number of studies have identified non-random somatic genome alterations. Using comparative genomic hybridization (CGH) to screen the DNA of prostate cancer, the most common chromosomal alterations in prostate cancer are losses at 1p, 6q, 8p, 10q, 13q, 16q, and 18q and gains at 1q, 2p, 7, 8q, 18q, and Xq (436,1246,1924,2737). Numerous genes have now been implicated in prostate cancer progression. Several genes have been implicated in the earliest development of prostate cancer. The pi-class of Glutathione S-transferase (GST), which plays a caretaker role by normally preventing stress related damage, demonstrates hypermethylation in high percentage of prostate cancers, thus preventing expression of this protective gene (1465, 1505,1732). NKX3.1, a homeobox gene located at 8p21 has also been implicated in prostate cancer (304,1047,1319, 2741). Although no mutations have been identified in this gene (2741), recent work suggests that decreased expression is associated with prostate cancer progression (304). PTEN encodes a phosphatase, active against both proteins and lipids, is also commonly altered in prostate cancer progression (1491, 2489). PTEN is believed to regulate the phosphatidylinositol 3'-kinase/protein kinase B (PI3/Akt) signaling pathway and therefore mutations or alterations lead to tumour progression (2850). Mutations are less common than initially thought in prostate cancer, however, tumour suppressor activity may occur from the loss of one allele, leading to decreased expres-
sion of PTEN (i.e. haploinsufficiency) (1418). A number of other genes have also been associated with prostate cancer including p27 (496, 975, 2867) and E-cadherin (1989, 2674). p53 mutations are late events in prostate cancer and tend to occur in advanced and metastatic prostate tumours (1052).

Another very common somatic genomic alteration in prostate and other cancers is telomere shortening (1697, 2461). This molecular alteration is gaining heightened awareness as it has become clear that critically short telomere may lead to genetic instability and increased epithelial cancers in p53+/- mice (121, 250).

Recent advances in genomic and proteomic technologies suggest that molecular signatures of disease can be used for diagnosis (33, 907), to predict survival (2238, 2551), and to define novel molecular subtypes of disease (2056). Several studies have used cDNA microarrays to characterize the gene expression profiles of prostate cancer in comparison with benign prostate disease and normal prostate tissue (604, 1574, 1591, 2426, 2807). Several interesting candidates include AMACR, hepsin, KLF6 and EZH2. Alpha-methylacyl-CoA racemase (AMACR), an enzyme that plays an important role in bile acid biosynthesis and β-oxidation of branched-chain fatty acids (748, 1366) was determined to be upregulated in prostate cancer (604, 1220, 1575, 2259). Hepsin is overexpressed in localized and metastatic prostate cancer when compared to benign prostate or benign prostatic hyperplasia (604, 1574, 1591, 2481). By immunohistochemistry, hepsin was found to be highly expressed in prostatic intraepithelial neoplasia (PIN), suggesting that dysregulation of hepsin is an early event in the development of prostate cancer (604). Kruppel-like factor 6 (KLF6) is a zinc finger is mutated in a subset of human prostate cancer (1870). EZH2, a member of the polycomb gene family, is a transcriptional repressor known to be active early in embryogenesis (796, 1601), showing decreased expression as cells differentiate. It has been demonstrated that EZH2 is highly over expressed in metastatic hormone refractory prostate cancer as determined by cDNA and TMA analysis (2711). EZH2 was also seen to be overexpressed in localized prostate cancers that have a higher risk of developing biochemical recurrence following radical prostatectomy.

The androgen receptor (AR) plays critical role in prostate development (2877). It has been known for many years that withdrawal of androgens leads to a rapid decline in prostate cancer growth with significant clinical response. This response is short-lived and tumour cells reemerge, which are independent of androgen stimulation (androgen independent). Numerous mutations have been identified in the androgen receptor gene (reviewed by Gelmann (847)). It has been hypothesized that through mutation, prostate cancers can grow with significantly lower circulating levels of androgens. In addition to common mutations, the amino-terminal domain encoded by exon one demonstrates a high percentage of polymorphic CAG repeats (2638). Shorter CAG repeat lengths have been associated with a greater risk of developing prostate cancer and prostate cancer progression (884, 2337). Shorter CAG repeat lengths have been identified in African American men (208).

**Prognosis and predictive factors**

The College of American Pathologists (CAP) have classified prognostic factors into three categories:

- **Category I – Factors proven to be of prognostic importance and useful in clinical patient management.**

### Table 3.01

<table>
<thead>
<tr>
<th>Susceptibility loci</th>
<th>Locus</th>
<th>Mode</th>
<th>Putative gene</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC1</td>
<td>1q24-25</td>
<td>AD</td>
<td>RNASEL</td>
<td>(377, 2451)</td>
</tr>
<tr>
<td>PCAP</td>
<td>1q42.2-43</td>
<td>AD</td>
<td>?</td>
<td>(230)</td>
</tr>
<tr>
<td>CAPB</td>
<td>1p36</td>
<td>AD</td>
<td>?</td>
<td>(871)</td>
</tr>
<tr>
<td>HPCX</td>
<td>Xq27-28</td>
<td>X-linked/AR</td>
<td>?</td>
<td>(2855)</td>
</tr>
<tr>
<td>HPC20</td>
<td>20q13</td>
<td>AD</td>
<td>?</td>
<td>(229)</td>
</tr>
<tr>
<td>HPC2</td>
<td>17p</td>
<td>AD</td>
<td>HPC2/ELAC2</td>
<td>(2584)</td>
</tr>
<tr>
<td></td>
<td>Bp22-23</td>
<td>AD</td>
<td>MSR1</td>
<td>(2857)</td>
</tr>
</tbody>
</table>

Key: Mode = suggested mode of inheritance; AD = autosomal dominant; AR = autosomal recessive.
Category II – Factors that have been extensively studied biologically and clinically, but whose importance remains to be validated in statistically robust studies.

Category III – All other factors not sufficiently studied to demonstrate their prognostic value.

Factors included in category I, were pre-operative PSA, histologic grade (Gleason score), TNM stage grouping, and surgical margin status. Category II included tumour volume, histologic type and DNA ploidy. Factors in Category III included such things as perineural invasion, neuroendocrine differentiation,

**Table 3.02**

Selected genes associated with prostate cancer progression.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Gene Name(s)</th>
<th>Locus</th>
<th>Functional Role</th>
<th>Molecular Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>GST-pi</td>
<td>Glutathione S-transferase pi</td>
<td>11q13</td>
<td>Caretaker gene</td>
<td>Hypermethylation</td>
</tr>
<tr>
<td>NXX3.1</td>
<td>NK3 transcription factor homolog A</td>
<td>8p21</td>
<td>Homeobox gene</td>
<td>No mutations</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog (mutated in multiple advanced cancers 1)</td>
<td>10q23.3</td>
<td>Tumour supressor gene</td>
<td>Mutations and haplotype insufficiency</td>
</tr>
<tr>
<td>AMACR</td>
<td>Alpha-methylacyl-CoA racemase</td>
<td>5p13.2-q11.1</td>
<td>B-oxidation of branched-chain fatty acids</td>
<td>Overexpressed in PIN/Pca</td>
</tr>
<tr>
<td>Hepsin</td>
<td>Hepsin</td>
<td>19q11-q13.2</td>
<td>Transmembrane protease, serine 1</td>
<td>Overexpressed in PIN/Pca</td>
</tr>
<tr>
<td>KLF-6</td>
<td>Kruppel-like factor 6/COPeB</td>
<td>10p15</td>
<td>Zinc finger transcription factor</td>
<td>Mutations and haplotype insufficiency</td>
</tr>
<tr>
<td>EZH2</td>
<td>Enhancer of zeste homolog 2</td>
<td>7q35</td>
<td>Transcriptional memory</td>
<td>Overexpressed in aggressive Pca</td>
</tr>
<tr>
<td>p27</td>
<td>Cyclin-dependent kinase inhibitor 1B (p27, Kip1)</td>
<td>12p13</td>
<td>Cyclin dependent kinases 2 and 4 inhibitor</td>
<td>Down regulated with Pca progression</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>E-cadherin</td>
<td>16q22.1</td>
<td>Cell adhesion molecule</td>
<td>Down regulated with Pca progression</td>
</tr>
</tbody>
</table>

Key: Pca=prostate cancer; PIN=prostatic intraepithelial neoplasia
microvessel density, nuclear features other than ploidy, proliferation markers and a variety of molecular markers such as oncogenes and tumour suppressor genes [290]. This classification was endorsed by a subsequent World Health Organization (WHO) meeting that focused mainly on biopsy-derived factors.

**Serum PSA**
PSA is the key factor in the screening for and detection of prostate cancer [2448], its serum level at the time of diagnosis is considered a prognostic marker that stratifies patients into differing diagnostic categories (1284,2023). Recent reports, however, indicate that the prognostic value is driven by patients with high PSA levels, which is significantly associated with increasing tumour volume and a poorer prognosis [2478]. In recent years, however, most newly diagnosed patients have only modestly elevated PSA (between 2 and 9 ng/ml), a range in which BPH and other benign conditions could be the cause of the PSA elevation. For patients within this category, it was reported that PSA has no meaningful relationship to cancer volume and grade in the radical prostatectomy specimen, and a limited relationship with PSA cure rates [2478]. Following treatment, serum PSA is the major mean of monitoring patients for tumour recurrence.

**Stages T1a and T1b**
Although the risk of progression at 4 years with stage T1a cancer is low (2%), between 16% and 25% of men with untreated stage T1a prostate cancer and longer (8-10 years) follow-up have had clinically evident progression [651]. Stage T1b tumours are more heterogeneous in grade, location, and volume than are stage T2 carcinomas. Stage T1b cancers tend to be lower grade and located within the transition zone as compared with palpable cancers. The relation between tumour volume and pathologic stage also differs, in that centrally located transition zone carcinomas may grow to a large volume before reaching the edge of the gland and extending out of the prostate, whereas stage T2 tumours that begin peripherally show extraprostatic extension at relatively lower volumes [461,940,1685]. This poor correlation between volume and stage is also attributable to the lower grade.
many stage T1b cancers.

**Stage T2**

Most of the pathological prognostic information obtained relating to clinical stage T2 disease comes from data obtained from analysis of radical prostatectomy specimens.

**Pathologic examination of the radical prostatectomy specimen**

The key objectives of evaluating the RP specimens are to establish tumour pathologic stage and Gleason score. It is important to paint the entire external surface of the prostate with indelible ink prior to sectioning. In most centers, the apical and bladder neck margins are removed and submitted either as shave margins *en face* (with any tumour in this section considered a positive surgical margin (+SM)), or preferably, these margins (especially the apical) are removed as specimens of varying width, sectioned parallel to the urethra, and submitted to examine the margins in the perpendicular plane to the ink. In this method, any tumour on ink is considered to be a +SM.

The extent of sampling the radical prostatectomy specimen varies, only 12% of pathologists responding to a recent survey indicated that they processed the entire prostate [705,2283,2645]. It was reported that a mean of 26 tissue blocks was required to submit the entire prostate {712,1944}. SVI has often been shown in numerous studies to be a +SM.

**Histologic grade (Gleason)**

Gleason score on the radical prostatectomy specimen is one of the most powerful predictors of progression following surgery. Gleason score on the needle biopsy also strongly correlates with prognosis following radiation therapy.

**Extraprostatic extension (EPE)**

This is defined as invasion of prostate cancer into adjacent periprostatic tissues. The prostate gland has no true capsule although posterolaterally, there is a layer which is more fibrous than muscular that serves as a reasonable area to denote the boundary of the prostate {143}. At the apex and everywhere anteriorly in the gland (the latter being the fibromuscular stroma), there is no clear demarcation between the prostate and the surrounding structures. These attributes make determining EPE for tumours of primarily apical or anterior distribution difficult to establish.

EPE is diagnosed based on tumour extending beyond the outer condensed smooth muscle of the prostate. When tumour extends beyond the prostate it often elicits a desmoplastic stromal reaction, such that one will not always see tumour with EPE situated in extra-prostatic adipose tissue. It has been reported that determining the extent of EPE as "focal" (only a few glands outside the prostate) and "established or non focal" (anything more than focal) is of prognostic significance [713,714]. Focal EPE is often a difficult diagnosis Modifications to this approach with emphasis on the "level" of prostate cancer distribution relevant to benign prostatic acini and within the fibrous "capsule" where it exists, has been suggested and claimed to have further value in classifying patients into prognostic categories following radical prostatectomy [2812]. More detailed analysis has not been uniformly endorsed [705].

**Seminal vesicle invasion (SVI)**

Seminal vesicle invasion is defined as cancer invading into the muscular coat of the seminal vesicle [712,1944]. SVI has been shown in numerous studies to be a significant prognostic indicator [393,536,579,2589]. Three mechanisms by which prostate cancer invades the seminal vesicles were described by Ohori et al. as: (I) by extension up the ejaculatory duct complex; (II) by spread across the base of the prostate without other evidence of EPE (Ila) or by invading the seminal vesicles from the periprostatic and periseminal vesicle adipose tissue (Ib); and (III) as an isolated tumour deposit without continuity with the primary prostate cancer tumour focus. While in almost all cases, seminal vesicle invasion occurs in glands with EPE, the latter cannot be documented in a minority of these cases. Many of these patients had only minimal involvement of the seminal vesicles, or involve only the portion of the seminal vesicles that is at least partially intraprostatic. Patients in this category were reported to have a favourable prognosis, similar to otherwise similar patients without SVI and it is controversial whether SVI without EPE should be diagnosed [712].

**Lymph nodes metastases (+LN)**

Pelvic lymph node metastases, when present, are associated with an almost uniformly poor prognosis in most studies. Fortunately, however, the frequency of +LN has decreased considerably over time to about 1-2% today [393,705]). Most of this decrease has resulted primarily from the widespread PSA testing and to a lesser extent from better ways to select patients for surgery preoperatively. As a consequence of this decline in patients with +LN, some have proposed that pelvic lymph node dissection is no longer necessary in appropriately selected patients [198,256]. The detection of +LN can be enhanced with special techniques such as immunohistochemistry or reverse transcriptase-polymerase chain reaction (RT-PCR) for PSA or hK2-L.
perineural invasion (PNI) by prostate cancer is seen in radical prostatectomy specimens in 75-84% of cases. Due to the near ubiquitous presence of PNI in radical prostatectomy specimens and studies have not shown radical prostatectomy PNI to be an independent prognostic parameter, this finding is not routinely reported. One study has noted that the largest diameter of PNI in the radical prostatectomy was independently related to an increased likelihood of biochemical failure after radical prostatectomy; verification of this result is needed before it can be adopted in clinical practice (1641). Numerous studies have also evaluated the significance of PNI on cancer in needle biopsy specimens. Whereas almost all reports have noted an increased risk of EPE in the corresponding radical prostatectomy specimen, there are conflicting data as to whether PNI provides independent prognostication beyond that of needle biopsy grade and serum PSA levels (180, 663,715). It has also been demonstrated that the presence of PNI on the needle biopsy is associated with a significantly higher incidence of disease progression following radiotherapy and following radical prostatectomy (270). As PNI is of prognostic significance and easy to assess histologically, its reporting on needle biopsy is recommended.

Tumour volume
Tumour volume can be measured most accurately with computerized planimetric methods, although a far simpler “grid” method has been described (1147). Total tumour volume is an important predictor of prognosis and is correlated with other pathologic features. However, in several large series it was not an independent predictor of PSA progression when controlling for the other features of pathologic stage, grade and margins. These results are different from earlier series, in which many of the patients were treated in the pre-PSA era and had large tumour volumes, which resulted in a strong correlation between tumour volume and prognosis.

Multiple techniques of quantifying the amount of cancer found on needle biopsy have been developed and studied, including measurement of the: 1) number of positive cores; 2) total millimeters of cancer in needle biopsy specimens; 3) percentage of each core occupied by cancer; 4) total percent of cancer in the entire specimen.
and 5) fraction of positive cores. There is no clear consensus as to superiority of one technique over the other. Numerous studies show associations between the number of positive cores and various prognostic variables. The other widely used method of quantifying the amount of cancer on needle biopsy is measurement of the percentage of each biopsy core and/or of the total specimen involved by cancer. Extensive cancer on needle biopsy in general predicts for adverse prognosis. However, limited carcinoma on needle biopsy is not as predictive of a favourable prognosis due to sampling limitations. A feasible and rationale approach would be to have pathologists report the number of cores containing cancer, as well as one other system quantifying tumour extent (e.g. percentage, length).

**Lymphovascular invasion in radical prostatectomy** (LVI)

The incidence rates of LVI have ranged widely from 14-53%. The differences in incidence rates amongst studies are most likely the result of the use of different criteria for the recognition of LVI. While most investigators do not recommend the use of immunohistochemistry for verification of an endothelial-lined space, retraction space artefact around tumour may cause difficulty in interpretation of LVI. Although several studies have found that LVI is important in univariate analysis, only two have reported independent significance in multivariate analysis (156, 1081, 2287).

**Biomarkers and nuclear morphometry** (reviewed in [705, 1773])

While the preponderance of studies suggest that DNA ploidy might be useful in clinical practice, a smaller number of studies analyzing large groups of patients have not found ploidy to be independently prognostically useful. A majority of studies have also demonstrated that overexpression of certain other markers (p53, BCL-2, p21WAF1) and underexpression of others (Rb) is associated with more aggressive prostate cancer behaviour, but further corroboration is necessary before these tests are used.

---

**Table 3.03**

| Location of positive surgical margins in radical prostatectomy specimens. |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                  | Number of +SM   | Apical           | Anterior         | Lateral          | Posterior        | Postero lateral  | Bladder neck     | Other            |
| Voges et al.     | 8               | 37               | 37               | -                | -                | -                | 25               | -               |
| (2744, 2745)     |                 |                  |                  |                  |                  |                  |                  |                 |
| Rosen et al.     | 27              | 33               | 18               | 4                | 11               | 33               | -                | -               |
| (2231)           |                 |                  |                  |                  |                  |                  |                  |                 |
| Epstein et al.   | 190             | 22               | -                | -                | 17               | 14               | 6                | -               |
| (713)            |                 |                  |                  |                  |                  |                  |                  |                 |
| Stamey et al.    | 32              | 69               | -                | -                | -                | 6                | -                | -               |
| (2480)           |                 |                  |                  |                  |                  |                  |                  |                 |
| Van Poppel et al.| 50              | 34               | -                | -                | -                | 54               | -                | 12              |
| (2699)           |                 |                  |                  |                  |                  |                  |                  |                 |
| Watson et al.    | 90              | 38               | 11               | -                | 26               | 17               | 9                | -               |
| (2790)           |                 |                  |                  |                  |                  |                  |                  |                 |
| Gomez et al.     | 22              | 46               | -                | -                | 14               | -                | 14               | 27              |
| (909)            |                 |                  |                  |                  |                  |                  |                  |                 |

**Fig. 3.58** Patterns of seminal vesicle invasion (SVI).

**pg 158-192  24.7.2006  16:22  Page 191**
clinically. There are conflicting studies as to the prognostic significance of quantifying microvessel density counts, Ki-67 (proliferation), and chromogranin (neuroendocrine differentiation), p27k^ip1, Her-2/neu, E-cadherin, and CD44. Numerous studies have correlated various nuclear measurements with progression following radical prostatectomy. These techniques have not become clinically accepted in the evaluation of prostate cancer since the majority of studies have come from only a few institutions, some of these nuclear morphometry measurements are patented and under control of private companies, and these techniques are time consuming to perform.

Preoperative and postoperative nomograms

Although there are nomograms to predict for stage prior to therapy (1284,2023), this and other prognostic factors are best assessed, following pathologic examination of the radical prostatectomy specimen, many of which have been incorporated in a new postoperative nomogram (1284). The prognostic factors have appreciable limitations when they are used as stand-alone. However, validation of the several nomograms proposed in the recent times is sometimes lacking whereas comparison for superiority amongst the proposed nomograms has not always been tested. A limitation of these nomograms is that they do not provide predictive information for the individual patient.

Stages T3 and T4

In general, patients with clinical stage T3 prostate cancer are not candidates for radical prostatectomy and are usually treated with radiotherapy. Between 50% and 60% of clinical stage T3 prostate cancers have lymph node metastases at the time of diagnosis. More than 50% of patients with clinical stage T3 disease develop metastases in 5 years, and 75% of these patients die of prostate carcinoma within 10 years. Distant metastases appear within 5 years in more than 85% of patients with lymph node metastases who receive no further treatment. In patients with distant metastases, the mortality is approximately 15% at 3 years, 80% at 5 years, and 90% at 10 years. Of the patients who relapse after hormone therapy, most die within several years.

Fig. 3.59 Preoperative PSA levels (ng/ml) and prostatic cancer recurrence.
Prostatic intraepithelial neoplasia

Definition
Prostatic intraepithelial neoplasia (PIN) is best characterized as a neoplastic transformation of the lining epithelium of prostatic ducts and acini. By definition, this process is confined within the epithelium therefore, intraepithelial.

ICD-O code 8148/2

Epidemiology
There is limited literature characterizing the epidemiology of high grade prostatic intraepithelial neoplasia (HGPIN) as the lesion has been well defined relatively recently with respect to diagnostic criteria and terminology. Based on few recent autopsy studies that included HGPIN in their analysis, it appears that similar to prostate cancer, HGPIN can be detected microscopically in young males, its prevalence increases with age and HGPIN shows strong association with cancer in terms of coincidence in the same gland and in its spatial distribution (1683,1993). In a contemporary autopsy series of 652 prostates with high proportion of young men, Sakr et al. identified HGPIN in 7, 26, 46, 72, 75 and 91% of African Americans between the third and eighth decades compared to: 8, 23, 29, 49, 53 and 67% for Caucasian men (2278). In addition to higher the prevalence, this study also suggested a more extensive HGPIN in younger African American men compared to Caucasians (2279). In an autopsy series of 180 African and White-Brazilian men older than 40, more extensive and diffuse HGPIN in African Brazilians tended to appear at a younger age compared to Whites (244).

Prevalence of HGPIN in surgical prostate samples

Biopsy specimens
There are significant variations in the reported prevalence of HGPIN in needle biopsies of the prostate. This is likely to result from several reasons:
– Population studied (ethnicity, extent of screening/early detection activities).
– Observers variability as there is an inherent degree of subjectivity in applying diagnostic criteria and in setting the threshold for establishing diagnosis.
– The technical quality of the material evaluated (fixation, section thickness and staining quality).
– The extent of sampling (i.e., number of core biopsies obtained).
The majority of large recent series, have reported a prevalence of 4-6% (296, 1133,1435,1926,2830). The European and the Japanese literature indicate a slightly lower prevalence of HGPIN on needle biopsies (58,572,594,1913,2046, 2434).

TURP specimens
The incidence of HGPIN in transurethral resection of the prostate is relatively uncommon with two studies reporting a rate of 2.3% and 2.8%, respectively (845,1996).

HGPIN in radical prostatectomy/ cystoprostatectomy specimens
The prevalence of HGPIN in radical prostatectomy specimens is remarkably high reflecting the strong association between the lesion and prostate cancer. Investigators have found HGPIN in 85-100% of radical prostatectomy specimens (568,2122,2125,2824). In a series of 100 cystoprostatectomy specimens, Troncoso et al. found 49% and 61% of the prostates to harbour HGPIN and carcinoma, respectively (2644). In 48 men who underwent cystoprostatectomy for reasons other than prostate cancer, Wiley et al. (2046) found 83% and 46% of the prostates to contain HGPIN and incidental carcinoma, respectively. More extensive HGPIN predicted significantly for the presence of prostate cancer in this study (2824).

Morphological relationship of HGPIN to prostate carcinoma
The associations of HGPIN and prostate cancer are several (1776):
– The incidence and extent of both lesions increase with patient age (2280).
– There is an increased frequency, severity and extent of HGPIN in prostate with cancer (1683,1993,2122,2279,2644).
– Both HGPIN and cancer are multifocal with a predominant peripheral zone distribution (2122).
– Histological transition from HGPIN to cancer has been described (1687).
– High-grade PIN shares molecular
there is limited data addressing the relationship between the presence and extent of HGPIN in the prostate and the pathologic stage of prostate cancer. It has been reported that the total volume of HGPIN increases with increasing pathologic stage with a significant correlation between volume of HGPIN and the number of lymph node metastases [2122].

**Molecular genetic associations of HGPIN and prostate cancer**

There is extensive literature indicating that HGPIN demonstrates a range of genetic abnormalities and biomarker expression profile that is more closely related to prostate cancer than to benign prostatic epithelium. These studies investigated aspects ranging from cell proliferation and death, histomorphometric analysis and a host of genetic alterations, inactivation of tumour suppressor genes or overexpression of oncogenes [721,1777,2007,2121,2281].

**Clinical features**

HGPIN does not result in any abnormalities on digital rectal examination. HGPIN may appear indistinguishable from cancer, manifesting as a hypoechoic lesion on transrectal ultrasound examination [1012]. HGPIN by itself does not appear to elevate serum PSA levels [57,2144,2227].

**Histopathology**

Initially, PIN was divided into three grades based on architectural and cytologic features recognizing that the changes cover a continuum. Subsequently, it has been recommended that the classification should be simplified into a two-tier system: low (previous grade I) and high (previous grades II and III) grade lesions [638]. The distinction between low and high grade PIN is based on the degree of architectural complexity and more importantly, on the extent of cytologic abnormalities. In low grade PIN, there is proliferation and "piling up" of secretory cells of the lining epithelium with irregular spacing. Some nuclei have small, usually inconspicuous nucleoli while a few may contain more prominent nucleoli. The basal cell layer

---

**Fig. 3.61 A** Flat and tufting pattern of growth of high grade PIN. **B** High grade PIN. Expanded duct with micropapillary proliferation of enlarged secretory epithelial cells with high nuclear cytoplasmic ratio and enlarged nucleoli.

**Fig. 3.62 A** Low grade PIN. **B** Low grade PIN. Higher magnification.
normally rimming ducts and acini is intact in low grade PIN. It is difficult to reproducibly distinguish low grade PIN from normal and hyperplastic epithelium (709).

High grade PIN is characterized by a more uniform morphologic alteration. Cytologically, the acini and ducts are lined by malignant cells with a variety of architectural complexity and patterns. The individual cells are almost uniformly enlarged with increased nuclear/ cytoplasmic ratio, therefore showing less variation in nuclear size than that seen in low grade PIN. Many cells of HGPIN contain prominent nucleoli and most show coarse clumping of the chromatin that is often present along the nuclear membrane. HGPIN can be readily appreciated at low power microscopic examination by virtue of the darker ‘blue’ staining of the lining that reflects the expanded nuclear chromatin area (294).

Architectural patterns of HGPIN
Four patterns of HGPIN have been described, which are flat, tufting, micro papillary, and cribriform: nuclear atypia without significant architectural changes (flat pattern); nuclei become more piled up, resulting in undulating mounds of cells (tufting pattern); columns of atypical epithelium that typically lack fibrovascular cores (micro papillary pattern); more complex architectural patterns appear such as Roman bridge and cribriform formation (cribriform pattern). The distinction between cribriform high grade PIN and ductal carcinoma in-situ is controversial (see duct carcinoma in-situ) (288). In high grade PIN, nuclei towards the centre of the gland tend to have blander cytology, as compared to peripherally located nuclei. The grade of PIN is assigned based on assessment of the nuclei located up against the basement membrane.

Histologic variants
Signet-ring variant. High grade prostatic intraepithelial neoplasia (PIN) with signet-ring cells is exceedingly rare with only three reported cases (2181). In all cases signet-ring cell PIN was admixed with adjacent, invasive signet-ring carcinoma. Histologically, cytoplasmic vacuoles displace and indent PIN cell nuclei. The vacuoles are mucin-negative by histochemical staining (mucicarmine, Alcian blue, PAS).
Mucinous variant. Mucinous high grade PIN exhibits solid intraluminal masses of blue tinged mucin that fill and distend the PIN glands, resulting in a flat pattern of growth. This is a rare pattern, with five reported cases. It is associated with adjacent, invasive, typical acinar adenocarcinoma (of Gleason score 5-7), but not mucinous adenocarcinoma.

Foamy variant. Two cases of foamy gland high-grade PIN have been published. Microscopically, foamy PIN glands are large, with papillary infoldings lined by cells with bland nuclei and xanthomatosus cytoplasm. In one case there was extensive associated Gleason grade 3+3=6 acinar adenocarcinoma, but no associated invasive foamy gland adenocarcinoma.

Inverted variant. The inverted, or honeycomb, variant is typified by polarization of enlarged secretory cell nuclei toward the glandular lumen of high-grade PIN glands with tufted or micropapillary architectural patterns. The frequency was estimated to be less than 1% of all PIN cases. In six of 15 reported needle biopsy cases, there was associated usual, small acinar Gleason score 6-7 adenocarcinoma.

Small cell neuroendocrine variant. Extremely rare examples with small cell neuroendocrine cells exist. Small neoplastic cells, with rosette-like formations, are observed in the centre of glands, which display peripheral, glandular-type PIN cells. In one case there was admixed, invasive mixed small cell adenocarcinoma. The small neoplastic cells are chromogranin and synaptophysin-positive, and harbour dense-core, membrane-bound, neurosecretory granules at the ultrastructural level.

Intraductal carcinoma is controversial as it has overlapping features with cribriform high grade PIN and can not be separated from intraductal spread of adenocarcinoma of the prostate. All three entities consist of neoplastic cells spanning prostatic glands, which are surrounded by basal cells. The most salient morphologic feature distin-
guishing “intraductal carcinoma” from high-grade cribriform PIN is the presence of multiple cribriform glands with prominent cytological atypia containing comedo necrosis. In practice, this distinction rarely poses a problem in the evaluation of a prostatectomy specimen as invasive cancer is always concurrently present. In prostate needle biopsies and TURP, this process may rarely be present without small glands of adenocarcinoma, where some experts consider it prudent to refer to the lesion as high grade cribriform PIN \({2256,2823}\) with a strong recommendation for repeat biopsy. Other experts will use the term “intraductal carcinoma” on biopsy with the recognition that definitive therapy may be undertaken, recognizing that infiltrating cancer will be identified upon further prostatic sampling \({719}\).

Somatic genetics

**Germ-line heritable alterations**
There is no evidence that the frequency or extent of high grade PIN is increased in patients with familial prostate cancer \({181}\).

**Somatic genomic alterations**
Genetic changes tend to be very similar to the chromosomal aberrations identified in prostatic adenocarcinoma \({204,1214,1588,2120}\). Frequent changes in PIN include both increases and decreases in chromosome 8 centromeric region, often with simultaneous loss of regions from 8p and gains of 8q. Other fairly common numeric changes include gains of chromosomes 10, 7, 12, and Y. Other regions of loss in both prostate cancer and PIN include chromosomes 10q, 16q and 18q. The overall incidence of any aneuploidy in high grade PIN using FISH is approximately 50-70%, which is usually found to be similar to, or somewhat lower than, invasive carcinoma, and usually lower than metastatic disease. While carcinoma foci generally contain more anomalies than paired PIN foci, at times there are foci of PIN with more anomalies than nearby carcinoma \({2120}\). Loss of regions of chromosome 8p, have been reported to be very common in high grade PIN \({694}\), as is known for prostate cancer \({276}\). While many of the acquired chromosome aberrations in PIN do not appear random, high grade PIN shares with invasive cancer some degree of chromosomal instability, as evidenced by telomere shortening \({204,1696,1698}\). Telomerase activity has been reported to occur in 16% of high grade PIN lesions \({1344}\) and 85% of invasive prostatic carcinomas \({2461}\) and may serve as an important biomarker in prostate carcinogenesis. Telomerase activity has been reported to occur in 16% of high grade PIN lesions \({1344}\) and 85% of invasive prostatic carcinomas \({2461}\) and may serve as an important biomarker in prostate carcinogenesis. Telomerase activity has been reported to occur in 16% of high grade PIN lesions \({1344}\) and 85% of invasive prostatic carcinomas \({2461}\) and may serve as an important biomarker in prostate carcinogenesis.

**Specific genes involved in the pathogenesis of PIN**
There is decreased protein expression in HGPIN of NKX3.1 and p27, paralleling that seen in carcinoma \({17,237,304,569,752,1520,2333}\). TP53 mutations and protein overexpression may be identified in at least some PIN lesions \({48,2873}\). C-MYC may be over-represented at times and PSCA is overexpressed in some lesions at the mRNA level \({2165}\). GSTP1 is hypermethylated in approximately 70% of HGPIN lesions \({325}\). GSTP1, which is known to inactivate carci-

Prognosis and predictive factors

**Needle biopsy**
High-grade PIN in needle biopsy tissue is, in most studies, a risk factor for the subsequent detection of carcinoma, while low-grade PIN is not. The mean incidence of carcinoma detection on re-biopsy after a diagnosis of high-grade PIN in needle biopsy tissue is about 30% \({559,1398,1926}\). In comparison, the re-biopsy cancer detection frequency is about 20% after a diagnosis of benign prostatic tissue \({715,1293}\), and 16% after a diagnosis of low-grade PIN. The large majority (80-90%) of cases of carcinoma are detected on the first re-biopsy \({1398}\), and re-biopsy may also detect persistent high-grade PIN in 5-43% of cases \({559,1398,1926}\). High-grade PIN with adjacent atypical glands seems to confer a higher risk for subsequent diagnosis of carcinoma compared to high-grade PIN alone, aver-

Fig. 3.68 A Ductal carcinoma in-situ with typical cribriform pattern on growth. B Ductal carcinoma in-situ with necrosis demonstrating retention of basal cell layer as revealed by high molecular weight cytokeratin staining.
aging 53% (70,1399,1926). Due to the magnitude of the risk, all men with this finding should undergo re-biopsy (1399). It is not settled whether serum PSA and digital rectal examination findings provide further information beyond PIN presence on risk for subsequent detection of carcinoma (995,1398,2010). There are inconsistent data as to whether the extent of HGPIN and its architectural pattern predict risk of subsequent carcinoma (559,1294,1398). Genetic abnormalities and/or immunophenotype of high-grade PIN are not currently utilized to stratify risk for subsequent detection of carcinoma.

Current standards of care recommend that patients with isolated high-grade PIN be re-biopsied in 0-6 months, irrespective of the serum PSA level and DRE findings. However, this recommendation may change with emerging data indicating a lower risk of prostate carcinoma following a needle biopsy showing HGPIN. The re-biopsy technique should entail at least systematic sextant re-biopsy of the entire gland (277,1435,2386), since high-grade PIN is a general risk factor for carcinoma throughout the gland. For example, in one study fully 35% of carcinomas would have been missed if only the side with the high-grade PIN had been re-biopsied (2386). Radical prostatectomy specimens removed for carcinoma detected after a diagnosis of high-grade PIN contain mostly organ-confined cancer, with a mean Gleason score of 6 (range 5-7) (1294). Treatment is currently not indicated after a needle biopsy diagnosis of high-grade PIN (994). Patients with isolated high-grade PIN in needle biopsy may be considered for enrollment into clinical trials with chemoprevention agents (1929, 2278).

**TURP**

Several studies have found that high grade PIN on TURP places an individual at higher risk for the subsequent detection of cancer (845,1996), whereas a long-term study from Norway demonstrated no association between the presence of high grade PIN on TURP and the incidence of subsequent cancer (1034). In a younger man with high grade PIN on TURP, it may be recommended that needle biopsies be performed to rule out a peripheral zone cancer. In an older man without elevated serum PSA levels, clinical follow-up is probably sufficient. When high grade PIN is found on TURP, some pathologists recommend sectioning deeper into the corresponding block and most pathologists recommend processing the entire specimen (1996).

Table 3.04
Risk of subsequent carcinoma detection after re-biopsy.

<table>
<thead>
<tr>
<th>Needle biopsy diagnosis</th>
<th>Percentage of patients with carcinoma on re-biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign prostatic tissue</td>
<td>20%</td>
</tr>
<tr>
<td>High grade PIN</td>
<td>30%</td>
</tr>
<tr>
<td>PINATYP&lt;sup&gt;2&lt;/sup&gt;</td>
<td>53%</td>
</tr>
</tbody>
</table>

<sup>1</sup>PIN: prostatic intraepithelial neoplasia.  
<sup>2</sup>PINATYP: high grade PIN with adjacent small atypical glands.
Ductal adenocarcinoma

Definition
Subtype of adenocarcinoma composed of large glands lined by tall pseudostratified columnar cells.

ICD-O code 8500/3

Synonyms
Several terms used in the past are no longer appropriate. Endometrial carcinoma was originally used to describe this entity because of its morphologic similarity to endometrium. This tumor was previously believed to be derived from a Müllerian structure named prostatic utricle (1706,1707). However, subsequent studies on favorable response to orchietomy, ultrastructural studies, histochemistry and immunohistochemistry have proven the prostatic origin of this tumor (1990,2205,2888,2919). Therefore, the term endometrial or endometrioid carcinoma should not be used. Prostatic duct carcinoma should be used with caution, because it could also refer to urothelial carcinoma involving prostatic ducts.

Epidemiology
In pure form, ductal adenocarcinoma accounts for 0.2-0.8% of prostate cancers (292,718,938). More commonly it is seen with an acinar component.

Etiology
No specific etiologic factors have been defined for this particular type.

Localization
Ductal adenocarcinoma may be located centrally around the prostatic urethra or more frequently located peripherally admixed with typical acinar adenocarcinoma. Both centrally and peripherally located ductal adenocarcinoma components can be present in the same prostate. A centrally located adenocarcinoma may also be associated with a peripherally located acinar adenocarcinoma.

Clinical features

Signs and symptoms
Periurethral or centrally located ductal adenocarcinoma may cause hematuria, urinary urgency and eventually urinary retention. In these cases, there may be no abnormalities on rectal examination. Tumors arising peripherally may lead to enlargement or induration of the prostate. Although ductal adenocarcinoma strongly expresses prostate specific antigen (PSA) immunohistochemically, they are associated with variable serum PSA levels (323).

Methods of diagnosis
Serum PSA levels may be normal particularly in a patient with only centrally located tumor. In most cases, transurethral resections performed for diagnosis or relief of the urinary obstruction will provide sufficient diagnostic tis-

Fig. 3.69 Ductal adenocarcinoma of the prostate. A Papillary type of growth. B Cribriform pattern.
sue. Transrectal needle core biopsies may also obtain diagnostic tissue when the tumour is more peripherally located (323). In addition, areas of ductal adenocarcinoma may be incidentally identified in prostatectomy specimens.

**Macroscopy/Urethroscopy**

Centrally occurring tumours appear as exophytic polypoid or papillary masses protruding into the urethra around the verumontanum. Peripherally occurring tumours typically show a white-grey firm appearance similar to acinar adenocarcinoma.

**Tumour spread and staging**

Ductal adenocarcinoma usually spread along the urethra or into the prostatic ducts with or without stromal invasion. Other patterns of spread are similar to that of acinar prostatic adenocarcinoma with invasion to extraprostatic tissues and metastasis to pelvic lymph nodes or distal organs. However, ductal adenocarcinomas appear to have a tendency to metastasize to lung and penis (491, 2654). The metastasis of ductal adenocarcinoma may show pure ductal, acinar or mixed components.

**Histopathology**

Ductal adenocarcinoma is characterized by tall columnar cells with abundant usually amphophilic cytoplasm, which form a single or pseudostratified layer reminiscent of endometrial carcinoma. The cytoplasm of ductal adenocarcinoma is often amphophilic and may occasionally appear clear. In some cases, there are numerous mitoses and marked cytological atypia. In other cases, the cytological atypia is minimal, which makes a diagnosis difficult particularly on needle biopsy. Peripherally located tumours are often admixed with cribriform, glandular or solid patterns as seen in acinar adenocarcinoma. Although ductal adenocarcinomas are not typically graded, they are mostly equivalent to Gleason patterns 4. In some cases comedo necrosis is present whereby they could be considered equivalent to Gleason pattern 5. In contrast to ordinary acinar adenocarcinoma, some ductal adenocarcinomas are associated with a prominent fibrotic response often including haemosiderin-laden macrophages. Ductal adenocarcinoma displays a variety of architectural patterns, which are often intermingled (286,720).

![Fig. 3.70 Ductal adenocarcinoma. Infiltrating cribriform and papillary growth pattern.](image)

![Fig. 3.71 A Mixed cribriform acinar and papillary ductal adenocarcinoma. B High magnification shows tall pseudostratified arrangement of nuclei diagnosed as ductal adenocarcinoma despite bland cytology.](image)
Papillary pattern can be seen in both centrally or peripherally located tumours, yet is more common in the former. Cribriform pattern is more commonly seen in peripherally located tumours, although they may be also present in centrally located tumours. The cribriform pattern is formed by back-to-back large glands with intraglandular bridging resulting in the formation of slit-like lumens. Individual gland pattern is characterized by single glands. Solid pattern can only be identified when it is associated with other patterns of ductal adenocarcinoma. The solid nests of tumour cells are separated by incomplete fibrovascular cores or thin septae. Ductal adenocarcinoma must be distinguished from urothelial carcinoma, ectopic prostatic tissue, benign prostatic polyps, and proliferative papillary urethritis. One of the more difficult differential diagnoses is cribriform high grade prostatic intraepithelial neoplasia. Some patterns of ductal adenocarcinoma may represent ductal carcinoma in situ.

Immunoprofile
Immunohistochemically ductal adenocarcinoma is strongly positive for PSA and PAP. Tumour cells are typically negative for basal cell specific high molecular weight cytokeratin (detected by 34βE12), however, preexisting ducts may be positive for this marker.

Prognosis and predictive factors
Most studies have demonstrated that ductal adenocarcinoma is aggressive. Some reported that 25-40% of cases had metastases at the time of diagnosis with a poor 5-year survival rate ranging from 15-43% (462,718,2205). It is not known whether prognosis correlates with the degree of cytological atypia or growth patterns. Even limited ductal adenocarcinoma on biopsy warrants definitive therapy. Androgen deprivation therapy may provide palliative relief, even though these cancers are less hormonally responsive than acinar adenocarcinoma.

Fig. 3.72 A Separate acinar (left) and ductal adenocarcinoma (right). B Individual glands of prostatic duct adenocarcinoma, resembling colonic adenocarcinoma. C Ductal adenocarcinoma of the prostate showing close morphologic resemblance to endometrial carcinoma.
Urothelial carcinoma

Definition
Urothelial carcinoma involving the prostate.

ICD-O code 8120/3

Epidemiology
The frequency of primary urothelial carcinoma ranges from 0.7-2.8% of prostatic tumours in adults (942,943). Most patients are older with a similar age distribution to urothelial carcinoma of the bladder (range 45-90 years) (942,1231). In patients with invasive bladder carcinoma, there is involvement of the prostate gland in up to 45% of cases (1596,1907,2837). This is highest when there is multifocality or carcinoma in situ associated with the invasive carcinoma (1907).

Etiology
Primary urothelial carcinomas presumably arise from the urothelial lining of the prostatic urethra and the proximal portions of prostatic ducts. It has been postulated that this may arise through a hyperplasia to dysplasia sequence, possibly from reserve cells within the urothelium (696,1278,2673). Secondary urothelial carcinoma of the prostate is usually accompanied by CIS of the prostatic urethra (2673). Involvement of the prostate appears to be by direct extension from the overlying urethra, since in the majority of cases the more centrally located prostatic ducts are involved by urothelial neoplasia to a greater extent than the peripheral ducts and acini. Less commonly, deeply invasive urothelial carcinoma from the bladder directly invades the prostate.

Localization
Primary urothelial carcinoma is usually located within the proximal prostatic ducts. Many cases are locally advanced at diagnosis and extensively replace the prostate gland.

Clinical features
Signs and symptoms
Primary urothelial carcinoma presents in a similar fashion to other prostatic masses including urinary obstruction and haematuria (943,2159). Digital rectal examination is abnormal in the majority but is infrequently the presenting sign (1951). There is limited data on PSA levels in patients with urothelial carcinoma of the prostate. In one series 4 of 6 patients had elevated serum PSA (>4 ng/ml) in the absence of prostatic adenocarcinoma (1951). In some cases patients present with signs and symptoms related to metastases (2159).

Methods of diagnosis
Most cases are diagnosed by transurethral resection or less often needle biopsy (1951). In all suspected cases the possibility of secondary involvement from a bladder primary must be excluded; the bladder tumour can be occult and random biopsies may be necessary to exclude this possibility (2313,2905). Biopsies of the prostatic urethra and suburethral prostate tissue are often recommended as a staging procedure to detect secondary urothelial cancer involving the prostate of patients undergoing conservative treatment for superficial bladder tumours.

Tumour spread and staging
In situ carcinoma can spread along ducts and involve acini, or the tumour can spread along ejaculatory ducts and into seminal vesicles. Subsequent spread is by invasion of prostatic stroma. Local spread beyond the confines of the prostate may occur. Metastases are to regional lymph nodes and bone (2556). Bone metastases are osteolytic. These tumours are staged as urethral tumours (944). For tumours involving the prostatic ducts, there is a T1 category for invasion of subepithelial connective tissue distinct from invasion of prostatic stroma (T2). The prognostic importance of these categories has been confirmed in clinical studies (442).

Histopathology
The full range of histologic types and grades of urothelial neoplasia can be seen in primary and secondary urothelial neoplasms of the prostate (442). A few examples of papillary urothelial neoplasms arising within prostatic ducts are described (1278). The vast majority, however, are high-grade and are associated with an in situ component (442,899,1893,1951,2445,2580). The in situ component has the characteristic histologic features of urothelial carcinoma in situ elsewhere with marked nuclear pleomorphism, frequent mitoses and apoptotic bodies. A single cell pattern of pagetoid spread or burrowing of tumour cells between the basal cell and secretory cell layers of the prostate is characteristic. With extensive tumour involvement, urothelial carcinoma fills and expands ducts and often develops central comedonecrosis. Stromal invasion is associated with a prominent desmoplastic stromal response with tumour cells arranged in small irregular nests, cords and single cells. Inflammation in the adjacent stroma frequently accompanies in situ disease but without desmoplasia. With stromal invasive tumours, squamous or glandular differentiation can be seen. Angioymphatic invasion is often identified. Incidental adenocarcinoma of the prostate is found in up to 40% of cystoprostatectomy specimens removed for urothelial carcinoma of the bladder and can accompany primary urothelial carcinoma (1772). In cases of direct invasion of the prostate from a poorly differentiated urothelial carcinoma of the bladder, a common prob-
lem is its distinction from a poorly differentiated prostatic adenocarcinoma. Poorly differentiated urothelial carcinomas have greater pleomorphism and mitotic activity compared to poorly differentiated adenocarcinomas of the prostate. Urothelial carcinomas tend to have hard glassy eosinophilic cytoplasm or more prominent squamous differentiation, in contrast to the foamy, pale cytoplasm of prostate adenocarcinoma. Urothelial cancer tends to grow in nests.
as opposed to cords of cells or focal cribriform glandular differentiation typical of prostatic adenocarcinoma.

**Immunoprofile**
The tumour cells are negative for PSA and PAP (440, 1951). Prostatic secretions in the ductal lumens can react positively resulting in faint staining of tumour cells at the luminal surface, a finding that should not be misinterpreted as positive staining. Tumour cells express CK7 and CK20 in the majority of cases and high molecular weight cytokeratin or P63 in about 50% of cases (1951). Residual basal cells are frequent in the in situ areas (440). Urothelial cancers may also express thrombomodulin and uroplakins, which are negative in prostate adenocarcinoma.

**Prognosis and predictive factors**
For patients with either primary or secondary urothelial carcinoma of the prostate the single most important prognostic parameter is the presence of prostatic stromal invasion. In one series, survival was 100% for patients with noninvasive disease treated by radical cystoprostatectomy (442). With stromal invasion or extension beyond the confines of the prostate prognosis is poor (261, 442, 943, 1437). In one series, overall survival was 45% at 5 years in 19 patients with stromal invasion (442). In 10 cases of primary urothelial carcinoma reported by Goebbels et al. mean survival was 28.8 months (range 1 to 93 months) (899). However, even if only intraductal urothelial carcinoma is identified on TURP or transurethral biopsy in a patient followed for superficial bladder cancer, patients usually will be recommended for radical cystoprostatectomy as intravesical therapy is in general not thought to be effective in treating prostatic involvement.
**Squamous neoplasms**

**Definition**
Tumours with squamous cell differentiation involving the prostate.

**ICD-O codes**
- Adenosquamous carcinoma 8560/3
- Squamous cell carcinoma 8070/3

**Epidemiology**
The incidence of squamous cell carcinoma of the prostate is less than 0.6% of all prostate cancers [1814,1861]. There are 70 cases reported in literature. Even more rare is adenosquamous carcinoma of the prostate, with about 10 cases reported so far. For primary prostatic squamous cell carcinoma an association with Schistosomiasis infection has been described [44]. Approximately 50% of adenosquamous carcinomas may arise in prostate cancer patients subsequent to endocrine therapy or radiotherapy [179].

**Localization**
Squamous cell carcinomas may originate either in the periurethral glands or in the prostatic glandular acini, probably from the lining basal cells, which show a divergent differentiation pathway [606,931]. Adenosquamous carcinomas are probably localized more commonly in the transition zone of the prostate accounting for their more frequent detection in transurethral resection specimens [179,2613].

**Clinical features**
Most, if not all pure squamous cell carcinomas become clinically manifest by local symptoms such as urinary outflow obstruction, occasionally in association with bone pain and haematuria. Most patients have at the time of diagnosis metastatic disease, and bone metastases are osteolytic. PSA levels are not typically elevated. The age range of patients is between 52 and 79 years [1861]. Hormone treatment and chemotherapy are not effective, except for a single case with non-progressive disease after local irradiation and systemic chemotherapy [2657]. In cases of organ-confined disease, radical prostatectomy or cystoprostatectomy, including total urethrectomy is recommended [1513]. Adenosquamous carcinomas may be detected by increased serum PSA, but more typically by obstruction of the urinary outflow, requiring transurethral resection [179]. Patients may also present with metastatic disease. A proportion of cases show an initial response to hormone therapy [32,1176].

**Tumour spread**
Both squamous cell carcinomas and adenosquamous carcinomas tend to metastasize rapidly with a predilection for the skeletal bones [841,1861].

**Histopathology**
By definition pure squamous cell carcinoma does not contain glandular features and it is identical to squamous cell carcinoma of other origin. With rare exception, it does not express PSA or PAP [1861,2657]. Primary prostatic squamous cell carcinoma must be distinguished on clinical grounds from secondary involvement of the gland by bladder or urethral squamous carcinoma. Histologically, squamous cell carcinoma must be distinguished from squamous metaplasia as may occur in infarction or after hormonal therapy.

Adenosquamous carcinoma is defined by the presence of both glandular (acinar) and squamous cell carcinoma components. Some authors considered the possibility that adenosquamous carcinomas consist of collision tumours with a de novo origin of adenocarcinoma and squamous cell carcinoma [841]. The glandular tumour component generally expresses PSA and PAP, whereas the squamous component displays high molecular weight cytokeratins [179].

---

**Fig. 3.79**
A Cross section of squamous cell carcinoma. B Squamous cell carcinoma of the prostate with focal keratinization.
Definition
This is a neoplasm composed of prostatic basal cells. It is believed that a subset of basal cells are prostatic epithelial stem cells, which can give rise to a spectrum of proliferative lesions ranging from basal cell hyperplasia to basal cell carcinoma (271,1139,2007,2410).

ICD-O code  8147/3

Clinical features
Patients are generally elderly, presenting with urinary obstruction with TURP being the most common tissue source of diagnosis. The youngest reported case was 28 years old (597).

Histopathology
Some tumours resemble its namesake in the skin, comprising large basaloid nests with peripheral palisading and necrosis. Other patterns have histologic similarity to florid basal cell hyperplasia or the adenoid basal cell pattern of basal cell hyperplasia (the latter pattern of cancer occasionally referred to as adenoid cystic carcinoma). Histologic criteria for malignancy that distinguish it from basal cell hyperplasia include an infiltrative pattern, extraprostatic extension, perineural invasion, necrosis and stromal desmoplasia.

Basal cell carcinoma shows immunoreactivity for keratin 34βE12, confirming its relationship with prostatic basal cells. S-100 staining is described as weak to intensely positive in about 50% of tumour cells (954,2893), raising the possibility of myoepithelial differentiation; but there is no corroborative anti-smooth muscle actin (HHF35) reactivity (954) nor ultrastructural evidence of a myoepithelial nature (2893). Distinction from basal cell hyperplasia with a pseudoinfiltrative pattern or prominent nucleoli can be difficult; basal cell carcinoma shows strong BCL2 positivity and high Ki-67 indices as compared to basal cell hyperplasia (2868).

Prognosis
The biologic behaviour and treatment of basal cell carcinoma is not well elucidated in view of the few cases with mostly short follow-up. Local extra-prostatic extension may be seen, along with distant metastases (597,1160). A benign morphologic counterpart to basal cell carcinoma (basal cell adenoma) has been proposed, although it should be considered as florid nodular basal cell hyperplasia.
Neuroendocrine tumours

Definition
Neuroendocrine differentiation in prostatic carcinoma has three forms:
1. Focal neuroendocrine differentiation in conventional prostatic adenocarcinoma
2. Carcinoid tumour (WHO well differentiated neuroendocrine tumour) and
3. Small cell neuroendocrine carcinoma (new WHO classification poorly differentiated neuroendocrine carcinoma)

ICD-O codes
Focal neuroendocrine differentiation in prostatic adenocarcinoma 8574/3
Carcinoid 8240/3
Small cell carcinoma 8041/3

Focal neuroendocrine differentiation in prostatic adenocarcinoma

All prostate cancers show focal neuroendocrine differentiation, although the majority shows only rare or sparse single neuroendocrine cells as demonstrated by neuroendocrine markers. In 5-10% of prostatic carcinomas there are zones with a large number of single or clustered neuroendocrine cells detected by chromogranin A immunostaining [29,31,272,609-611,1016,1064,1066]. A subset of these neuroendocrine cells may also be serotonin positive. Immunostaining for neuron-specific enolase, synaptophysin, bombesin/gastrin-releasing peptide and a variety of other neuroendocrine peptides may also occur in individual neoplastic neuroendocrine cells, or in a more diffuse pattern [1178] and receptors for serotonin [16] and neuroendocrine peptides [1017,2537] may also be present. Vascular endothelial growth factor (VEGF) may also be expressed in foci of neuroendocrine differentiation [1026].

The definitional context of these other neuroendocrine elements (other than chromogranin A and serotonin) remains to be elucidated. There are conflicting studies as to whether advanced androgen deprived and androgen independent carcinomas show increased neuroendocrine differentiation [446,1185,1222,1395,1822,2582]. The prognostic significance of focal neuroendocrine differentiation in primary untreated prostatic carcinoma is controversial with some showing an independent negative effect on prognosis [267,478,2802], while others have not shown a prognostic relationship [30,335,384,1915,2352,2465]. In advanced prostate cancer, especially androgen independent cancer, focal neuroendocrine differentiation portends a poor prognosis [446,1222,1395,2582] and may be a therapeutic target [228,2317,2918]. Serum chromogranin A levels (and potentially other markers such as pro-gastrin-releasing peptide) [2537,2582,2853,2802,2871] may be diagnostically and prognostically useful, particularly in PSA negative, androgen independent carcinomas [227,1183,1500,2871,2918].

Carcinoid tumours

True carcinoid tumours of the prostate, which meets the diagnostic criteria for carcinoid tumour elsewhere are exceedingly rare [609,2472,2583]. These tumours show classic cytologic features of carcinoid tumour and diffuse neuroendocrine differentiation (chromogranin A and synaptophysin immunoreactivity). They should be essentially negative for PSA. The prognosis is uncertain due to the small number of reported cases. The
term "carcinoid-like tumours" has been used to refer to a variety of miscellaneous entities, most of which refer to ordinary acinar adenocarcinoma of the prostate with an organoid appearance and focal neuroendocrine immunoreactivity.

**Small cell carcinoma**

**Clinical features**
Many patients have a previous history of a hormonally treated acinar adenocarcinoma. As the small cell carcinoma component predominates, serum PSA level falls and may be undetectable. While most small cell carcinomas of the prostate lack clinically evident hormone production, they account for the majority of prostatic tumours with clinically evident ACTH or antidiuretic hormone production.

**Histopathology**
Small cell carcinomas of the prostate histologically are identical to small-cell carcinomas of the lung (2210,2600). In approximately 50% of the cases, the tumours are mixed small cell carcinoma and adenocarcinoma of the prostate. Neurosecretory granules have been demonstrated within several prostatic small cell carcinomas. Using immunohistochemical techniques small cell components are negative for PSA and PAP. There are conflicting studies as to whether small cell carcinoma of the prostate is positive for thyroid transcription factor-1 (TTF-1), in order to distinguish them from a metastasis from the lung (37,1969).

**Prognosis**
The average survival of patients with small cell carcinoma of the prostate is less than a year. There is no difference in prognosis between patients with pure small cell carcinoma and those with mixed glandular and small cell carcinoma. The appearance of a small cell component within the course of adenocarcinoma of the prostate usually indicates an aggressive terminal phase of the disease. In a review of the literature of genitourinary small cell carcinoma, whereas cisplatin chemotherapy was beneficial for bladder tumours, only surgery was prognostic for prostate small cell carcinomas (1587). While this study concluded that hormonal manipulation and systemic chemotherapy had little effect on the natural history of disease in the prostate, the number of patients were small and others suggest to treat small cell carcinoma of the prostate with the same combination chemotherapy used to treat small cell carcinomas in other sites (75,2254).

![Fig. 3.84 Small cell carcinoma. A Note extensive necrosis. B Typical cytological appearance of small cell carcinoma.](image-url)
Mesenchymal tumours

Definition
A variety of rare benign and malignant mesenchymal tumours that arise in the prostate [1063,1774].

ICD-O codes
Stromal tumour of uncertain malignant potential 8935/1
Stromal sarcoma                         8935/3
Leiomyosarcoma                          8890/3
Rhabdomyosarcoma                        8900/3
Malignant fibrous histiocytoma          8830/3
Osteosarcoma                           9180/3
Chondrosarcoma                         9220/3
Malignant peripheral nerve sheath tumour 9540/3
Synovial sarcoma                        9040/3
Undifferentiated sarcoma                8805/3
Leiomyoma                               8890/0
Granular cell tumour                    9580/0
Fibroma                                 8810/0
Solitary fibrous tumour                 8815/0
Haemangiona                             9120/0
Chondroma                               9220/0

Epidemiology
Sarcomas of the prostate account for 0.1-0.2% of all malignant prostatic tumours.

Tumours of specialized prostatic stroma

Sarcomas and related proliferative lesions of specialized prostatic stroma are rare. Lesions have been classified into prostatic stromal proliferations of uncertain malignant potential (STUMP) and prostatic stromal sarcoma based on the degree of stromal cellularity, presence of mitotic figures, necrosis, and stromal overgrowth [844]. There are several different patterns of STUMP, including those that resemble benign phyllodes tumour, hypercellular stroma with scattered atypical yet degenerative cells, and extensive overgrowth of hypercellular stroma with the histology of a stromal nodule. STUMPs are considered neoplastic, based on the observations that they may diffusely infiltrate the prostate gland and extend into adjacent tissues, and often recur. Although most cases of STUMP do not behave in an aggressive fashion, occasional cases have been documented to recur rapidly after resection and a minority have progressed to stromal sarcoma. STUMPs encompass a broad spectrum of lesions, a subset of which is focal as seen on simple prostatectomy, which neither recurs nor progresses, and could be termed in these situations as glandular-stromal or stromal nodule with atypia. The appropriate treatment of STUMPs is unknown. When these lesions are extensive or associated with a palpable mass definitive therapy may be considered. Stromal sarcomas may have the overall glandular growth pattern of phyllodes tumours with obviously malignant stroma with increased cellularity, mitotic figures, and pleomorphism. Other stromal sarcomas consist of sheets of hypercellular atypical stroma without the fascicular growth pattern of leiomyosarcomas. The behaviour of stromal sarcomas is not well understood due to their rarity, although some cases have gone on to metastasize to distant sites. Rare cases of adenocarcinoma of the prostate involving a phyllodes tumour have been identified.

Immunohistochemical results show that STUMP and stromal sarcomas both are typically positive for CD34 and may be used to distinguish them from other prostatic mesenchymal neoplasms, such as rhabdomyosarcoma and leiomyosarco-

Fig. 3.85 STUMP (prostatic stromal proliferations of uncertain malignant potential) with benign glands and atypical stromal cells.

Fig. 3.86 Benign phyllodes tumour. A Typical clover leaf architecture. B Higher magnification discloses low cellularity and lack of atypia in epithelial and stromal elements.

Mesenchymal tumours 209
ma. Both STUMP and stromal sarcomas characteristically express progesterone receptors (PR) and uncommonly express estrogen receptors (ER), supporting the concept that STUMP and stromal sarcomas are lesions involving hormonally responsive prostatic mesenchymal cells, the specialized prostatic stroma. STUMPS typically react positively with actin, whereas prostatic stromal sarcomas react negatively, suggesting that the expression of muscle markers in these lesions is a function of differentiation.

**Leiomyosarcoma**

Leiomyosarcomas are the most common sarcomas involving the prostate in adults (443). The majority of patients are between 40 and 70 years of age, though in some series up to 20% of leiomyosarcomas have occurred in young adults. Leiomyosarcomas range in size between 2 cm and 24 cm with a median size of 5 cm. Histologically, leiomyosarcomas range from smooth muscle tumours showing moderate atypia to highly pleomorphic sarcomas. As with leiomyosarcomas found elsewhere, these tumours immunohistochemically can express cytokeratins in addition to muscle markers. There have been several well circumscribed lesions with a variable amount of nuclear atypia and scattered mitotic activity which have been referred to as atypical leiomyoma of the prostate (2233), giant leiomyoma of the prostate (2162), or circumscribed leiomyosarcoma of the prostate (2505). Following either local excision or resection of prostatic leiomyosarcomas, the clinical course tends to be characterized by multiple recurrences. Metastases, when present, are usually found in the lung. The average survival with leiomyosarcoma of the prostate is between 3 and 4 years. Because smooth muscle tumours of the prostate are rare, the criteria for distinguishing between leiomyosarcoma and leiomyoma with borderline features have not been elucidated. Although most "atypical leiomyomas" have shown no evidence of disease with short follow-up, a few have recurred.

**Rhabdomyosarcoma**

Rhabdomyosarcoma is the most frequent mesenchymal tumour within the prostate in childhood (1522). Rhabdomyosarcomas of the prostate occur from infancy to early adulthood with an average age at diagnosis of 5 years. Most present with stage III disease, in which there is gross residual disease following incomplete resection or biopsy. A smaller, but significant proportion of patients present with distant metastases. Localized tumour that may be complete-

---

**Fig. 3.87** A Malignant phyllodes tumour. High cellularity and cellular pleomorphism are obvious even at this magnification. B Leiomyosarcoma. Fascicular arrangement, high cellularity and mitotic activity are characteristic.

**Fig. 3.88** A Rhabdomyosarcoma. Note strap cells. B Angiosarcoma with slit-like spaces lined by atypical cells.
ly resected is only rarely present. Because of their large size at the time of diagnosis, distinction between rhabdomyosarcoma originating in the bladder and that originating in the prostate may be difficult. Histologically, most prostate rhabdomyosarcomas are of the embryonal subtype and are considered to be of favourable histology. The use of immunohistochemical, ultrastructural, and molecular techniques may be useful in the diagnosis of embryonal rhabdomyosarcoma. Following the development of effective chemotherapy for rhabdomyosarcomas, those few patients with localized disease (stage I) or microscopic regional disease (stage II) stand an excellent chance of being cured. While the majority of patients with gross residual disease (stage III) have remained without evidence of disease for a long period of time, approximately 15-20% die of their tumour. The prognosis for patients with metastatic tumour (stage IV) is more dismal, with most patients dying of their tumour. Following biopsy or partial excision of the tumour, the usual therapy for localized disease is intensive chemotherapy and radiotherapy. If tumour persists despite several courses of this therapy, then radical surgery is performed. It is important to identify those rare cases of alveolar rhabdomyosarcoma involving the prostate since this histologic subtype is unfavourable and necessitates more aggressive chemotherapy.

Miscellaneous sarcomas

Rare cases of malignant fibrous histiocytoma (158,450,1403,1741,2369), angiosarcoma (2446), osteosarcoma (59,1899), chondrosarcoma (631), malignant peripheral nerve sheath tumours (2143), and synovial sarcoma (1189) have been reported.

Leiomyoma

The arbitrary definition of a leiomyoma, to distinguish it from a fibromuscular hyperplastic nodule, is a well-circumscribed proliferation of smooth muscle measuring 1 cm or more (1724). According to this definition, less than one hundred cases are reported. Its morphology is similar to uterine leiomyoma, and even subtypes, such as the bizarre leiomyoma, are described (1277).

Miscellaneous benign mesenchymal tumours

Various benign soft tissue tumours have been described as arising in the prostate including granular cell tumour (824), and solitary fibrous tumour (928,1912,2079). Other benign mesenchymal tumours such as haemangiomas (1112), chondromas (2439), and neural tumours (1872) have also been described.
**Haematolymphoid tumours**

The prostate is a rare site of extranodal lymphoma with a total of 165 cases arising in or secondarily involving the prostate reported. Of patients with chronic lymphocytic leukaemia, 20% are reported to have prostate involvement at autopsy (2731). The most frequent symptoms are those related to lower urinary obstruction.

In a recent large series of 62 cases, 22, 30 and 10 cases were classified as primary, secondary and indeterminate respectively. Sixty cases were non-Hodgkin lymphoma (predominately diffuse large cell followed by small lymphocytic lymphoma). Rarely Hodgkin lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma were reported (291,1216).

**Secondary tumours involving the prostate**

**Definition**

Metastatic tumours arise outside of the prostate and spread to the gland by vascular channels. Contiguous spread from other pelvic tumours into the prostate does not constitute a metastasis. Haematolymphoid tumours of the prostate are discussed separately.

**Epidemiology**

True metastases from solid tumours were reported in 0.1% and 2.9% of all male postmortems (185,1699) and 1% and 6.3% of men in whom tumours caused death (1699,2930) and in 0.2% of all surgical prostatic specimens (185). Lung was the most common primary site of metastases to the prostate (185). In all series direct spread of bladder carcinoma is the commonest secondary prostatic tumour (185,2905).

**Histopathology and prognosis**

Metastases from lung, skin (melanoma), gastrointestinal tract, kidney, testis and endocrine glands have been reported (185,2905,2930). Clinical context, morphological features and immunocytochemical localization of PSA and PSAP clarify the differential diagnosis. Prognosis reflects the late stage of disease in which prostatic metastases are seen.
**Miscellaneous tumours**

**ICD-O codes**
- Cystadenoma 8440/0
- Wilms tumour (nephroblastoma) 8960/3
- Malignant rhabdoid tumour 8963/3
- Clear cell adenocarcinoma 8310/3
- Melanoma of the prostate 8720/3
- Paraganglioma 8680/1
- Neuroblastoma 9500/3

**Cystadenoma**

Also known as multilocular cyst or giant multilocular prostatic cystadenoma, it is a rare entity characterized by benign multilocular prostatic cysts that can enlarge massively. Affected men are aged 20-80 years, presenting with obstructive urinary symptoms, with or without a palpable abdominal mass (1324). Postulated causes include obstruction, involutional atrophy (1594), or retrovesical ectopic prostatic tissue with cystic change (2872).

It occurs between the bladder and the rectum (62,1501,1611,2872), either separate from the prostate or attached to it by a pedicle. Similar lesions can be found within the prostate gland.

Cystadenomas weigh up to 6,500 grams, ranging from 7.5 cm to 20 cm in size. They are well-circumscribed, resembling nodular hyperplasia with multiple cysts macroscopically. Atrophic prostatic epithelium lines the cysts, reacting with antibodies to PSA and PSAP, with high grade prostatic intraepithelial neoplasia reported in one case (62). When cystadenomas occur within the prostate, distinction from cystic nodular hyperplasia may be difficult. Intraprostatic cystadenoma should be diagnosed only when half the prostate appears normal, while the remaining gland is enlarged by a solitary encapsulated cystic nodule (1323,1704).

Prostatic cystadenomas are not biologically aggressive (1611), but can recur if incompletely excised. Extensive surgery may be necessary because of their large size and impingement on surrounding structures.

**Wilms tumour (nephroblastoma)**

Wilms tumour rarely occurs in the prostate (386).

**Malignant rhabdoid tumour**

Malignant rhabdoid tumour may be found in the prostate (673).

**Germ cell tumours**

Primary germ cell tumours of the prostate have been rarely described (1046,1725,2586). It is critical to exclude a metastasis from a testicular primary.

**Clear cell adenocarcinoma**

Clear cell adenocarcinoma resembling those seen in the Müllerian system may affect the prostate. It can develop from the prostatic urethra (636), Müllerian derivatives such as Müllerian duct cyst (874), or exceptionally, from the peripheral parenchyma (2004). Histologically, it is composed of tubulocystic or papillary structures lined by cuboidal or hobnail cells with clear to eosinophilic cytoplasm. The tumour cells immunohistochemically do not express prostate specific antigen and prostate acid phosphatase, but may express CA-125. The patient may have elevated serum level of CA-125.

**Melanoma of the prostate**

Primary malignant melanomas of the prostate are extremely rare (2493). Malignant melanoma of the prostate should be distinguished from melanosis and cellular blue nevus of the prostate (2208).

**Paraganglioma**

Several case reports of paragangliomas originating in the prostate have been reported, including one in a child (599,2747). Although extra-adrenal paragan-
glomias should not be designated as "phaeochromocytomas", they have been published as such. Clinical symptoms are similar to those of the adrenal (hypertension, headaches, etc.). The laboratory tests used to diagnose prostatic paragangliomas are the same as used to diagnose paragangliomas occurring elsewhere in the body. In some cases, symptoms have been exacerbated by urination (micturition attacks), identical to what is seen with paragangliomas occurring in the bladder. Malignant behaviour has not been reported.

**Neuroblastoma**

Neuroblastoma, a primitive tumour of neuroectodermal origin, rarely affects the prostate. (1420). Pelvic organs may also be involved secondarily.

---

**Tumours of the seminal vesicles**

**Epithelial tumours of the seminal vesicle**

**Primary adenocarcinoma**

ICD-O code 8140/3

The seminal vesicle is involved by secondary tumours much more frequently than it contains primary adenocarcinoma. Strict criteria for this diagnosis of this lesion require the exclusion of a concomitant prostatic, bladder, or rectal carcinoma (1977). Acceptable reported cases numbered 48 (1977). Although most were in older men, 10 men were under age 40 (212, 1322).

Presenting symptoms usually included obstructive uropathy due to a non-tender peri-rectal mass (212,1940) and less commonly haematuria or haematospermia. Serum carcinoembryonic antigen may be elevated to 10 ng/ml.

The tumours are usually large (3-5 cm) and often invaded the bladder, ureter, or rectum (212,1940). Tumours can show a mixture of papillary, trabecular and glandular patterns with varying degrees of differentiation. Carcinomas with colloid features have been described. Tumour cytoplasm may show clear cell or hobnail morphology. It is important to exclude a prostatic primary using PSA and PAP. Immunoreactive carcinoembryonic antigen (CEA) is detectable in normal seminal vesicle and seminal vesicle adenocarcinoma. Besides CEA, tumour should be positive for cytokeratin 7 (unlike many prostatic adenocarcinomas), negative for cytokeratin 20 (unlike bladder and colonic carcinoma), and positive for CA-125 (unlike carcinoma arising in a Müllerian duct cyst and all the above).

The prognosis of primary seminal vesicle adenocarcinoma is poor, but can be improved with adjuvant hormonal manipulation (212). Most patients presented with metastases and survival was less than 3 years in 95% of cases; five of 48 patients survived more than 18 months (1977).

**Cystadenoma of the seminal vesicles**

ICD-O code 8440/0

Cystadenomas are rare benign tumours of the seminal vesicle. Patients range in age from 37-66 years and may be asymptomatic or have symptoms of bladder outlet obstruction {177,2292}. Ultrasound reveals a complex, solid-cystic pelvic mass (1427). Histologically, this is a well-circumscribed tumour containing variable-sized glandular spaces with branching contours and cysts with an investing spindle cell stroma. The glands are grouped in a vaguely lobular pattern, contain pale intraluminal secretions and are lined by one or two layers of cuboidal to columnar cells. No significant cytologic atypia, mitotic activity or necrosis is seen (177,1659,2292). Incompletely removed tumours may recur.

**Benign and malignant mixed epithelial stromal tumours**

Epithelial-stromal tumours fulfill the following criteria: they arise from the seminal vesicle and there is no normal seminal vesicle within the tumour; they usually do not invade the prostate (one exception (1451)), have a less conspicuous, less cellular stromal component than cystadenoma, and are not immunoreactive for prostatic markers or CEA (737,1451,1600,1656). Benign types include fibroadenoma and adenomyoma. These tumours have occurred in men aged 39-66 who presented with pain and voiding difficulty. Tumours were grossly solid and cystic, ranging from 3 to 15 cm. The distinction from malignant epithelial-stromal tumour NOS, low-grade (below) is based on stromal blandness and inconspicuous mitotic activity.

Four cases of malignant or probably malignant epithelial-stromal tumours have been reported (737,1451,1600,1656). These were categorized as low-grade or high-grade depending on mitotic activity and necrosis. The tumours occur in men in the sixth decade of life, who usually have urinary obstruction as the main presenting symptom. Grossly, the tumours were either multicystic or solid and cystic. Microscopically, the stroma was at least focally densely cellular and tended to condense around distorted glands lined by cuboidal to focally stratified epithelium. One man was cured by cystoprostatectomy (1451); two had pelvic recurrence after 2 years, one cured by a second exci-
Tumours of the seminal vesicles

Mesenchymal tumours of the seminal vesicles

Mesenchymal tumours that arise in the seminal vesicles as a primary site are rare. The frequency of these tumours, in order from highest to lowest, is leiomyosarcoma, leiomyoma, angiosarcoma, malignant fibrous histiocytoma, solitary fibrous tumour, liposarcoma and haemangiopericytoma. Clinical presentations include pelvic pain and urinary or rectal obstructive symptoms. Some may be asymptomatic, and detected by digital rectal examination and sonography. Needle or open biopsy is required to establish the diagnosis. It may be difficult to ascertain the site of origin when adjacent pelvic organs are involved.

Leiomyoma

ICD-O code 8890/0

Leiomyoma of the seminal vesicles is asymptomatic and exceedingly rare. Among seven reported cases, six were detected on digital rectal examination and one, by magnetic resonance imaging (155,850). The tumour, probably of Müllerian duct origin, measures up to 5 cm (850). Local excision has yielded no recurrences.

Leiomyosarcoma

ICD-O code 8890/3

By digital rectal examination and pelvic computed tomography as well as magnetic resonance imaging, a large pelvic mass in the region of the seminal vesicles of the prostate may be detected. Six patients with reported seminal vesicle leiomyosarcoma presented with pelvic pain and obstructive symptoms but not haematuria (unlike with prostatic sarcoma) (87,1923, 2332). When possible, resection of the tumour mass by radical prostatectomy and vesiculectomy is the therapy of choice. One patient was cured by radical cystoprostatectomy at 13-month follow-up (87), although another developed renal metastasis after 2 years (1823).

Angiosarcoma

ICD-O code 9120/3

Angiosarcoma of the seminal vesicles is a highly aggressive tumour, refractory to traditional surgical and adjuvant therapeutical modalities. Three cases were reported (451,1432,2006) and all presented with pelvic pain; two died of distant metastasis within two months after the diagnosis (451,1432).

Liposarcoma

ICD-O code 8850/3

There is one case described as a "collision" tumour composed of liposarcoma of the seminal vesicles and prostatic carcinoma (1252). The patient died of distant metastasis from prostatic carcinoma.

Malignant fibrous histiocytoma

ICD-O code 8830/3

This tumour is exceedingly rare in the seminal vesicle (538). Sonographic studies are important to establish the site of origin. The therapy should be the complete surgical resection, in most cases by radical prostatectomy and vesiculectomy.

Solitary fibrous tumour

ICD-O code 8815/0

Three cases were reported (1785,2808), and all were located in the right seminal vesicle. The clinical presentations were pelvic pain or haematuria. The origin of the tumour was established by transrectal ultrasonography, magnetic resonance imaging, or computed tomography. Complete local excision appears to be curative.

Haemangiopericytoma

ICD-O code 9150/1

A case of malignant haemangiopericytoma of the seminal vesicle has been reported (122). The patient presented with hypoglycemia, and was treated by cystoprostatectomy and vesiculectomy. He died of disseminated haemangiopericytoma 10 years later.

Miscellaneous tumours of the seminal vesicle

Choriocarcinoma

ICD-O code 9100/3

One case has been reported of primary choriocarcinoma of the seminal vesicles. (738). However, this case is not definitive as there was tumour in multiple organs, excluding the testes, with the largest deposit present in the seminal vesicle.