With more than 1.1 million deaths annually worldwide, lung cancer is the most frequent and one of the most deadly cancer types. In men, 85-90% of cases can be attributed to tobacco smoking. Some Western countries in which the smoking habit took off about 100 years ago, tobacco control programmes have led to a significant decline in mortality. Unfortunately, the habit has now spread to many newly industrialized countries, particularly in Asia, and in Europe, there is a worrying trend of increasing smoking prevalence in young women. The prognosis of lung cancer is still poor, with 5-years survival rates of approximately 10% in most countries. Thus, primary prevention by not starting or by stopping smoking remains the most promising approach.

The association between smoking and lung cancer is not solely based on epidemiological studies. Lung tumours of smokers frequently contain a typical, though not specific, molecular fingerprint in the form of G:C > T:A mutations in the TP53 gene which are probably caused by benzo[a]pyrene, one of the many carcinogens in tobacco smoke.
### Malignant epithelial tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Morphology Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Papillary</td>
<td>8052/3</td>
</tr>
<tr>
<td>Clear cell</td>
<td>8084/3</td>
</tr>
<tr>
<td>Small cell</td>
<td>8073/3</td>
</tr>
<tr>
<td>Basaloid</td>
<td>8083/3</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>8041/3</td>
</tr>
<tr>
<td>Combined small cell carcinoma</td>
<td>8045/3</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>8140/3</td>
</tr>
<tr>
<td>Acinar adenocarcinoma</td>
<td>8550/3</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>8260/3</td>
</tr>
<tr>
<td>Bronchioloalveolar carcinoma</td>
<td>8250/3</td>
</tr>
<tr>
<td>Nonmucinous</td>
<td>8252/3</td>
</tr>
<tr>
<td>Mucinous</td>
<td>8253/3</td>
</tr>
<tr>
<td>Mixed nonmucinous and mucinous or indeterminate</td>
<td>8254/3</td>
</tr>
<tr>
<td>Solid adenocarcinoma with mucin production</td>
<td>8230/3</td>
</tr>
<tr>
<td>Fetal adenocarcinoma</td>
<td>8333/3</td>
</tr>
<tr>
<td>Mucinous (&quot;colloid&quot;) carcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>8470/3</td>
</tr>
<tr>
<td>Signet ring adenocarcinoma</td>
<td>8490/3</td>
</tr>
<tr>
<td>Clear cell adenocarcinoma</td>
<td>8310/3</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>8012/3</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>8013/3</td>
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<tr>
<td>Combined large cell neuroendocrine carcinoma</td>
<td>8013/3</td>
</tr>
<tr>
<td>Basaloid carcinoma</td>
<td>8123/3</td>
</tr>
<tr>
<td>Lymphoepithelioma-like carcinoma</td>
<td>8082/3</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>8310/3</td>
</tr>
<tr>
<td>Large cell carcinoma with rhabdoid phenotype</td>
<td>8014/3</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
<td>8033/3</td>
</tr>
<tr>
<td>Pleomorphic carcinoma</td>
<td>8022/3</td>
</tr>
<tr>
<td>Spindle cell carcinoma</td>
<td>8032/3</td>
</tr>
<tr>
<td>Giant cell carcinoma</td>
<td>8031/3</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>8980/3</td>
</tr>
<tr>
<td>Pulmonary blastoma</td>
<td>8972/3</td>
</tr>
<tr>
<td>Carcinoid tumour</td>
<td>8240/3</td>
</tr>
<tr>
<td>Typical carcinoid</td>
<td>8240/3</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>8249/3</td>
</tr>
<tr>
<td>Salivary gland tumours</td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>8430/3</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>8200/3</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>8562/3</td>
</tr>
<tr>
<td>Preinvasive lesions</td>
<td></td>
</tr>
<tr>
<td>Squamous carcinoma <em>in situ</em></td>
<td>8070/2</td>
</tr>
<tr>
<td>Atypical adenomatous hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia</td>
<td></td>
</tr>
</tbody>
</table>

### Mesenchymal tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Morphology Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid haemangiendothelioma</td>
<td>9133/1</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>9120/3</td>
</tr>
<tr>
<td>Pleuropulmonary blastoma</td>
<td>8973/3</td>
</tr>
<tr>
<td>Chondroma</td>
<td>9220/0</td>
</tr>
<tr>
<td>Congenital peribronchial myofibroblastic tumour</td>
<td>8827/1</td>
</tr>
<tr>
<td>Diffuse pulmonary lymphangiomatosis</td>
<td></td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumour</td>
<td>8825/1</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>9174/1</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>9040/3</td>
</tr>
<tr>
<td>Monophasic</td>
<td>9041/3</td>
</tr>
<tr>
<td>Biphasic</td>
<td>9043/3</td>
</tr>
<tr>
<td>Pulmonary artery sarcoma</td>
<td>8800/3</td>
</tr>
<tr>
<td>Pulmonary vein sarcoma</td>
<td>8800/3</td>
</tr>
</tbody>
</table>

### Benign epithelial tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Morphology Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillomas</td>
<td></td>
</tr>
<tr>
<td>Squamous cell papilloma</td>
<td>8052/0</td>
</tr>
<tr>
<td>Exophytic</td>
<td>8052/0</td>
</tr>
<tr>
<td>Inverted</td>
<td>8053/0</td>
</tr>
<tr>
<td>Glandular papilloma</td>
<td>8260/0</td>
</tr>
<tr>
<td>Mixed squamous and glandular papilloma</td>
<td>8560/0</td>
</tr>
<tr>
<td>Adenomas</td>
<td></td>
</tr>
<tr>
<td>Alveolar adenoma</td>
<td>8251/0</td>
</tr>
<tr>
<td>Papillary adenoma</td>
<td>8260/0</td>
</tr>
<tr>
<td>Adenomas of the salivary gland type</td>
<td></td>
</tr>
<tr>
<td>Mucous gland adenoma</td>
<td>8140/0</td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>8940/0</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>8470/0</td>
</tr>
</tbody>
</table>

### Lymphoproliferative tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Morphology Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal zone B-cell lymphoma of the MALT type</td>
<td>9699/3</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>9680/3</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td>9766/1</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>9751/1</td>
</tr>
</tbody>
</table>

### Miscellaneous tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Morphology Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmatoma</td>
<td></td>
</tr>
<tr>
<td>Sclerosing hemangioma</td>
<td>8832/0</td>
</tr>
<tr>
<td>Clear cell tumour</td>
<td>8005/0</td>
</tr>
<tr>
<td>Germ cell tumours</td>
<td></td>
</tr>
<tr>
<td>Teratoma, mature</td>
<td>9080/0</td>
</tr>
<tr>
<td>Immature</td>
<td>9080/3</td>
</tr>
<tr>
<td>Other germ cell tumours</td>
<td></td>
</tr>
<tr>
<td>Intrapulmonary thymoma</td>
<td>8580/1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8720/3</td>
</tr>
</tbody>
</table>

### Metastatic tumours

1. Morphology code of the International Classification of Diseases for Oncology (ICD-O) (6) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
### TNM classification of the lung

#### T – Primary Tumour

**TX** Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

**T0** No evidence of primary tumour

**Tis** Carcinoma in situ

**T1** Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus, i.e., not in the main bronchus

**T2** Tumour with any of the following features of size or extent:
- More than 3 cm in greatest dimension
- Involves main bronchus, 2 cm or more distal to the carina
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

**T3** Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

**T4** Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; separate tumour nodule(s) in the same lobe; tumour with malignant pleural effusion

#### N – Regional Lymph Nodes

**NX** Regional lymph nodes cannot be assessed

**N0** No regional lymph node metastasis

**N1** Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

**N2** Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

**N3** Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

#### M – Distant Metastasis

**MX** Distant metastasis cannot be assessed

**M0** No distant metastasis

**M1** Distant metastasis, includes separate tumour nodule(s) in a different lobe (ipsilateral or contralateral)

#### Stage Grouping

<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult carcinoma</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage 0</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1, T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3</td>
<td>N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
</tr>
</tbody>
</table>

Notes:
1. The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.
2. Most pleural effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathological examinations of pleural fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, or T3.

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A help desk for specific questions about the TNM classification is available at http://www.uicc.org/tnm/

**The regional lymph nodes are the intrathoracic, scalene, and supraclavicular nodes.**
Geographical differences

Lung cancer is the most common cancer in the world today (12.6% of all new cancers, 17.8% of cancer deaths). There were an estimated 1.2 million new cases and 1.1 million deaths in 2000; the sex ratio (M:F) is 2.7. Lung cancer is relatively more important in the developed than developing countries as it accounts for 22% versus 14.6% of cancer deaths, respectively. In developed countries, geographic patterns are very much a reflection of past exposure to tobacco smoking [505].

In men, the areas with the highest incidence and mortality are Europe (especially Eastern Europe), North America, Australia/New Zealand, and South America. The rates in China, Japan and South East Asia are moderately high, while the lowest rates are found in southern Asia (India, Pakistan), and sub-Saharan Africa. In certain population subgroups (e.g. US blacks, New Zealand Maoris), incidence is even higher, and with current incidence rates, men in these two groups have about a 13% chance of developing a lung cancer before the age of 75.

In women, the geographic pattern is somewhat different, chiefly reflecting different historical patterns of tobacco smoking. Thus, the highest incidence rates are observed in North America and North West Europe (U.K., Iceland, Denmark) with moderate incidence rates in Australia, New Zealand and China.

Differences by histology

Almost all lung cancers are carcinomas (other histologies comprise well under 1%). In the combined data from the series published in Cancer Incidence in Five Continents [1554], small cell carcinomas comprise about 20% of cases and large cell /undifferentiated carcinomas about 9%. But for the other histological types, the proportions differ by sex: squamous cell carcinomas comprise 44% of lung cancers in men, and 25% in women, while adenocarcinomas comprise 28% cases in men and 42% in women. Incidence rates, and the estimated rates by histological subtype have been reported for 30 populations for which a relatively high proportion of cases had a clear morphological diagnosis [1554]. Figure 2 shows overall incidence rates, and the estimated rates by histological subtype for 30 populations for which a relatively high proportion of cases had a clear morphological diagnosis [1554]. Among men, only in certain Asian populations (Chinese, Japanese) and in North America (USA, Canada) does the incidence of adenocarcinoma exceed that of squamous cell carcinoma. In women, however, adenocarcinoma is the dominant histological type almost everywhere, except for Poland and England where squamous cell carcinomas predominate, and Scotland where small cell carcinoma is the most frequent subtype [1554]. Adenocarcinomas are particularly predominant in Asian females (72% cancers in Japan, 65% in Korea, 61% in Singapore Chinese). The differences in histological profiles are strongly influenced by the evolution of the epidemic of smoking-related lung cancer over time (see below).

Time trends

Because tobacco smoking is such a powerful determinant of risk, trends in lung cancer incidence and mortality are a reflection of population-level changes in smoking behaviour, including dose, duration, and type of tobacco used [685, 1206]. Study of time trends in lung cancer incidence or mortality by age group shows that the level of risk is closely related to birth cohort; in the U.K. and U.S. cohort-specific incidence is related to the smoking habits of the same generation [228,1152]. Thus, in men, the countries where smoking was first established were first to see a diminution in smoking prevalence, followed, in the same generations of men, by a decline in risk. Changes are first seen among younger age groups [1396], and as these generations of men reach the older age groups, where lung cancer is most common, a decline in overall incidence and mortality is seen. The U.K. was the first to show this incidence/mortality falling since 1970-74, followed by Finland, Australia, The Netherlands, New Zealand, the U.S.A., Singapore and, more recently, Denmark, Germany, Italy and Sweden [221].
most other countries there is a continuing rise in rates, and this is most dramatic in some countries of Eastern and Southern Europe (i.e. Hungary, Spain) (223,2042). In women, the tobacco habit has usually been acquired recently, or not at all. Thus, the most common picture in western populations is of rising rates, while in many developing countries (where female smoking generally remains rare), lung cancer rates remain very low. A few countries, where prevalence of smoking in women is declining, already show decreasing rates in younger women; in the U.K., where this trend is longest established, there is already a decline in overall incidence and mortality since about 1990 (221,2042).

There are, however, clear differences in time trends by histological type. In the U.S. (487,2027) squamous cell carcinoma reached maximum incidence in men in 1981, but the incidence of adenocarcinoma continued to rise (until about 1987 in black males, around 1991 in whites). As a result, adenocarcinoma is now the most frequent form of lung cancer in men in USA, while it had only constituted a small minority of cases (around 5%) in the 1950s (2027,2029). In contrast, the incidence of both histological types has continued to increase in females, though there is a suggestion that the incidence of squamous cell carcinomas had reached its maximum by 1990. These changes were related to specific birth cohorts, with maximum incidence in men in the 1925-29 cohort for squamous cell carcinomas and 1935-39 for adenocarcinomas, and in women some 10-20 years later (487,2241). Somewhat similar observations (increasing adenocarcinoma and decreasing squamous cell carcinoma) have been reported from the Netherlands (923), Japan (1843) and the U.K. (779). While part of this differential trend may be due to artefact (changes in classification and coding, improved diagnostic methods for peripheral tumours), the
incidence of adenocarcinomas is truly rising. In part, it may be due to an ever-increasing proportion of ex-smokers in the population, since the decline in risk of lung cancer on smoking cessation is faster for squamous cell tumours than for small cell carcinomas and adenocarcinomas [927, 1211]. It seems probable, too, that changes in cigarette composition, to low tar, low nicotine, filtered cigarettes, are also responsible, as switching to these “safer” brands results (in addicted smokers) to more intense smoking (more puffs, deeper inhalation), and hence greater exposure to these carcinogens in the peripheral lung where adenocarcinomas are more common [336,2177].

**Tobacco smoking**

There is overwhelming evidence that tobacco smoking is the major cause of lung cancer in most human populations [884]. The smoke inhaled by smokers of cigarettes and other tobacco products contains numerous carcinogens, as well as agents that cause inflammation.

An increased risk of lung cancer in smokers has been demonstrated in epidemiological studies conducted during the 1950s in the United States [2176] and United Kingdom [504], and the causal role of smoking has been recognized by public health and regulatory authorities since the mid-1960s. The geographical and temporal patterns of lung cancer today largely reflect tobacco consumption dating from two or three decades back. Because of the strong carcinogenic potency of tobacco smoke, a major reduction in tobacco consumption would result in the prevention of a large fraction of human cancers, including lung cancer (2155).

**Relative risk (RR)**

The risk among smokers relative to the risk among never-smokers is in the order of 8-15 in men and 3-10 in women. For those who smoke without quitting, recent relative risk estimates are as high as 20 to 30. The overall relative risk reflects the contribution of the different aspects of tobacco smoking: average consumption, duration of smoking, time since quitting, age at start, type of tobacco product and inhalation pattern [192].

**Risk attributed to tobacco smoking**

The proportion of lung cancer cases due to tobacco smoking has been estimated by comparing incidence (or mortality) rates in different areas, with the rates in non-smokers observed in large cohort studies [1553,1589]. Based on the worldwide incidence rates estimated for 2000. Worldwide, 85% of lung cancer in men and 47% of lung cancer in women is estimated as being the consequence of tobacco smoking.

**Dose and duration**

Several large cohort and case-control studies have provided detailed information on the relative contribution of duration and amount of cigarette smoking in excess lung cancer risk. Duration of smoking is the strongest determinant of risk, but this also increases in proportion to the number of cigarettes smoked [884]. The strong role of duration of smoking explains the observation that early age of starting is associated with a morbid lung cancer risk later in life.

**Effect of cessation of smoking**

An important aspect of tobacco-related lung carcinogenesis is the effect of cessation of smoking. The excess risk sharply decreases in ex-smokers after approximately 5 years since quitting; in some studies the risk after 20 or more years since cessation approaches that of never-smokers. However an excess risk throughout life likely persists even in long-term quitters [884]. Thus, smoking cessation is beneficial at all ages.

**Type of cigarettes and inhalation**

Some studies show a lower lung cancer risk among smokers of low-tar and low-nicotine cigarettes than among other smokers [192], but recent evidence suggests that low tar cigarettes are not less harmful, and may be worse. A similar effect has been observed among long-term smokers of filtered cigarettes, or compared to smokers of unfiltered cigarettes. Smokers of black (air-cured) tobacco cigarettes are at two- to three-fold higher relative risk of lung cancer than smokers of blond (flue-cured) tobacco cigarettes. Tar content, presence of filter and type of tobacco are interdependent; high-tar cigarettes tend to be unfiltered and, in regions where black and blond tobacco are used, more frequently made of black tobacco. A 1.5- to 3-fold difference in relative risk of lung cancer has been observed in several studies between smokers who deeply inhale cigarette smoke and smokers of comparable amounts who do not inhale or inhale slightly.

**Type of tobacco products**

Although cigarettes are the main tobacco product smoked in western countries, a dose-response relationship with lung cancer risk has been shown also for cigars, cigarillos and pipe, with a similar carcinogenic effect of these products [191]. A stronger carcinogenic effect of cigarettes than of cigars and pipe in some studies might arise due to different inhalation patterns or composition of cigars [902].

An increased risk of lung cancer has also been shown with the bidis widely smoked in India and water pipes in China [884]. Adequate epidemiological data are not available on lung cancer risk following consumption of other tobacco products, such as narghile in western Asia and northern Africa, and hooka in India.

**Lung cancer type**

Tobacco smoking increases the risk of all major histological types of lung cancer, but appears to be strongest for squamous cell carcinoma, followed by small cell carcinoma and adenocarcinoma. The association between adenocarcinoma and smoking has become stronger.
over time, and adenocarcinoma has become the most common type in many Western countries.

**Impact of sex and ethnicity**
Whilst earlier studies have suggested a difference in risk of lung cancer between men and women who have smoked a comparable amount of tobacco, more recent evidence does not support this notion: the carcinogenic effect of smoking on the lung appears to be similar in men and women.

The higher rate of lung cancer among Blacks in the United States as compared to other ethnic groups is likely explained by higher tobacco consumption (486). Indeed, there is no clear evidence of ethnic differences in susceptibility to lung carcinogenesis from tobacco.

**Involuntary smoking**
The collective epidemiologic evidence and biologic plausibility lead to the conclusion of a causal association between involuntary tobacco smoking and lung cancer risk in non-smokers (884). This evidence has been challenged on the basis of possible confounding by active smoking, diet or other factors, and of possible reporting bias. However, when these factors were taken into account, the association was confirmed (884). Several large-scale studies and meta-analyses consistently reported an increased risk of lung cancer in the order of 20–25% (190,603,754).

Additional evidence of a carcinogenic effect of involuntary smoking comes from the identification in people exposed to involuntary smoking of nicotine-derived carcinogenic nitrosamines such as NNK, of haemoglobin adducts of 4-aminobiphenyl, a carcinogen in tobacco smoke and of albumin adducts of polycyclic aromatic hydrocarbons (884). The comparison of levels of cotinine, the main metabolite of nicotine, suggests that exposure to involuntary smoking entails an exposure equivalent of 0.1-1.0 cigarettes per day; the extrapolation of the relative risk found in light smokers is consistent with the relative risk detected in people exposed to involuntary tobacco smoking.

**Occupational exposure**
The important role of specific occupational exposures in lung cancer etiology is well established in reports dating back to the 1950s (192). The table lists the occupational agents recognized as lung carcinogens by the International Agency for Research on Cancer (IARC). The most important occupational lung carcinogens include asbestos, crystalline silica, radon, mixtures of polycyclic aromatic hydrocarbons and heavy metals. Welding and painting were consistently associated with increased risk of lung cancer. However, the exact agent(s) in these jobs have not yet been identified. Although their contribution to the global burden of lung cancer is relatively small, occupational carcinogens are responsible for an important proportion of tumours among exposed workers. For most known occupational carcinogens, some synergism has been shown with tobacco smoking.

**Table 1.01**
Occupational agents and exposure circumstances classified by the IARC Monographs Programme (http://monographs.iarc.fr), as carcinogenic to humans, with the lung as target organ.

<table>
<thead>
<tr>
<th>Agents, mixture, circumstance</th>
<th>Main industry, use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic and arsenic compounds</td>
<td>Glass, metals, pesticides</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Insulation, filters, textiles</td>
</tr>
<tr>
<td>Beryllium and beryllium compounds</td>
<td>Aerospace</td>
</tr>
<tr>
<td>Bis(chloromethyl)ether</td>
<td>Chemical intermediate</td>
</tr>
<tr>
<td>Cadmium and cadmium compounds</td>
<td>Dye/pigment</td>
</tr>
<tr>
<td>Chromium(VI) compounds</td>
<td>Metal plating, dye/pigment</td>
</tr>
<tr>
<td>Dioxin (TCDD)</td>
<td>Chemical industry</td>
</tr>
<tr>
<td>Nickel compounds</td>
<td>Metallurgy, alloy, catalyst</td>
</tr>
<tr>
<td>Plutonium-239</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Radon-222 and its decay products</td>
<td>Mining</td>
</tr>
<tr>
<td>Silica, crystalline</td>
<td>Stone cutting, mining, glass, paper</td>
</tr>
<tr>
<td>Talc containing asbestiform fibers</td>
<td>Paper, paints</td>
</tr>
<tr>
<td>X- and gamma-radiation</td>
<td>Medical, nuclear</td>
</tr>
<tr>
<td>Coal-tar pitches</td>
<td>Construction, electrodes</td>
</tr>
<tr>
<td>Coal-tars</td>
<td>Fuel</td>
</tr>
<tr>
<td>Soots</td>
<td>Pigments</td>
</tr>
</tbody>
</table>

| Exposure circumstances             |                                           |
|------------------------------------|                                           |
| Aluminum production                |                                           |
| Coal gasification                  |                                           |
| Coke production                    |                                           |
| Haematite mining (underground)     |                                           |
| with exposure to radon             |                                           |
| Iron and steel founding            |                                           |
| Painter (occupational exposure)    |                                           |
Clinical features and staging

Signs and symptoms
Patients with lung cancer present with progressive shortness of breath, cough, chest pain/oppression, hoarseness or loss of voice, haemoptysis (mostly with squamous cell carcinoma). Pneumonia (often recidivant) is the presenting feature in many patients. Relative to other forms of non small cell lung cancer, adenocarcinoma is more often asymptomatic, being more frequently identified in screening studies or as an incidental radiologic finding [5,391]. Patients with small cell lung cancer (SCLC) differ in many ways from those with non-small cell lung cancer (NSCLC), in that they often present with symptoms referable to distant metastases (see below). About 10% of patients with SCLC present with superior vena cava syndrome. Stridor and haemoptysis are rare symptoms in patients with SCLC. Symptoms related to disseminated disease include weight loss, abdominal pain due to involvement of the liver, adrenals and pancreas, and pain due to bone (marrow) metastases. At presentation brain metastases are identified in 5-10% of patients with SCLC and neurological symptoms occur, but CNS involvement develops during the course of the disease in many patients and multiple lesions are usually found in autopsy in patients with CNS involvement [848,1048,1493].

Paraneoplastic symptoms
Paraneoplastic symptoms are common in lung cancer. Endocrine and paraneoplastic syndromes are less common in adenocarcinoma than in other histologic types of lung cancer. SCLC is characterized by neuroendocrine activity and some of the peptides secreted by the tumour mimic the activity of pituitary hormones. About 10% have abnormal ACTH like activity. Latent diabetes may become symptomatic but a Cushing syndrome is rare, probably because of short latency. Some SCLCs (15%) produce antidiuretic hormone (ADH) (Inappropriate ADH syndrome, Schwartz-Bartter syndrome) leading to water retention with oedema. The patients feel clumsy, tired and weak, and the plasma sodium is low. This is associated with an inferior prognosis [1523,1849]. Cerebrospinal metastases or meningeal seeding may cause neurological symptoms. Neurological symptoms may also be a paraneoplastic phenomenon, which might include sensory, sensorimotor, and autoimmune neuropathies and encephalomyelitis. The

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Table 1.02
Signs and symptoms of lung carcinoma. Approximately 5-20% of cases are clinically occult. Modified, from T.V. Colby et al. (391)

<table>
<thead>
<tr>
<th>Category</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td>Weight loss, loss of appetite, malaise, fever</td>
</tr>
<tr>
<td><strong>Local /direct effects</strong></td>
<td>From endobronchial growth and/or invasion of adjacent structures including chest wall and vertebral column Cough, dyspnoea, wheeze, stridor, haemoptysis Chest pain/back pain Obstructive pneumonia (+/- cavitation) Pleural effusion</td>
</tr>
<tr>
<td><strong>Extension to mediastinal structures</strong></td>
<td>Nerve entrapment: recurrent laryngeal nerve (hoarseness), phrenic nerve (diaphragmatic paralysis), sympathetic system (Horner syndrome), brachial plexopathy from “superior sulcus” tumours Vena cava obstruction: superior vena cava syndrome Pericardium: effusion, tamponade Myocardium: arrhythmia, heart failure Oesophagus: dysphagia, bronchoesophageal fistula Mediastinal lymph nodes: pleural effusion</td>
</tr>
<tr>
<td><strong>Metastatic disease</strong></td>
<td>Direct effects related to the organ(s) involved</td>
</tr>
<tr>
<td><strong>Paraneoplastic syndromes</strong></td>
<td>Dermatomyositis/polymyositis Clubbing Hypertrophic pulmonary osteoarthropath Encephalopathy Peripheral neuropathies Myasthenic syndromes (including Lambert-Eaton) Transverse myelitis Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td><strong>Hematologic/coagulation defects</strong></td>
<td>Disseminated intravascular coagulation Recurrent venous thromboses Nonbacterial thrombotic (marantic) endocarditis Anemia Dysproteinemia Granulocytosis Eosinophilia Hypoalbuminemia Leukomyeloblastosis Marrow plasmacytosis Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Miscellaneous (very rare)</strong></td>
<td>Henoch-Schönlein purpura Glomerulonephritis, Nephrotic syndrome Hypouricemia, Hyperamylasemia Amyloidosis Lactic acidosis Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>
symptoms may precede the primary diagnosis by many months, and might in some cases be the presenting complaint. They may also be the initial sign of relapse from remission. A specific example is the Lambert-Eaton myasthenic syndrome resulting in proximal muscular weakness that improves with continued use and hypoflexia and dysautonomy. Characteristic electromyographic findings confirm the diagnosis. This syndrome may also occur months before the tumour is disclosed [1497]. The weakness often improve when the tumour respond on therapy. Hypercalcemia is rare in SCLC, and almost pathognomic for squamous cell carcinoma.

Relevant diagnostic procedures
Fiberoptic bronchoscopy allows macroscopic examination of the respiratory tree up to most of the subsegmental bronchi and biopsies associated to bronchial aspiration and brushing. Biopsies of bone, liver, lymph node (mediastinoscopy), skin and adrenal gland may also be used for diagnosis if they are metastatically involved. Pulmonary function tests are performed if surgery seems possible. Serum tumour markers are not routinely recommended. Because of its central location squamous cell carcinoma is readily diagnosed by bronchoscopic biopsy and/or brush and/or sputum cytology [532]. Fluorescence bronchoscopy may be useful for assessing the extent of associated intraepithelial neoplasia. For peripheral lesions transthoracic CT guided fine needle aspiration biopsy is now generally preferred. Due to common central location, small cell carcinoma is often diagnosed via bronchoscopically retrieved histologic and cytologic samples and to a lesser extent sputum cytology. Small peripheral lesions are often subjected to fine needle aspiration biopsy, transbronchial biopsy, or sometimes wedge resection for initial diagnosis.

Staging of NSCLC
The internationally accepted TNM staging system is recommended. The stage of the disease is important for prognosis and treatment planning. Pathologic staging is based on the pathologic evaluation of sampled tissues according to the TNM system. For patients in whom surgical resection is attempted, there are surgical protocols for sampling the lymph node stations, including superior mediastinal nodes (numbered 1-4), aortic nodes (numbered 5 and 6), inferior mediastinal nodes (numbered 7-9) and nodes associated with the lobectomy specimen labeled “N1” nodes (numbered 10-14).

Staging of SCLC
The TNM staging classification is generally not utilized in SCLC, as it does not predict well for survival. SCLC is usually staged as either limited or extensive disease. The consensus report of the International Association for the Study of Lung Cancer (IASLC) modified the older VALG classification in accordance with the revised TNM system:

Limited disease
Disease restricted to one hemithorax with regional lymph node metastases including:

Table 1.03
Tumour markers found in the serum of patients with lung carcinoma. From refs [5,13,391].

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Serum proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Alpha fetoprotein (AFP)</td>
</tr>
<tr>
<td>MSH</td>
<td>Carcinoembryonic antigen (CEA)</td>
</tr>
<tr>
<td>hCG</td>
<td>Placental alkaline phosphatase (PAP)</td>
</tr>
<tr>
<td>HPL</td>
<td>Histaminase</td>
</tr>
<tr>
<td>PTH</td>
<td>L-dopa decarboxylase</td>
</tr>
<tr>
<td>ADH</td>
<td>Anti-Purkinje cell antibodies</td>
</tr>
<tr>
<td>NSE</td>
<td>Antineuronal nuclear antibodies (ANNA)</td>
</tr>
<tr>
<td>SER</td>
<td>Ferritin</td>
</tr>
</tbody>
</table>

Table 1.04
Imaging techniques in lung cancer staging. From T.V. Colby et al. (391).

<table>
<thead>
<tr>
<th>Conventional radiographs</th>
<th>Primary detection/characterization of parenchymal tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of main bronchi/tracheal involvement</td>
<td></td>
</tr>
<tr>
<td>Detection of chest wall invasion</td>
<td></td>
</tr>
<tr>
<td>Assessment of hilar and mediastinal invasion/adenopathy</td>
<td></td>
</tr>
<tr>
<td>Detection of obstructive atelectasis/pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Detection of pleural effusion</td>
<td></td>
</tr>
</tbody>
</table>

| CT | Assessment of main bronchi/tracheal involvement |
| Detection of chest wall invasion |
| Assessment of hilar and mediastinal invasion/adenopathy |
| Detection of liver, adrenal, brain metastases |

| MRI | Detection of chest wall invasion (particularly superior sulcus [tumours]) |
| Detection of mediastinal or spinal canal invasion |
| Assessment of hilar and mediastinal adenopathy in patients with equivocal CT examinations or contraindications to intravenous contrast media |
| Characterization of isolated adrenal masses |

| Ultrasound | Detection of pleural effusion/guidance for thoracentesis |
| Guidance for biopsy of peripheral lung or mediastinal mass |

| Gallium-67 scan | Detection of hilar and mediastinal adenopathy |
| Detection of distal metastases |

| Pulmonary angiography | Evaluation of central pulmonary artery invasion |
Hilar ipsilateral and contralateral
Mediastinal ipsilateral and contralateral
Supraclavicular ipsilateral and contralateral
Ipsilateral pleural effusion (independent of cytology)

Limited disease is equivalent to stage I-III of the TNM system.

Extensive disease
All patients with sites of disease beyond the definition of limited disease, equivalent to stage IV in the TNM system.

Staging Procedures
The staging procedures have the primary goal to distinguish patients who are candidates for surgery, those with loco-regional disease, and those with metastatic disease.

Standard procedures include chest X-ray, general physical examination, bronchoscopy and blood samples. If findings at these procedures do not preclude surgery or radiotherapy, staging proceeds with a CT-scan of chest and upper abdomen. Staging stops here if the CT scan shows definitive signs of inoperable disease such as tumour invasion of the mediastinum or distant metastases to the liver or the adrenals. If, however, surgery seems possible, lymph nodes in the mediastinum must be examined for metastatic deposits. If none of the lymph nodes are enlarged (greatest diameter >1.5 cm) and the tumour is proven to be of the squamous cell type, lymph node biopsies can be omitted; otherwise a preoperative mediastinoscopy with biopsies is recommended. In recent years this invasive procedure has been enhanced by PET scan, although the accuracy (diagnostic sensitivity and specificity) of this imaging procedure has not yet been fully validated in lung cancer. If PET is not available, ultrasonography is still a very helpful procedure and allows fine needle biopsies from suspect lesions in abdominal sites plus other deeply located structures such as axillary lymph nodes and the thyroid gland. SCLC is characterized by a rapid dissemination to extrathoracic organs. Autopsy studies performed 1 month after surgical resection showed that 63% (12 of 19 patients) with SCLC had distant metastases compared to 14-40% of patients with NSCLC [848].

Staging of SCLC includes bronchoscopy, chest X-ray, chest CT scan, upper abdominal CT scan or ultrasonography plus a bone marrow examination and/or a bone scintigram. Bone scintigrams are still used but this procedure will probably be left with the increasing availability of PET scanners. Finally, magnetic resonance imaging (MRI) scans are useful if bone metastases or central nervous system metastases are suspected. Patients with neurological symptoms should have a cranial CT or MR scan.

Staging of SCLC will prove extensive stage disease in about 65% of the patients due to metastases to one or more of the following sites: the contralateral lung (10%), skin or distant lymph nodes (10%), brain (10%), liver (25%), adrenals (15%), bone marrow (20%), retroperitoneal lymph nodes (5%), or pancreas (5%). Osteolytic bone metastases and hypercalcaemia are rarely seen, but are almost pathognomonic for squamous cell carcinoma. Enlarged adrenals might represent metastases but can also be a glandular hypertrophy due to ectopic ACTH secretion from the tumour, which is observed in about 10% of patients with SCLC [780,847,887,1849].

Table 1.05
Chest radiographic findings at presentation according to histologic type of lung carcinoma. From ref [391].

<table>
<thead>
<tr>
<th>Radiographic Feature</th>
<th>Squamous Cell Carcinoma</th>
<th>Adenocarcinoma</th>
<th>Small Cell Carcinoma</th>
<th>Large Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule &lt;or= 4 cm</td>
<td>14%</td>
<td>46%</td>
<td>21%</td>
<td>18%</td>
</tr>
<tr>
<td>Peripheral location</td>
<td>29%</td>
<td>65%</td>
<td>26%</td>
<td>61%</td>
</tr>
<tr>
<td>Central location</td>
<td>64%</td>
<td>5%</td>
<td>74%</td>
<td>42%</td>
</tr>
<tr>
<td>Hilar/perihilar mass</td>
<td>40%</td>
<td>17%</td>
<td>78%</td>
<td>32%</td>
</tr>
<tr>
<td>Cavitation</td>
<td>5%</td>
<td>3%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Pleural/cHEST wall involvement</td>
<td>3%</td>
<td>14%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Hilar adenopathy</td>
<td>38%</td>
<td>19%</td>
<td>61%</td>
<td>32%</td>
</tr>
<tr>
<td>Mediastinal adenopathy</td>
<td>5%</td>
<td>9%</td>
<td>14%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 1.06

<table>
<thead>
<tr>
<th>Stage</th>
<th>Squamous</th>
<th>Adenocarcinoma</th>
<th>Small cell</th>
<th>Large cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>21.5%</td>
<td>22.2%</td>
<td>8.2%</td>
<td>15.2%</td>
</tr>
<tr>
<td>Regional</td>
<td>38.5%</td>
<td>33.1%</td>
<td>26.1%</td>
<td>31.5%</td>
</tr>
<tr>
<td>Distant</td>
<td>25.2%</td>
<td>35.9%</td>
<td>52.8%</td>
<td>40.3%</td>
</tr>
<tr>
<td>Unstaged</td>
<td>14.8%</td>
<td>8.8%</td>
<td>12.8%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

Table 1.07
Stage and survival in NSCLC*. Modified, from [232].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 yr</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
</tr>
<tr>
<td>cIA (n = 687)</td>
<td>71</td>
</tr>
<tr>
<td>cIB (n = 1189)</td>
<td>46</td>
</tr>
<tr>
<td>cIIA (n = 29)</td>
<td>38</td>
</tr>
<tr>
<td>cIIB (n = 357)</td>
<td>33</td>
</tr>
<tr>
<td>cIIIA (n = 511)</td>
<td>18</td>
</tr>
<tr>
<td>cIIIB (n = 1,030)</td>
<td>7</td>
</tr>
<tr>
<td>cIV (n = 1,427)</td>
<td>2</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
</tr>
<tr>
<td>pIA (n = 511)</td>
<td>80</td>
</tr>
<tr>
<td>pIB (n = 549)</td>
<td>67</td>
</tr>
<tr>
<td>pIIB (n = 76)</td>
<td>66</td>
</tr>
<tr>
<td>pIIIA (n = 375)</td>
<td>46</td>
</tr>
<tr>
<td>pIIIB (n = 399)</td>
<td>32</td>
</tr>
</tbody>
</table>

* Includes patients with stages IA, IB, IIA, IIB, IIIA, IIIB, IV, N2, N3.
Tissue collection and interpretation

Optimal tissue collection is important for a precise classification of lung tumours. Several diagnostic approaches are available, including sputum cytology, bronchoalveolar lavage, bronchoscopic biopsies, brushing and washing, thoracoscopic biopsies, resected surgical material, and needle biopsies as well as pleural cytology. Rapid fixation and minimal trauma are important. Small specimens may not show differentiation when the tumour is excised; it is, therefore, advisable to limit categorization to SCLC and NSCLC. The current classification is largely based on standard H&E sections. Some lung carcinomas remain unclassified. They usually fall into the “non-small cell carcinoma” category or are cases where small biopsies or cytology specimens preclude definitive histologic typing.

Histologic heterogeneity

Lung cancers frequently show histologic heterogeneity, with variation in appearance and differentiation from microscopic field to field and from one histologic section to the next [1676]. Almost 50% of lung carcinomas exhibit more than one of the major histologic types. This fact has important implications for lung tumour classification and must be kept in mind, especially when interpreting small biopsies. The designation of a minimum requirement such as 10% for the adenocarcinoma and squamous cell carcinoma components of adenocarcinoma or the spindle and/or giant cell carcinoma component of pleomorphic carcinomas set in the 1999 WHO classification are maintained in this classification, recognizing that they are an arbitrary criterion since the extent of histologic sampling will influence classification of such tumours [584,2024]. Although these tumours may be suspected on small specimens such as bronchoscopic or needle biopsies, a definitive diagnosis requires a resected specimen. If this problem arises in a resected tumour, additional histologic sections may be helpful. Nevertheless, defining a specific percentage for a histologic component can be a useful criterion for entities such as adenosquamous carcinoma and pleomorphic carcinoma.

The concept of pulmonary neuroendocrine tumours

Tumours with neuroendocrine morphology

Neuroendocrine tumours of the lung are a distinct subset of tumours, which share morphologic, ultrastructural, immunohistochemical and molecular characteristics and although these tumours are classified into different morphologic categories within the WHO classification, certain concepts relating specifically to neuroendocrine tumours merit discussion. The major categories of morphologically identifiable neuroendocrine tumours are small cell carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), typical carcinoid (TC), and atypical carcinoid (AC). Historical terms such as well-differentiated neuroendocrine carcinoma, neuroendocrine carcinoma (grade 1-3), intermediate cell neuroendocrine carcinoma, malignant carcinoid and peripheral small cell carcinoma resembling carcinoid, should be avoided [1999].

With regard to nomenclature, the terms typical and atypical carcinoid are preferred for a number of reasons. Clinicians are familiar with these diagnostic terms and the tumours share a distinctive basic microscopic appearance, resembling carcinoids found at other body sites. Spindle cell, oncocytic and melanocytic patterns and stromal ossification occur in both typical and atypical carcinoids. Patients with typical and atypical carcinoids are also significantly younger than those with SCLC and LCNEC. Within the high-grade neuroendocrine tumours, LCNEC and SCLC are morphologically distinct and it has not been proven that chemotherapy used for SCLC is effective for patients with LCNEC.

With regard to distinguishing the four main types of neuroendocrine tumours, all show varying degrees of neuroendocrine morphologic features by light microscopy including organoid nesting, palissading, a trabecular pattern, and rosette-like structures, with the cardinal distinguishing features being mitotic activity and the presence or absence of necrosis. For mitotic activity, Arrigoni, et al. [75] originally proposed that atypical carcinoids had between 5-10 mitoses per 2 mm² (10 high power fields – see below for mitosis counting method) [2028]. The presence of necrosis also distinguishes atypical from typical carcinoid. Cytologic atypia is unreliable as a diagnostic feature.

A mitotic count of 11 or more mitoses per 2 mm² (10 high power fields) is the main criterion for separating LCNEC and SCLC from atypical carcinoid [2028]. LCNEC and SCLC usually have very high mitotic rates, with an average of 70-80 per 2 mm² (10 high power fields in some microscope models). LCNEC and SCLC also generally have more extensive necrosis than atypical carcinoid. LCNEC are separated from SCLC using a constellation of criteria, which include larger cell size, abundant cytoplasm, prominent nucleoli, vesicular or coarse chromatin, polygonal rather than fusiform shape, less prominent nuclear molding and less conspicuous deposition of hematoxylin-stained material (DNA) in blood vessel walls. LCNEC cells more closely resemble those of a large cell carcinoma than a carcinoid tumour. Mitoses should be counted in the areas of highest mitotic activity and the fields counted should be filled with as many viable tumour cells as possible. Since the area viewed in a high power field varies considerably depending on the microscope model, we define the mitotic range based on the area of viable
atypical carcinoids are non-smokers while virtually all patients with SCLC and LCNEC are cigarette smokers. In contrast to SCLC and LCNEC, both typical and atypical carcinoids can occur in patients with Multiple Endocrine Neoplasia (MEN) type I [464]. In addition, neuroendocrine cell hyperplasia with or without tumourlets is relatively frequent in both typical and atypical carcinoids but not in LCNEC or SCLC. Histologic heterogeneity with other major histologic types of lung carcinoma (squamous cell carcinoma, adenocarcinoma, etc.) occurs with both SCLC and LCNEC but not with typical or atypical carcinoids [2024]. In contrast to large cell neuroendocrine carcinoma, most typical and atypical carcinoids are readily diagnosed by light microscopy without the need for immunohistochemistry or electron microscopy. There are also genetic data indicating that SCLC is closer to LCNEC than to the TC and AC, in that abnormalities in many genetic markers such as p53 [1516,1622], bcl2/bax [217], cyclin D1 [746], RB loss and LOH at 3p [726] are seen in a high percentage of both SCLC and LCNEC with minimal and intermediate percentages of TC and AC showing abnormalities, respectively (see below).

There is substantial reproducibility (kappa statistic of .70) for this subclassification scheme. The greatest reproducibility is seen with SCLC and typical carcinoid. The most common disagreements involve LCNEC vs SCLC, followed by typical carcinoid vs atypical carcinoid, and atypical carcinoid vs LCNEC. Additional research on atypical carcinoid and LCNEC is needed to better define their clinical characteristics and optimal therapy.

Interestingly, despite separation into four main groups, there is increasing evidence that TC and AC are more closely associated to each other than to LCNEC and SCLC. Clinically, approximately 20-40% of patients with both typical and atypical carcinoids are non-smokers

### Table 1.08
Criteria for diagnosis of neuroendocrine tumours. From W.D. Travis et al. (2024)

<table>
<thead>
<tr>
<th><strong>Typical carcinoid</strong></th>
<th>A tumour with carcinoid morphology and less than 2 mitoses per 2 mm² (10 HPF), lacking necrosis and 0.5 cm or larger</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atypical carcinoid</strong></td>
<td>A tumour with carcinoid morphology with 2-10 mitoses per 2 mm² (10 HPF) OR necrosis (often punctate)</td>
</tr>
</tbody>
</table>
| **Large cell neuroendocrine carcinoma** | 1. A tumour with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae)  
2. High mitotic rate: 11 or greater per 2 mm² (10 HPF), median of 70 per 2 mm² (10 HPF)  
3. Necrosis (often large zones)  
4. Cytoplasmic features of a non-small cell carcinoma (NSCLC): large cell size, low nuclear to cytoplasmic ratio, vesicular, coarse or fine chromatin, and/or frequent nucleoli. Some tumours have fine nuclear chromatin and lack nucleoli, but qualify as NSCLC because of large cell size and abundant cytoplasm.  
5. Positive immunohistochemical staining for one or more NE markers (other than neuron specific enolase) and/or NE granules by electron microscopy. |
| **Small cell carcinoma** | Small size (generally less than the diameter of 3 small resting lymphocytes)  
1. Scant cytoplasm  
2. Nuclei: finely granular nuclear chromatin, absent or faint nucleoli  
3. High mitotic rate (11 or greater per 2 mm² (10 HPF), median of 80 per 2 mm² (10 HPF)  
4. Frequent necrosis often in large zones |

### Table 1.09
The spectrum of neuroendocrine (NE) proliferations and neoplasms. From W.D. Travis et al. (2024)

| **Neuroendocrine cell hyperplasia and tumourlets** | NE cell hyperplasia  
NE cell hyperplasia with fibrosis and/or inflammation  
NE cell hyperplasia adjacent to carcinoid tumours  
Diffuse idiopathic NE cell hyperplasia with or without airway fibrosis  
Tumourlets |
| **Tumours with NE morphology** | Typical carcinoid  
Atypical carcinoid  
Large cell neuroendocrine carcinoma  
Small cell carcinoma |
| **Non-small cell carcinomas with NE differentiation** |  
| **Other tumours with NE properties** | Pulmonary blastoma  
Primitive neuroectodermal tumour  
Desmoplastic round cell tumour  
Carcinomas with rhabdoid phenotype  
Paraganglioma |
Genetic and molecular alterations

Molecular and pathological diversity of lung cancers

Lung cancers result from complex, genetic and epigenetic changes characterized by stepwise malignant progression of cancer cells in association with accumulation of genetic alterations. This process, referred to as multistep carcinogenesis, develops through the clonal evolution of initiated lung cells. Initiation consists in the acquisition of defined genetic alterations in a small number of genes that confer a proliferative advantage that facilitates progression towards invasive carcinoma. Many environmental carcinogens present in tobacco smoke or in industrial pollutants can act as initiators for bronchial or bronchiolar-alveolar epithelial cells [807,2145]. These carcinogens often have a global effect on the entire bronchial tree, resulting in the frequent occurrence of several primary lesions within the same, exposed organ. This observation has led to the concept of field carcinogenesis. Over the past 25 years, evidence has accumulated for stepwise accumulation of genetic changes in all major histological types of lung cancers. These changes include allelic losses (LOH), chromosomal instability and imbalance, mutations in oncogenes and tumor suppressor genes, epigenetic gene silencing through promoter hypermethylation and aberrant expression of genes involved in the control of cell proliferation [564,687,1235,1323,2209]. Although many of these genetic changes occur independently of histological type, their frequency and timing of occurrence with respect to cancer progression is different in small cell lung carcinomas (SCLC), that may originate from epithelial cells with neuro-endocrine features, and non-small cell lung carcinomas (NSCLC), that originate from bronchial or alveolar epithelial cells. Furthermore, a number of genetic and epigenetic differences have been identified between squamous cell carcinoma (SCC), that arises from bronchial epithelial cells through a squamous metaplasia/dysplasia process, and adenocarcinoma (ADC), that derives from alveolar or bronchiolar epithelial cells [2017,2209].

Genetic changes frequent in all major histological types

Invasive lung carcinoma display multiple genetic alterations, such as LOH at many different loci including 3p14-23 [220,1210,1446], 8q21-23 [2159], 9p21 [670,1299], 13q, 17q, 18q and 22p [687,1268,1996,2209]. However, three frequent aberrations emerge as common changes in all histological types of lung cancers.

TP53 mutations

The most frequent one is mutation in the tumor suppressor gene TP53, encoding the p53 protein that plays multiple, anti proliferative roles, in particular in response to genotoxic stress [881,1947]. Inactivating TP53 mutations (mostly missense mutations) are detected in up 50% of NSCLC and in over 70% of SCLC [1591]. In both SCC and ADC, there is evidence that mutation can occur very early in cancer progression and that their prevalence increases from primary, in situ lesions to advanced, metastatic carcinomas.

Retinoblastoma pathway

The second most common alteration is inactivation of the pathway controlling RB1 (retinoblastoma gene, 13q11), a suppressor gene encoding the Rb protein that acts as a “gatekeeper” for the G1 to S transition of cell cycle [215,2209]. The most common mechanisms for inactivation of this pathway are loss of RB1 expression, silencing of INK4 (also termed CDKN2a, encoding p16) through LOH (9p21) and promoter hypermethylation, and overexpression of CCND1 (encoding cyclin D1), sometimes consecutive to gene amplification [112]. These three genes act in a sequential manner within the signalling cascade that controls Rb inactivation by phosphorylation. There is a constant inverse correlation between loss of Rb protein, inactivation of p16 and overexpression of cyclin D1, consistent with the notion that these events have essentially similar functional consequences [215]. Interestingly, the mechanism by which this pathway is altered differs between NSCLC and SCLC. Loss of Rb protein expression is detectable in over 80-100% of high grade neuroendocrine tumors, most of them retaining normal p16 and cyclin D1 expression [189,670]. In contrast, loss of Rb protein is less common in NSCLC (15%) but inactivation of INK4 is present in up to 70% of the cases, whereas amplification of CCND1 is detectable in a significant proportion of SCC (10%) [215,2209]. It should also be noted that the INK4 gene locus contains a reading frame encoding another protein, p14arf, which is different from p16 but also plays roles in growth suppression. Initial studies suggested that the expression of p14arf is often lost in SCLC, suggesting that alterations of the INK4 locus may have functional consequences other than deregulation of the cascade controlling RB1 [669]. Recent reports indicate that p14arf methylation does not play a role in the development of SCLC and NSCLC [1550,1746].

LOH 3p

The third common genetic event that occurs in all lung cancers irrespective of their histological type is LOH on chromosome 3p, detectable in up to 80% of NSCLC as well as SCLC [220,1210,1446]. This region encompasses several potential tumor suppressor genes, including FHIT, RASSF1 and SEMA3B [1167,1183,2209]. The FHIT gene (Fragile Histidine Triad) is located in a highly fragile chromosomal site where it is particularly prone to partial deletion as a result of direct DNA damage by carcinogens present in tobacco smoke [895]. FHIT encodes a protein with ADP hydro sylase activity that has been proposed to have various intracellular functions, including regulation of DNA replication and signalling stress responses [112]. RASSF1 encodes a protein involved in the control of the activity of members of the Ras family of oncogenes. SEMA3B encodes semaphorin 3B, a member of a family of genes encoding secreted proteins with critical roles in development of neuronal and epithelial tissues. The contributions of these genes to the development of lung cancers is still poorly under-
Similarly, LOH on chromosome 5q are infrequent in non-metastatic NSCLC but are frequent at early stages of SCLC but are frequent at early stages of SCLC but are infrequent in non-metastatic NSCLC (2209). The target gene on chromosome 5q is still not identified.

The gradual increase of molecular abnormalities along the spectrum of neuroendocrine lung tumours strongly supports the grading concept of typical carcinoid as low grade, atypical carcinoid as intermediate grade and large cell neuroendocrine carcinoma and small cell lung carcinoma as high-grade neuroendocrine lung tumours. MEN1 gene mutation and LOH at the MEN1 gene locus 11q13 was recently demonstrated in 65% of sporadic atypical carcinoids [463] and was not found in high grade neuroendocrine tumours [464].

Although epigenetic silencing of genes, mainly through promoter hypermethylation, is widespread in all forms of lung cancers, the methylation profile of tumors varies with histological type. SCLC, carcinoids, SCC and ADC have unique profiles of aberrantly methylated genes. In particular, the methylation rates of APC, CDH13 and RARb are significantly higher in ADC than in SCC [2017].

Several striking differences also exist at the level of gene expression. The p63 protein, encoded by TP63, a member of the TP53 gene family located on chromosome 3q, is highly expressed and sometimes amplified in SCC but not in other histological types [826]. This protein plays a role in squamous differentiation and its presence may be required for the development of SCC. As there is no squamous epithelium in the normal lung, deregulation of p63 expression may be a fundamental event in the pathogenesis of the metaplasia that precedes SCC.

DNA adducts and mutagen fingerprints
About 90% of lung cancers in Western countries, and a rapidly growing number of cancers in non-western countries, are caused by smoking. Tobacco smoke is a mixture of over 4800 chemicals, including over 60 that were classified as carcinogens by the International Agency for Research on Cancer. They belong to various classes of chemicals, including polycyclic aromatic hydrocarbons (PAH), aza-arenes, N-nitrosamines, aromatic amines, heterocyclic aromatic amines, aldehydes, volatile hydrocarbons, nitro compounds, miscellaneous organic compounds, and metals and other inorganic compounds [807,1591]. Although the dose of each carcinogen per cigarette is quite small, the cumulative dose in a lifetime of smoking can be considerable. In target cells, most of these carcinogens are converted to intermediates by Cytochrome P450 enzymes, which catalyze the addition of an oxygen to the carcinogen, increasing its water solubility. The resulting metabolites are readily converted to excretory soluble forms by glutathione S-transferase, providing an efficient detoxification mechanism. However, during this process, electrophilic (electron-deficient) intermediates are formed, that are highly reactive with DNA, resulting in the formation of DNA adducts [2145].

Cells are equipped with elaborate systems to eliminate DNA adducts from the genome, including the nucleotide excision repair pathway (NER, that preferentially eliminates so-called bulky DNA adducts consisting of large chemical groups covalently attached to DNA), the base excision repair systems (BER), that removes DNA bases altered by attachment of small chemical groups or fragmented by ionizing radiation or oxidation, as well as a specialized, direct repair system that acts through the enzyme O6-methylguanine DNA methyltransferase (O6MGMT), which repairs the miscoding methylated base O6-methylguanine. Many of these enzymes are polymorphic.
in the human population. Thus, the balance between metabolic activation, detoxification and repair varies among individuals and is likely to affect cancer risk (1570,1970).

Carcinogens can damage DNA in specific ways depending upon their chemical nature (881). TP53 mutations are more frequent in lung cancers of smokers than in non-smokers (1591,2058). Studies of data compiled in the IARC TP53 mutation database (see www.iarc.fr) have shown that the pattern of TP53 mutations in lung cancers of smokers is unique, with an excess of transversions at G bases (G to T, 30%) that are uncommon in non-tobacco-related cancers (9%). In lung cancers of non-smokers, the overall prevalence of G to T transversions is 13%. In subjects with the highest reported exposure to tobacco, G to T transversions represent almost 50% of all mutations. These transversions preferentially occur at a limited number of codons (157, 158, 245, 248, 273) that have been experimentally identified as sites of adduction for metabolites of benzo(a)pyrene, one of the major PAH in tobacco smoke (477,1591). Mutations at these codons can be found in histologically normal lung tissues adjacent to cancers in smokers, as well as in lung tissues of smokers without lung cancers (880). This observation provides direct evidence that some tobacco compounds can act as carcinogens in lung cells. Comparisons between histological types reveal an excess of G to T transversions for all histological types in smokers, implying a general, causal effect of tobacco carcinogens (1591). However, there are considerable differences in TP53 mutation patterns according to histological type and, significantly, gender. Interestingly, the vast majority of lung cancers with TP53 mutations in non-smokers are adenocarcinomas occurring in women (1588,2020). Thus, the difference in G to T transversions between smokers and non-smokers is mainly due to female non-smokers having a low frequency of these transversions compared to female smokers.

Several other genes also show different rates of alterations in smokers and non-smokers. These genes include mutations in KRAS, that are more frequent in smokers (30%) than in non-smokers (5%), as well as hypermethylation of INK4 and FHIT genes (1236, 2017,2058, 2162).

**Impact of genetic studies on lung cancer therapy**

Despite accumulating knowledge on the specificity of the genetic pathways leading to different histological types of lung cancers, there is still little understanding of how these events cooperate with each other in cancer progression. One of the main challenges remains the identification of events that are predictive of the rate of progression towards metastatic cancer. However, the identification of a limited number of genes that are often altered at early stages of lung cancers (such as methylation of INK4 or of genes on 3p, mutations in TP53 and in KRAS) represent an interesting opportunity for developing approaches for early detection, for example using material from bronchial lavages and expectorations (1322). In the future, many of these alterations may provide interesting targets for designing new, alternative therapeutic strategies.
Genetic susceptibility

The risk of lung cancer in subjects with a family history of this tumour is about 2.5 (1781). Given the strong link between exposure to carcinogens (mostly tobacco smoke) and lung cancer, the study of genetic polymorphisms as possible risk modifiers has focused on enzymes involved in Phase I/xenobiotic metabolism, DNA-repair and the effects on nicotine addiction.

Phase I
CYP1A1 bioactivates polycyclic aromatic hydrocarbons (PAH). Several variant alleles are known (http://www.imm.ki.se/CYPalleles/cyp1a1.htm). Two closely linked polymorphisms, Mspl at 6235 nt and I462V, have been extensively studied in relation to lung cancer, yielding inconsistent results. In a pooled analysis an OR of 2.36 (95% confidence interval (CI) 1.16 - 4.81) for the Mspl homozygous variant genotype in Caucasians was found [2086]. The OR was not significant for this variant in a meta-analysis including both Caucasians and Asians [870]. The frequencies of CYP1A1 allelic variants are substantially lower in Caucasians than in Asians and the functional significance has not been convincingly shown. PAH-exposed individuals with variant CYP1A1 alleles had higher levels of PAH-DNA adducts in WBC and lung tissue [37], particularly in conjunction with GSTM1 null. CYP1B1 present in lung, bioactivates many exogenous procarcinogens including PAH and also estrogens. There is polymorphic inducibility in lymphocytes (2004). Five SNPs result in amino acid substitutions, of which 2 are located in the heme binding domain (1998). Ser119 has been shown to be associated with SCC in Japanese [2111]. Ethnic variation in allelic frequency has been demonstrated.

CYP2D6 metabolizes clinically important drugs and also the tobacco specific nitrosamine, NNK (poor substrate). Among at least 40 SNPs and different allelic variants, many lead to altered CYP2D6 activity. The much-studied association between lung cancer and polymorphic expression of CYP2D6 has remained inconsistent: A meta-analysis reported a small decrease in lung cancer risk for the poor metaboliser phenotype, which the genotype analysis could not confirm [1696].

CYP2A13, a highly polymorphic gene, is expressed in the human lung and efficiently bioactivates NNK. Among several variant alleles, only one SNP is located in the coding region, leading to an A257C amino acid change; the 257C variant was less active than the wild-type protein. Inter-ethnic differences in allelic variant frequencies have been found [2239A]. CYP2A6 is also important for the bioactivation of NNK. There are several polymorphisms for this gene, with some positive studies in Japanese [73] and Chinese [1968], but overall the data are conflicting [1208,1642]. The microsomal epoxide hydrolase (MEH3) may affect lung cancer risk based on pooled analysis of 8 studies (His/His OR = 0.70, CI = 0.51-0.96), which was not observed in a meta-analysis of the same studies [1154]. There are some positive studies for MEH4 [1303, 2175,2240].

Phase II
Glutathione-S-transferases (GST) detoxify tobacco carcinogens such as PAH by conjugation. Individuals lacking GSTM1 (null polymorphism e.g. in 50% of Caucasians) appear to have a slightly elevated risk of lung cancer: A meta-analysis of 43 studies found an OR of 1.17 (CI 1.07 - 1.27) for the null genotype. When the original data from 21 case-control studies (9500 subjects) were analysed no evidence of increased lung cancer risk among null carriers, nor an interaction between GSTM1 genotype and smoking was found [144]. A base-substitution polymorphism in GSTM1 seems to affect squamous cell cancer risk in non-smokers [1228]. GSTM1 genotype affects internal carcinogen dose levels: DNA adduct levels were higher in lung tissue and white blood cells from GSTM1 null individuals exposed to PAH [37]. Because adduct levels are affected by a range of genetic polymorphisms [697] results from all GSTM1 studies were not consistent. Among two GST-Pi polymorphisms studied, one in exon 6 has been associated with lung cancer risk [1891,2106], although other studies did not [944, 1447]. Studies of environmental tobacco smoke further support a role of this polymorphism in lung cancer [1312]. Studies on a deletion polymorphism in GST-T1 are mostly negative [944,1447,1891] or contradictory for the “at-risk” allele [869]. A role for younger persons with lung cancer has been suggested [1943]. N-Acetyltransferases (NAT) 1 and 2 with distinct but overlapping substrate specificities activate and/or detoxify aromatic amines. From 11 studies on lung cancer ORs, fast acetylation vs. slow NAT2 ranged from 0.5 – 3.0; most studies found no significant association, but in some, fast NAT2 acetylators were at increased risk [2243]. The NAT1*10 allele, (a putative fast allele) has inconsistently been associated with an increased risk for lung cancer.

Myeloperoxidase (MPO): 11 Lung cancer case-control studies have reported ORs from 0.54 - 1.39 for the G/A genotype, 0.20 - 1.34 for the A/A genotype and 0.58 - 1.27 for the (G/A + A/A) genotypes. A large study did not find the A-allele to be protective for lung cancer, while a meta-analysis (excluding this study) showed marginally significant inverse correlations of the A/A and/or G/A genotype prevalence and lung cancer risk [576]. Carriers of the A-allele had a significantly reduced capacity to bioactivate B(a)P into its epoxide in coal tar treated skin [1678].

DNA repair genes
DNA repair genes are increasingly studied, for example PADPRP (193bp deletion), XPD (Codons 751, 312), AGT (Codons 143, 160), XRCC3 (Codon 241), and XRCC1 (codons 194, 280 or 399). As most study sizes were small, only a
few were statistically significant, including an OR of 1.86 (CI 1.02 - 3.4) for XPD codon 312 (genotype AA) [260], an OR of 1.8 (1.0 - 3.4) for XRCC1 codon 280 (AA+AG) [1641], and an OR of 2.5 (1.1 - 5.8) for XRCC1 Codon 399 (AA) [500A]. In the latter study there was inconsistency among ethnic groups (Caucasians OR 3.3, 1.2 - 10.7; Hispanics OR 1.4, 0.3 - 5.9). In one study [744] a strong effect of PADPRP (193bp deletion) was observed only in African-Americans (OR 30.3, 1.7 - 547) and in Hispanics (OR 2.3, 1.22 - 4.4), but not in Caucasians (OR 0.5, 0.1 - 1.9); the biological plausibility is hard to assess [160, 161].

hOGG1, which repairs oxidative DNA damage (8-oxo-dG) [1045] has been studied. Functional effects of the variants and a few positive lung cancer associations have been reported [914,1145,1899]. In the p53 gene there is a genetic polymorphism in codon 72, and several haplotypes are known. A functional effect by these variants has not been described, but an association with lung cancer risk was found [169,554,978,1193]. The risk was more elevated in persons, when combined with GSTM1 null [1193,2003] and GST Pi [1313] variants. Also, an interaction with CYP1A1 has been reported [978].

Phenotypic DNA repair studies found consistently an increased risk of lung cancer associated with putative impaired repair functions [160,161].

**Smoking behaviour and addiction**

Evidence for a genetic component for nicotine addiction (an obvious risk factor for lung cancer) comes from twin studies [291,805,806]. Most polymorphism studies have focused on dopamine neuronal pathways in the brain, including genes coding for dopamine receptors, dopamine transporter reuptake (SL6A3) and dopamine synthesis. Many of these polymorphic genes result in altered protein function, but the data for any specific candidate polymorphism are not consistent [396,1163-1166,1482,1715,1800,1864].

**Combinations**

The risk modifying effect of any one SNP may be more pronounced when it occurs in combination with other ‘at risk’ genotypes of biotransformation and repair enzymes implicated in pathways of a given carcinogen. The combined genotypes for CYPs and GSTs have shown an enhanced effect on lung cancer risk and an impact on intermediate end-points (e.g. DNA adduct level and mutations) [117,260]. Gene-gene interactions for a combination of GST polymorphisms [944,1006,1024,1891] are known and prospective studies confirmed the increased risk [1570]. An interaction for p53 and GST genotypes [978,1193,2003], might be more important in younger persons [1313].

**Conclusions**

Studies on genetic polymorphisms and lung cancer risk have identified a number of candidate genes involved in xenobiotic metabolism, DNA repair and possibly nicotine addiction. Certain variants of these genes and combinations thereof were shown to modify the risk of tobacco related lung cancer. Their influence varied by ethnicity, by histological lung tumour types, by exposure and by other host-/life-style factors. Due to this complexity, to date lung cancer risk cannot be predicted at an individual level.
Squamous cell carcinoma

**Definition**
Squamous cell carcinoma (SCC) is a malignant epithelial tumour showing keratinization and/or intercellular bridges that arises from bronchial epithelium.

**ICD-O code**
- Squamous cell carcinoma 8070/3
- Papillary carcinoma 8052/3
- Clear cell carcinoma 8084/3
- Small cell carcinoma 8073/3
- Basaloid carcinoma 8083/3

**Synonym**
Epidermoid carcinoma

**Epidemiology - Etiology**
Over 90% of squamous cell lung carcinomas occur in cigarette smokers (1860). Arsenic is also strongly associated with squamous cell carcinoma and other causes are summarized in Table 1.

**Sites of involvement**
The majority of squamous cell lung carcinomas arise centrally in the mainstem, lobar or segmental bronchi (2007).

**Imaging**
**Radiography.** In central SCC, lobar or entire lung collapse may occur, with shift of the mediastinum to the ipsilateral side (263,264,614,1676). Central, segmental or subsegmental tumours can extend into regional lymph nodes and appear as hilar, perihilar or mediastinal masses with or without lobar collapse (264). Peripheral tumours present as solitary pulmonary nodules (< 3 cm) or masses (> 3 cm). Squamous cell carcinoma is the most frequent cell type to cavitate giving rise to thick walled, irregular cavities with areas of central lucency on the chest film. When located in the superior sulcus of the lung, they are called Pancoast tumours and are frequently associated with destruction of posterior ribs and can cause Horner’s syndrome. The chest radiograph may be normal in small tracheal or endobronchial tumours (1820). Hilar opacities, atelectasis or peripheral masses may be associated with pleural effusions, mediastinal enlargement or hemidiaphragmatic elevation.

**CT and spiral CT.** The primary tumour and its central extent of disease is usually best demonstrated by CT scan (614). Spiral CT may assess better the thoracic extension of the lesion, reveal small primary or secondary nodules invisible on chest radiograph, and exhibit lymphatic spread.

**PET scan.** This is now the method of choice to identify metastases (excluding brain metastases which may require MRI) (195,614,2061). Bone metastases are typically osteolytic.

**Cytology**
The cytologic manifestations of squamous cell carcinoma depend on the degree of histologic differentiation and the type of sampling (673,936). In a background of necrosis and cellular debris, large tumour cells display central, irregular hyperchromatic nuclei exhibiting one or more small nucleoli with an abundant cytoplasm. Tumour cells are usually isolated and may show bizarre shapes such as spindle-shaped and tadpole-shaped cells. They may appear in cohesive aggregates, usually in flat sheets with elongated or spindle nuclei. In well-differentiated squamous cell carcinoma keratinized cytoplasm appears robin’s egg blue with the Romanowsky stains, whereas with the Papanicolaou stain, it is orange or yellow. In exfoliative samples, surface tumour cells predominate and present as individually dispersed cell with prominent cytoplasmic keratinization and dark pyknotic nuclei. In contrast, in brushings, cells from deeper layers are sampled, showing a much greater proportion of cohesive aggregates.

**Macroscopy and localization**
The tumours are usually white or grey and, depending on the severity of fibrosis, firm with focal carbon pigment deposits in the centre and star-like retractions on the periphery. The tumour may grow to a large size and may cavitate. Central tumours form intraluminal polyloid masses and / or infiltrate through the bronchial wall into the surrounding tis-

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sues and may occlude the bronchial lumen resulting in stasis of bronchial secretions, atelectasis, bronchial dilatation, obstructive lipoid pneumonia and infective bronchopneumonia. A minority of cases may arise in small peripheral airways. This may be changing since a recent study reported 53% of squamous cell carcinomas were found in the peripheral lung [640].

**Tumour spread and staging**

Central squamous cell carcinoma is characterized by two major patterns of spread: intraepithelial (in situ) spread with or without subepithelial invasion, and endobronchial polypoid growth [391,1220]. Extensive intraepithelial spreading is common in major bronchi, and the epithelia of bronchial glands or ducts may often be involved. Two patterns of early invasive squamous cell carcinoma have been described: One grows laterally along the bronchial mucosa replacing surface epithelium, with submucosal microinvasion and involvement of the glandular ducts (“creeping type”); the other appears as small polypoid mucosal lesions with downward invasion (“penetrating type”) [1424]. Direct involvement of hilar mediastinal tissue including lymph nodes may be encountered in advanced cases. Peripheral squamous cell carcinoma characteristically forms a solid nodule, commonly with intrabronchiolar nodular growth, intraepithelial extension, or both [640]. In advanced cases, peripheral squamous cell carcinoma may involve the chest wall or diaphragm directly through the pleura.

Staging is usually performed according to the TNM system [738,2045]. In general, squamous cell carcinoma tends to be locally aggressive involving adjacent structures by direct contiguity. Metastases to distant organs is much less frequent than in adenocarcinoma or other histologic types of primary lung cancer [1629]. For peripheral tumours less than 2 cm in diameter, regional lymph node metastases are exceptional [77]. Tumours with poorly differentiated histology may metastasize early in their clinical course to organs such as the brain, liver, adrenals, lower gastrointestinal tract, and lymph nodes. Locoregional recurrence after surgical resection is more common in squamous cell carcinoma than in other cell types [276].

**Histopathology**

Squamous cell carcinoma shows keratinization, pearl formation and/or intercellular bridges. These features vary with degree of differentiation, being prominent in well-differentiated tumours and focal in poorly differentiated tumours.
Papillary variant of SCC. This may show exophytic and endobronchial growth in some proximal tumors. Sometimes there may be a very limited amount of intraepithelial spread without invasion; but invasion is seen in most cases [218,519].

Clear cell variant of SCC is composed predominantly or almost entirely of cells with clear cytoplasm [634,971]. This variant requires separation from large cell carcinoma, adenocarcinoma of the lung with extensive clear cell change and metastatic clear cell carcinoma from kidney.

Small cell variant is a poorly differentiated squamous cell carcinoma with small tumour cells that retain morphologic characteristics of a non-small cell carcinoma and show focal squamous differentiation. This variant must be distinguished from combined small cell carcinoma and show focal squamous differentiation. Focal intracellular mucin can also be present. Even though invasive growth is not identified, papillary SCC can be diagnosed if there is sufficient cytologic atypia. Small biopsy specimens that show very well differentiated papillary squamous epithelium should be interpreted with caution since separation of a papillary squamous carcinoma from a papilloma can be difficult. The pattern of verrucous carcinoma is very rare in the lung and is included under papillary squamous carcinoma.

Massive involvement of the anterior mediastinal tissue can make differential diagnosis from thymic squamous cell carcinoma difficult and requires careful correlation with operative and radiologic findings. In the lung parenchyma, squamous cell carcinoma may entrap alveolar pneumocytes, which sometimes results in histological misinterpretation as adenosquamous carcinoma [391]. Squamous metaplasia with cytologic atypia in diffuse alveolar damage (DAD) may also raise concern for squamous carcinoma. The presence of overall features of DAD such as hyaline membranes, diffuse alveolar septal connective tissue proliferation with pneumocyte hyperplasia and bronchiolocentricity of the squamous changes would favor a metaplastic process.

Somatic genetics

Cytogenetics and CGH

Several differences have been found between lung squamous cell carcinomas and adenocarcinomas. Squamous cell carcinoma of the lung is either a near diploid or hyperdiploid-aneuploid neoplasm with mean chromosome numbers in the triploid range [104,1582]. Detection of aneuploidy by DNA measurement has been shown to be predictive for bad prognosis [1581]. Cytogenetics and CGH indicated a multitude of alterations with amplifications of the telomeric 3q region being most characteristic for the squamous carcinoma phenotype [1582]. Gain of 3q24-qter is present in the majority of squamopus cell carcinomas and in a minority of adenocarcinomas [104,176]. While the gene in the amplicon has not been identified with certainty, one candidate is the PIK3CA gene, which encodes the catalytic sub-
unit of phosphatidylinositol-3 kinase, an essential component of many cell signaling pathways [104]. Deletions on the short arm of chromosome 3 are also frequent. Additional recurrent alterations are deletions on chromosomes 4q, 5q, 8p, 9p, 10q, 11p, 13q, 17p, 18q and 21q along with overrepresentations of chromosomes 5p, 8q, 11q13 and 12p [104, 125, 898, 1301, 1330, 1582]. The number of chromosomal imbalances accumulates during progression [370, 1584]. Small interstitial deletions have a tendency to increase in size resulting into a deletion pattern similar to small cell carcinoma. In contrast, overrepresentations of entire chromosome arms may condense into smaller amplicons. Specific alterations, in particular deletions of 3p12-p14, 4p15-p16, 8p22-p23, 10q, 21q and overrepresentation of 1q21-q25, 8q11-q25 have been associated with the metastatic phenotype [1584].

**Molecular genetics**

Squamous cell carcinoma commonly shows distinct molecular genetic characteristics. ErbB (EGFR, HER2/neu, KRAS) pathway abnormalities are common in non-small cell carcinoma but absent in SCLC. An average of 84% of squamous cell carcinomas are EGFR positive [608]. Lung cancers with detectable levels of epidermal growth factor receptor protein are significantly more frequent among squamous cell carcinomas than among other types of lung tumour [152]. HER2/neu expression, while relatively frequent in adenocarcinoma, is relatively rare in squamous cell carcinoma [845]. While activating mutations of the KRAS gene are frequent (~30%) in adenocarcinoma, they are rare in squamous cell carcinoma [845]. While activating mutations of the KRAS gene are frequent (~30%) in adenocarcinoma, they are rare in squamous cell carcinoma. Disruption of normal p53 gene function, usually by point mutations, is frequent in all types of lung cancers. Mutations, while more frequent in SCLC, occur in the majority of NSCLC tumours including squamous cell carcinomas. Disruption of the RB gene pathway is universal in lung cancers [981]. While mutations of the RB gene are the usual method of disruption in SCLC, they are rare in NSCLC. In NSCLC the mechanism of disruption is via the upstream pathway. In particular, inactivation of p16Ink4 as demonstrated by immunohistochemistry, occurs via epigenetic or genetic mechanisms (homozygous deletions, mutations, methylation), while cyclin D1 and E are overexpressed [215].

Most squamous cell carcinomas demonstrate large 3p segments of allelic loss, whereas most adenocarcinomas and preneoplastic/preinvasive lesions have smaller chromosome areas of 3p allele loss [2158]. One well studied gene is FHIT (fragile histidine triad) at chromosome 3p14.2, by deletions or by a combination...
of deletion and promoter region methylation {1855}. The status of another gene located at 3p21.3, the RASSF1A gene, while more frequently inactivated in SCLC, does not demonstrate differences in the methylation frequencies between NSCLC types {238}.

**Epigenetic gene silencing**
The major mechanism is methylation, although histone deacetylation plays an important co-operative role. Most silenced genes are known or suspected tumour suppressor genes. The methylation profile varies with the tumour type and the methylation rates of APC, CDH13 and RAR-beta are significantly higher in adenocarcinomas than in squamous cell carcinomas [2017].

**Gene expression profiles**
Squamous cell lung carcinoma is characterized by high-level expression of keratin genes and histologic evidence of keratinization. Markers of squamous cell lung carcinoma have been analyzed using oligonucleotide and cDNA microarray hybridisation {163,661} and serial analysis of gene expression or SAGE {623,1420}. When results are compared across experimental platforms, significant overlap can be seen. Genes for keratin 5, 6, 13, 14, 16, 17, and 19 are prominent among the gene expression markers for squamous cell lung carcinoma. Other genes found as squamous cell lung carcinoma markers in more than one data set include collagen VII alpha 1, galectin 7, the ataxia-telangiectasia group D-associated protein, the s100 calcium binding protein A2, and bullous pemphigoid antigen 1. In addition, squamous cell lung carcinomas are characterized by over-expression of the p53-related gene p63. Using gene expression profile generated by SAGE, a transcriptome map integrating the gene expression profile along each arm of the human chromosomes has been generated {623}. This transcriptome map revealed known chromosome regions and a novel locus with significantly altered gene expression patterns in squamous cell carcinoma. The identification of these molecular changes may provide potential markers for lung cancer.

**Histopathological criteria**
Currently, the stage of disease and the performance status at diagnosis remain the most powerful prognostic indicators for survival for primary squamous cell carcinoma. Nevertheless, histologic subtyping carries independent prognostic information. For example, well-differentiated squamous cell carcinoma tends to spread locally within the chest directly involving adjacent mediastinal structures. Poorly differentiated squamous cell carcinoma tends to metastasize early and to distant sites. The alveolar space-filling pattern of peripheral squamous cell carcinoma appears to carry a more favourable prognosis [641].
Definitions
Small cell carcinoma of the lung (SCLC) A malignant epithelial tumour consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The cells are round, oval and spindle-shaped. Nuclear molding is prominent. Necrosis is typically extensive and the mitotic count is high.

Combined small cell carcinoma
Small cell carcinoma combined with an additional component that consists of any of the histologic types of non-small cell carcinoma, usually adenocarcinoma, squamous cell carcinoma or large cell carcinoma but less commonly spindle cell or giant cell carcinoma.

ICD-O code
Small cell carcinoma 8041/3
Combined small cell carcinoma 8045/3

Synonyms
Previous classifications used terms such as oat cell carcinoma, small cell anaplastic carcinoma, undifferentiated small cell carcinoma, intermediate cell type, and mixed small cell/large cell carcinoma but these are no longer recognised.

Clinical features
Signs and symptoms
Symptoms reflect central location and locoregional spread, although stridor and haemoptysis are comparatively rare while hoarsness and vocal cord paralysis are more common, when compared to locoregional spread of squamous cell carcinoma. However, clinical symptoms more often reflect disseminated disease (e.g bone marrow and liver metastases). At the time of primary diagnosis, brain metastases are diagnosed in a minority of patients, but tend to develop during the course of disease [568,933,1797]. Paraneoplastic syndromes are also common in association with small cell carcinoma.

Imaging
Small cell carcinomas appear as hilar or perihilar masses often with mediastinal lymphadenopathy and lobar collapse [263,614]. Often, the primary tumour is not detected on radiographic studies. CT depicts mediastinal nodal involvement and superior vena caval obstruction with greater detail than the chest radiograph. Peripheral small cell carcinomas are radiographically indistinguishable from other pulmonary neoplasms.

Cytology
Cytologic specimens show loose and irregular or syncytial clusters, as well as individual tumour cells frequently arranged in a linear pattern [673,936,2231]. Within cohesive aggregates, nuclear moulding is well developed. Mitoses are easily seen. Each neoplastic cell has a high nuclear/cytoplasmic ratio with an ovoid to irregular nuclear contour. Well-preserved cells feature finely granular and uniformly distributed chromatin, yielding the classic “salt and pepper” quality, while poorly preserved cells have a very dark blue structureless chromatin. Conspicuous nucleoli are absent or rare [1410,2099,2231]. Due to the fragility of the malignant nuclei, chromatin streaks are commonly seen in smears of all types, especially in aspiration biopsies and brushings. In addition, the smear background often contains apoptotic bodies and granular necrotic debris.

Macroscopy and localization
Tumours are typically white-tan, soft, friable perihilar masses that show extensive necrosis and frequent nodal involve-
Within the lung the tumour typically spreads along bronchi in a submucosal and circumferential fashion, often involving lymphatics. Approximately 5% of SCLC present as peripheral coin lesions [427].

**Histopathology (including variants)**

Architectural patterns include nesting, trabeculae, peripheral palisading, and rosette formation as shared by other neuroendocrine tumours. Sheet-like growth without these neuroendocrine morphologic patterns is common. Tumour cells are usually less than the size of three small resting lymphocytes and have round, ovoid or spindled nuclei and scant cytoplasm. Nuclear chromatin is finely granular and nucleoli are absent or inconspicuous. Cell borders are rarely seen and nuclear moulding is common. There is a high mitotic rate, averaging over 60 mitoses per 2mm². The tumour is by definition high grade, thus grading is inappropriate. No in-situ phase is recognised. In larger specimens, the cell size may be larger and scattered pleomorphic, giant tumour cells, dispersion of nuclear chromatin prominent nucleoli, extensive necrosis, brisk apoptotic activity, and crush artifact with encrustation of basophilic nuclear DNA around blood vessels (Azzopardi effect) may all be seen [1470,2024].

The combined small cell carcinoma variant refers to the admixture of non-small cell carcinoma elements including squamous cell, adenocarcinoma and less commonly spindle cell or giant cell carcinoma. For combined small cell and large cell carcinoma there should be at least 10% large cells present [1470].

**Immunohistochemistry**

While small cell carcinoma is a light microscopic diagnosis, electron microscopy shows neuroendocrine granules approximately 100 nm in diameter in at least two-thirds of cases and immunohistochemistry is positive for CD56, chromogranin and synaptophysin in most cases [1470]. Less than 10% of SCLC are negative for all neuroendocrine markers [750]. Small cell carcinoma is also positive for TTF-1 in up to 90% of cases [600,975].

**Differential diagnosis**

The differential diagnosis includes lymphoid infiltrates, other neuroendocrine tumours, other “small round blue cell tumours” (SRBCT), and primary or metastatic non-small cell carcinomas. Crush artifact can occur not only with small cell carcinomas, but also carcinoids, lymphocytes of inflammation or...
lymphomas and poorly differentiated non-small cell carcinomas. In crushed specimens some preserved tumour cells must be seen for a SCLC diagnosis. Immunohistochemical staining for cytokeratin vs leukocyte common antigen as well as neuroendocrine markers and TTF-1 may be helpful. Carcinoïd tumours, typical and atypical, do not show the degree of necrosis, mitotic and apoptotic activity of small cell carcinomas (1470,2024). Other SRBCTs including primitive neuroectodermal tumours (PNET) are less mitotically active than SCLC but also mark for MIC-2 (CD99) and not for cytokeratin or TTF-1 (765, 1214). Positive staining for Cytokeratin 20, but not for Cytokeratin 7 or TTF-1 distinguishes Merkel cell carcinoma from SCLC (326,351).

Morphologic separation of SCLC from NSCLC can be difficult (846,1240,1470, 2024,2089). Examination of a good quality H&E stained section of well-fixed tissue is essential. The distinction does not rest on a single feature but incorporates cell size, nuclear: cytoplasmic ratio, nuclear chromatin, nucleoli, and nuclear molding. Corresponding cytology specimens may show much better-preserved tumour cell morphology.

Histogenesis
While the precise cell of origin is not known for SCLC, there is likely to be a pluripotent bronchial precursor cell that can differentiate into each of the major histologic types of lung cancer. However, within the spectrum of neuroendocrine tumours, there is closer morphologic and genetic similarity between large cell neuroendocrine carcinoma and small cell carcinoma than either typical or atypical carcinoid.

Somatic genetics

Cytogenetics and CGH
SCLCs are invariably aneuploid neoplasms although DNA cytometry frequently suggests a near diploid chromosome content. Cytogenetics and CGH revealed a characteristic pattern of chromosomal imbalances with a high incidence of deletions on chromosomes 3p, 4, 5q, 10q, 13q and 17p along with DNA gains on 3q, 5p, 6p, 8q, 17q, 19 and 20q (104). Chromosome 3p deletions are present in nearly 100% of cases and are often associated with a 3q isochromosome formation. Amplification of chromosomal subregions occurs particularly during tumour progression and in pretreated patients. DNA gain of chromosome 17q24-q25 is a potential marker for brain metastasis formation (1583).

Molecular genetic alterations
SCLC and pulmonary carcinoids are classic neuroendocrine (NE) tumours and they reflect all of the characteristic features of NE cells. However while SCLC is highly associated with smoking, carcinoids are not. While these two NE tumours share certain molecular abnormalities (269,727,1516), there are also differences. SCLC tumours have a higher rate of p53 mutations (1516) while carcinoids are characterized by mutations in the menin gene (463). There are similarities and differences in the genetic profiles of SCLC and NSCLC (269,727,2244). Most of these differences are relative. The absolute differences between these two major divisions of lung cancer are relatively few and include the presence of Ras gene mutations (1668) and Cox-2 (827,1248) over expression in NSCLC, while amplification of MYC (931) and methylation of caspase-8 (1814), a key antiapoptotic gene, are characteristic of SCLC. While loss of cell cycle controls is a hallmark of cancers, the mechanism by which the two major types of lung cancer achieve this aim are very dif-
ferent. Inactivation of the retinoblastoma (RB) gene and overexpression of E2F1 are almost universal in SCLC (549,981). SCLC but rarely NSCLC, show more frequent inactivation of the 14-3-3 sigma and p14arf, two important G2 checkpoint genes (551,1471,1520).

Most small cell lung carcinomas and squamous cell carcinomas demonstrate large 3p segments of allele loss, whereas most of the adenocarcinomas and preneoplastic/preinvasive lesions have smaller chromosome areas of 3p allele loss (2158). Because these regions are gene rich, and the genes seldom demonstrate mutations, identification of the TSGs took nearly two decades. Putative TSGs have been identified at four widely separated regions, 3p12-13 (ROBO1/DUTT1), 3p14.2 (FHIT), 3p21.3 (multiple genes including RASSF1A, FUS1, HYAL2, BAP1, Sema3B, Sema3F, and beta-catenin at 3p21.3), and 3p24-6 (VHL and RAR-beta) (2228). Of these, the FHIT, RASSF1A and RAR-beta genes are the best studied.

Mutations of the p53 gene are the most frequent genetic abnormality identified in human cancers, and are more common in SCLC than in NSCLC. Mutations are the most common mechanism of deregulation of gene activity. The frequency, type, and pattern of mutations in lung cancer are strongly related to cigarette smoking, with G to T transversions being more common in smokers (especially women) than in never smokers (1666).

Multiple other changes occur frequently in SCLC, including upregulation of the proapoptotic molecule Bcl-2, activation of autocrine loops (bombesin like peptides, c-kit/stem cell factor), upregulation of telomerase, loss of laminin 5 chains and inhibitors of matrix metalloproteinases, and expression of vascular growth factors. In contrast to inactivation of TSGs (most often by epigenetic phenomena, especially methylation), the genes involved at sites of chromosomal gains have seldom been identified (with the exception of the MYC family). SCLC specific preneoplastic changes have not been identified and little is known about the molecular changes preceding this tumour, although frequent allelic losses have been identified in histologically normal or hyperplastic bronchial epithelium adjacent to invasive tumours (2160).

**Table 1.10**

<table>
<thead>
<tr>
<th>Limited stage SCLC</th>
<th>Extensive stage disease</th>
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<tbody>
<tr>
<td>Patients with disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsi-, and contralateral mediastinal, or supraclavicular nodes.</td>
<td>All patients with disease who cannot be included in the limited stage.</td>
</tr>
<tr>
<td>Patients with contralateral mediastinal lymph nodes and supraclavicular lymph nodes since the prognosis is somewhat better than that of distant metastatic sites.</td>
<td></td>
</tr>
<tr>
<td>Patients with ipsilateral pleural effusion (benign or malignant)</td>
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Gene expression profiles
Gene expression analysis can readily identify markers for small cell lung carcinoma. Given the histological and immunohistochemical features of neuroendocrine differentiation, it is not surprising that many of the gene expression markers are neuroendocrine genes including chromogranin B, chromogranin C, and l-aromatic amino acid decarboxylase. Experimental studies of gene expression in SCLC include analysis of primary tumours by oligonucleotide arrays (163), analysis of primary tumours with cDNA arrays (661), and analysis of cell lines with oligonucleotide arrays (1901). Strikingly, the three studies identify sets of overlapping genes. All three studies identified insulinoma-associated gene 1 (IA-1) and the human achaete-scute homolog 1 (hASH1) as SCLC markers. Two of the three studies identified forkhead box g1b (FOXG1B), the Isl1 transcription factor, thymosin beta, and tripartite motif-containing 9.

**Prognosis and predictive factors**
Adverse clinical prognostic factors include ‘extensive’ stage of disease, poor performance status, elevated serum LDH or alkaline phosphatase, low plasma albumin and low plasma sodium levels (1523,1849). No histologic or genetic factors are predictive of prognosis (1470). A small percentage of low stage tumours may be successfully resected.
Adenocarcinoma

Definition
A malignant epithelial tumour with glandular differentiation or mucin production, showing acinar, papillary, bronchioalveolar or solid with mucin growth patterns or a mixture of these patterns.

ICD-O codes
Adenocarcinoma 8140/3
Adenocarcinoma mixed subtype 8255/3
Acinar adenocarcinoma 8550/3
Papillary adenocarcinoma 8260/3
Bronchioalveolar carcinoma 8250/3
Nonmucinous 8252/3
Mucinous 8253/3
Mixed nonmucinous and mucinous or indeterminate 8254/3
Solid adenocarcinoma with mucin production 8230/3

Variants
Fetal adenocarcinoma 8333/3
Mucinous (“colloid”) carcinoma 8480/3
Mucinous cystadenocarcinoma 8470/3
Signet ring adenocarcinoma 8490/3
Clear cell adenocarcinoma 8310/3

Epidemiology
Adenocarcinoma has surpassed squamous carcinoma as the most common histologic subtype of lung cancer in many countries [391]. Although most cases are seen in smokers, it develops more frequently than any other histologic type of lung cancer in individuals (particularly women) who have never smoked [391,1002].

Imaging
Compared to other lung cancers, adenocarcinomas are most frequently peripheral nodules under 4.0 cm in size [391, 614]. They infrequently present in a central location as a hilar or perihilar mass and only rarely show cavitation. Pleura and chest wall involvement is seen in approximately 15% of cases and this is more frequent than with other forms of lung cancer. Hilar adenopathy is less frequent with adenocarcinoma than with other forms of lung cancer.

Adenocarcinomas account for the majority of small peripheral cancers identified radiologically. By CT screening, adenocarcinoma is often distinct from the other histologic subtypes of lung cancer. Solid nodules (solid-density), ground glass opacities (non-solid, air-containing) and mixed solid/ground glass (part solid, subsolid) opacities are all recognized patterns of adenocarcinoma [817,1050, 1425,1952]. Increased use of CT has lead to increased identification of small peripheral nodules, many of which prove to be adenocarcinomas. The larger the proportion of solid compared to ground glass component in a lung adenocarcinoma, the greater the likelihood of invasive growth and a less favorable outcome.

Cytology
Diagnosis of adenocarcinoma by cytology is based on a combination of individual cell cytomorphology and architectural features of cell clusters [673, 936,1826]. Adenocarcinoma cells may be single or arranged in three-dimensional morulae, acini, pseudopapillae, true papillae with fibrovascular cores and/or sheets of cells. Borders of cell clusters are typically sharply delineated. Cytoplasm varies in volume but is usually relatively abundant. It is typically cyanophilic and more translucent in comparison with squamous cell carcinoma. In most cells the cytoplasm is distinctly homogeneous or granular and in others is foamy due to abundant small indistinct vacuoles. A single large mucin-filled vacuole may be prominent and, in some cases, distends the cytoplasm and compresses the nucleus to one margin, forming a so-called signet-ring cell.

Nuclei are usually single, eccentric and round to oval with relatively smooth contours and minimal nuclear irregularity. Chromatin tends to be finely granular and evenly dispersed in better-differentiated tumours and coarse and irregularly distributed or hyperchromatic in poorly differentiated tumours. In most tumours,

Fig. 1.19 A. Bronchioalveolar carcinoma. High-resolution CT of a part-solid nodule in the right upper lobe in a 71 year-old women. Solid components are central-ly located, surrounded by non-solid component. B. Adenocarcinoma. This peripheral tumor consists of a lobulated white mass with central anthracosis and scar-ring. At the periphery there is a yellow area of bronchioalveolar carcinoma with preservation of airspaces. C. Adenocarcinoma. A predominantly bronchioalveolar pattern prevailed histologically (alveolar spaces can just be seen on the tumour cut surface); the white and solid foci showed invasive disease.
nucleoli are prominent and characteristically they are single, macronucleoli, varying from smooth and round to irregular. Cytologic pleomorphism reflects histologic grade and has recently been reported to be related, in part, to tumour size. Morishita et al [1388] concluded that cells from BAC less than 2 cm in diameter are relatively small and round to ovoid when compared with other small-sized adenocarcinomas (invasive adenocarcinoma).

Although certain cytologic features have been proposed to favor a diagnosis of BAC over other adenocarcinoma patterns [1218,1607], the diagnosis of BAC requires thorough histologic evaluation to exclude the presence of invasive growth. Mucinous BAC may be suggested based on the cytologic features in the appropriate radiologic setting. BAC cells in washings and bronchoalveolar lavage tend to be homogeneous with uniform, round, smooth, pale nuclei and inconspicuous nucleoli. BAC often shows clusters of uniform cells that display a three-dimensional “depth of focus”, especially with the mucinous type, presumably due to their abundant cytoplasm. Tissue fragments in aspiration specimens may show histologic features such as growth along intact alveolar septal surfaces [1218], but this does not exclude an unsampled invasive component. On occasion, individual BAC cells resembling alveolar macrophages are dispersed in a smear but can be recognized because nuclei are rounder and larger than macrophage nuclei and a few cohesive clusters are usually present.

Currently, there are no established criteria for diagnosing AAH on cytology and to distinguish it from nonmucinous BAC. Anecdotally there is apparent overlap of the cytologic features. The Early Lung Cancer Action Project (ELCAP) has a cytology protocol, which includes a category of lesions designated “atypical bronchioloalveolar cell proliferation” when the findings are suspicious for, but not diagnostic of BAC [817,818]. The designation applies to lesions, which, when resected, may prove to be either atypical adenomatous hyperplasia (AAH) or BAC.

**Macroscopy and localization**
Pulmonary adenocarcinomas may be single or multiple and have a wide range in size. The vast majority of pulmonary adenocarcinomas present with one of six macroscopic patterns and these all have corresponding radiologic correlates. Combinations of these patterns may also occur. The most common pattern is a peripheral tumour [1809]. Gray-white central fibrosis with pleural puckering may be apparent. The central area underlying pleural puckering is often a V-shaped area of desmoplastic fibrosis associated with anthracotic pigmentation. Invasion, when present histologically, is identified in areas of fibrosis and may be accompanied by necrosis, cavitation, and hemorrhage. The edges of the tumour may be lobulated or ill defined with stellate borders. In small tumours with a contiguous nonmucinous BAC pattern some alveolar structure may be grossly apparent at the edge of the solid portion of the nodule corresponding to the ground glass opacity noted radiologically in these lesions. Some peripheral adenocarcinomas may present with a diffuse pattern that cannot be distinguished from AAH on cytology.

**Fig. 1.20** Adenocarcinoma of mixed subtypes in a nonsolid nodule which developed a solid component. A High-resolution CT of a nonsolid nodule in the right middle lobe in a 78 year-old woman. B High resolution CT four years later shows the development of a solid component without any increase in the overall size of the nodule. C One year later the solid component has increased.

**Fig. 1.21** Adenocarcinoma cytology. A Three-dimensional, large cluster of uniform malignant cells with distinct nuclear structure, nucleoli and finely vacuolated cytoplasm. Bronchial brushing. Liquid Based Cytology. Papanicolaou stain. B Cohesive three-dimensional cluster with papillary pattern. Fine needle aspiration, conventional cytology. Papanicolaou stain. C This cluster of malignant cells lacks definite cytoplasmic borders but shows vacuolization. Pale nuclei have small but distinct nucleoli. Fine needle aspiration, conventional cytology. Papanicolaou stain.
carcinomas may have a gelatinous quality due to abundant mucin production. A second pattern of adenocarcinoma is a central or endobronchial tumour (1042). The neoplasm may grow as a plaque or in a polypoid fashion with preservation of the overlying mucosa. With increasing degrees of bronchial luminal obstruction, the distal parenchyma may show obstructive “golden” (lipoid) pneumonia. The third pattern is a diffuse pneumonia-like, lobar consolidation with preservation of underlying architecture, typical of mucinous BAC.

A fourth pattern consists of diffuse bilateral lung disease. In some cases this manifests as widespread nodules (varying from tiny to large) involving all lobes; in other cases the appearance suggests an interstitial pneumonia due to widespread lymphangitic spread of carcinoma.

In the fifth pattern, the tumour preferentially invades and extensively disseminates along the visceral pleura, resulting in a rind-like thickening mimicking malignant mesothelioma (pseudomesotheliomatous carcinoma) (1060). Finally adenocarcinoma may develop in the background of underlying fibrosis, either a localized scar or diffuse interstitial fibrosis (391). Adenocarcinoma arising in association with a focal scar is quite rare, in contrast to the relatively common central secondary scarring that develops in localized peripheral adenocarcinomas.

**Tumour spread and staging**

Adenocarcinoma spreads primarily by lymphatic and hematogenous routes.

Aerogenous dissemination commonly occurs in bronchioloalveolar carcinoma and is characterized by spread of tumour cells through the Airways forming lesions separate from the main mass. Aerogenous dissemination can include involvement of the same lobe or different lobes in the ipsilateral and/or contralateral lung resulting in the multicentricity seen in bronchioloalveolar cell carcinoma. Peripheral adenocarcinomas occasionally spread over the pleural surfaces mimicking mesothelioma. Approximately one fifth of newly diagnosed adenocarcinomas present with distant metastases. Brain, bone, adrenal glands and liver are the most common metastatic sites (1629). Isolated local recurrence after resection is less common in adenocarcinoma than in other non-small cell types (276). Adenocarcinomas are staged according to the international TNM system (738, 2045).

**Histopathology**

*Adenocarcinomas mixed subtype.* These are the most frequent subtype, representing approximately 80% of resected adenocarcinomas (1993). In addition to the mixture of histologic subtypes, different degrees of differentiation (well, moderate, poor) and cytologic atypia (mild, moderate, marked) are typically encountered, varying from field to field and block to block. Any of the histologic subtypes may have a component with a loss of cellular cohesion with individual tumour cells filling alveolar spaces. The major individual histologic patterns/subtypes are acinar, papillary, bronchioloalveolar, and solid adenocarcinoma with mucin production (2024). Adenocarcinomas consisting purely of one of these histologic subtypes are uncommon compared to the mixed histologic subtype, especially in larger tumours. Well, moderate, and poorly differentiated histologies are recognized among the acinar and papillary tumours. The bronchioloalveolar pattern is virtually always moderately or well differentiated. The acinar pattern is characterized by acini and tubules composed of cuboidal or columnar cells which may be mucin...
producing and resemble bronchial gland or bronchial lining epithelial cells, including Clara cells (2024). The papillary pattern is characterized by papillae with secondary and tertiary papillary structures that replace the underlying lung architecture (2024). Necrosis and lung invasion may be present. Bronchioloalveolar carcinomas that have simple papillary structures within intact alveolar spaces are excluded from this definition. The lining cells in papillary adenocarcinoma may be cuboidal to columnar, mucinous or non-mucinous and some cases may mimic papillary carcinoma of the thyroid. Some evidence suggests a micropapillary pattern of adenocarcinoma, in which papillary tufts lack a central fibrovascular core, may be prognostically unfavourable (1335).

A bronchioloalveolar carcinoma (BAC) pattern shows growth of neoplastic cells along pre-existing alveolar structures (lepidic growth) without evidence of stromal, vascular, or pleural invasion (2024). Septal widening with sclerosis is common in bronchioloalveolar carcinomas, particularly the non-mucinous variant. When there is marked alveolar collapse with increase in elastic tissue in the thickened alveolar septa, distinction between sclerosing BAC and early invasive adenocarcinoma may be difficult. Invasion is generally characterized by significant increase in cytologic atypia, a fibroblastic stromal reaction, and usually an acinar pattern of growth. The non-mucinous variant of BAC typically shows Clara cell and/or type II cell differentiation (2024). Clara cells are recognized as columnar with cytoplasmic snouts and pale eosinophilic cytoplasm. Nuclei may be apical in location. Type II cells are cuboidal or dome-shaped with fine cytoplasmic vacuoles or clear to foamy cytoplasm. Intranuclear eosinophilic inclusions may be present. In non-mucinous BAC there is no known clinical significance in distinguishing Clara from type II cells. Mucinous BAC is by definition low grade, composed of tall columnar cells with basal nuclei and pale cytoplasm, sometimes resembling goblet cells, with varying amounts of cytoplasmic mucin and typically showing mucin production with mucus pooling in the surrounding alveolar spaces (2024). Cytologic atypia is generally minimal. Aerogenous spread is characteristic and satellite tumours surrounding the main mass are typical. Extensive consolidation is common, sometimes with a lobar and/or pneumonic pattern. By convention small lesions, even those a few millimeters in size, showing this histology are considered mucinous BAC. Rarely BACs are composed of a mixture of mucinous and non-mucinous cells. Mucinous and nonmucinous BAC may be solitary lesions, multifocal or consolidative (eg lobar) and the latter two are interpreted as aerogenous spread. Most solitary BACs encountered are of the nonmucinous subtype. Solid adenocarcinoma with mucin is composed of sheets polygonal cells lacking acini, tubules, and papillae but

*Fig. 1.24* Acinar adenocarcinoma. A This tumour forms irregular-shaped glands with cytologically malignant cells exhibiting hyperchromatic nuclei in a fibroblastic stroma. B Positive immunohistochemical staining for TTF-1 in an acinar adenocarcinoma. The nuclear staining varies.

*Fig. 1.25* Papillary adenocarcinoma. Tumour cells show a complex papillary glandular proliferation along fibrovascular cores. From Travis et al. (2024).

*Fig. 1.26* A, B Invasive adenocarcinoma. Central area of invasion in an adenocarcinoma that at the periphery consisted of a non-mucinous bronchioloalveolar carcinoma. Invasion is associated with a significant increase in cytologic atypia and myofibroblastic stroma.
with mucin present in at least 5 tumour cells in each of two high power fields confirmed with histochemical stains for mucin [2024]. Squamous carcinomas and large cell carcinomas of the lung may show rare cells with intracellular mucin production, but this does not indicate classification as adenocarcinoma. Adenocarcinoma with mixed histologic patterns is an invasive tumour in which there is a mixture of histologic subtypes. The pathologic diagnosis of adenocarcinoma with mixed histologic patterns should include the histologic subtype with a comment about the pattern(s) identified: for example “adenocarcinoma with acinar, papillary and bronchioloalveolar patterns”. The extent of the stromal inflammation and fibrosis varies [391]. Small tumours (<2 cm.) with a BAC component should be histologically sectioned entirely to search for foci of invasion and to measure the size of fibrotic scars. Complete sampling is required for a diagnosis of localized nonmucinous BAC. In tumours that exhibit a component of nonmucinous BAC, the size and extent of invasion and scarring should be noted, as these may have prognostic importance. Tumours with localized fibrosis less than 5 mm. in diameter (regardless of the presence or absence of invasion) appear to have a 100% 5-year survival similar to localized BAC [1484, 1929, 1993, 2208]. This localized fibrosis differs from the mild alveolar septal sclerosis and elastosis that is common in nonmucinous BAC. Central scars typically present as alveolar collapse with dense elastosis or active fibroblastic proliferation; when invasive carcinoma is present it is usually identified in regions of active fibroblastic proliferation and associated with increased atypia of the neoplastic cells. In some cases the distinction between elastotic sclerosis with trapping of airspaces lined by atypical cells from focci of fibroblastic proliferation with invasion may be difficult. In the setting of underlying diffuse interstitial fibrosis (from a variety of causes) there is significant fibrosis with honeycomb changes. However, all histologic types of lung cancer, not just adenocarcinoma, may arise in this setting [91]. Multifocal invasive adenocarcinomas may be encountered. If a component of nonmucinous BAC can be confirmed contiguous with the invasive carcinoma, a presumptive diagnosis of a primary carcinoma can be made. Separate primary adenocarcinomas should be distinguished from satellite lesions that may be
encountered adjacent to the main tumour. Histologic disimilarity between the tumours also favors separate primaries. A definitive diagnosis of multifocality requires proof of molecular/genetic differences between the tumours, but such studies are often not feasible. Whether a tumour is classified as a separate primary or an intrapulmonary metastasis has implications regarding staging.

**Fetal adenocarcinoma**

Synonyms: well differentiated fetal adenocarcinoma, pulmonary adenocarcinoma of fetal type, pulmonary endodermal tumour resembling fetal lung. This is a distinctive adenocarcinoma variant consisting of glandular elements composed of tubules of glycogen-rich, non-ciliated cells that resemble fetal lung tubules. Subnuclear and supranuclear glycogen vacuoles give the tumour an endometrioid appearance. Rounded morules of polygonal cells with abundant eosinophilic and finely granular cytoplasm are common (2024) (and resemble squamous morules in endometrioid adenocarcinomas). Some cases show a clear cell pattern. Rarely, fetal adenocarcinomas are associated with other histologic types of lung cancer including other subtypes of adenocarcinoma. Most fetal adenocarcinomas are well differentiated; Nakatani, et al (1436) has recently described a variant designated poorly differentiated fetal adenocarcinoma. When fetal adenocarcinoma is associated with a sarcomatous primitive blastemal stroma the tumour is classified as pulmonary blastoma.

**Mucinous (“colloid”) adenocarcinoma**

A lesion identical to their counterparts in the gastrointestinal tract, with dissecting pools of mucin containing islands of neoplastic epithelium (2024). The epithelium in such cases may be extremely well differentiated and sometimes tumour cells float within the pools of mucin.

**Mucinous cystadenocarcinomas**

A circumscribed tumour that may have a partial fibrous tissue capsule. Centrally there is cystic change with mucin pooling and the neoplastic mucinous epithelium grows along alveolar walls.

**Signet ring adenocarcinoma**

Signet ring adenocarcinoma in the lung is usually a focal pattern associated with other histologic subtypes of adenocarcinoma. Exclusion of a metastasis, particularly from the gastrointestinal tract is important.

**Clear cell adenocarcinoma.**

This morphological feature is most often focal, but rarely it may be the major component of the tumour (clear cell adenocarcinoma) and it may occur in any of the major patterns of adenocarcinoma (391, 2024). Metastatic renal cell carcinoma is an important consideration in such cases.

**Immunohistochemistry**

The immunohistochemical features of adenocarcinomas vary somewhat with the subtype and the degree of differentiation. Expression of epithelial markers (AE1/AE3, CAM 5.2, epithelial membrane antigen, and carcinoembryonic antigen) is typical (391). CK7 is more frequently expressed than CK20 (1702). TTF-1 staining is usually present, especially in better-differentiated tumours (1137, 2201). In TTF-1 positive cases, a negative thyroglobulin helps to exclude metastatic thyroid carcinoma. Staining for surfactant apoprotein is seen less frequently than TTF-1 but is more problematic due to potential absorption of surfactant by metastatic tumour cells from the surrounding lung (14). Mucinous tumours, especially mucinous BAC may represent exceptions, being TTF-1 negative and positive for CK7 and frequently CK20 (1136,1790).

**Differential diagnosis**

The differential diagnosis includes metastatic adenocarcinoma, mesothe-
Adenocarcinoma, AAH, and reactive pneumocyte atypia associated with scars or organizing alveolar injury. Patients with metastatic adenocarcinoma usually have a history of primary carcinoma and present with multiple lesions in the lung. Obtaining the histologic slides from the primary carcinoma for comparison with the histology of the lung lesion can be very informative. If the lesion in the lung is solitary, differentiation between primary and metastatic carcinoma may be more difficult. The presence of heterogeneity of histologic subtypes is characteristic of lung adenocarcinoma and this feature may be helpful in separating pulmonary primary from metastatic carcinomas, since the latter tend to be more homogeneous. The presence of a bronchioloalveolar carcinoma (BAC) component favours primary adenocarcinoma of the lung over a metastasis. However, some metastatic adenocarcinomas may rarely spread along the alveolar septa and mimic bronchioloalveolar carcinoma.

Adenocarcinomas of the lung often show differentiation toward Type II cells or Clara cells and express markers found normally in these cell types. Up to 60% of pulmonary adenocarcinomas express surfactant proteins (SP-A, pro-SP-B, pro-SP-C) [138]. Thyroid transcription factor 1 (TTF-1), a transcription factor that plays an important role in the lung specific expression of surfactant proteins, is expressed in up to 75% of pulmonary adenocarcinomas [2232]. Metastatic adenocarcinomas with the exception of carcinomas of thyroid origin are negative for TTF-1. Negative mucin stains and positive staining for thyroglobulin help separate metastatic thyroid carcinoma from an adenocarcinoma of the lung. This topic is discussed in more detail below in the section on metastases. Cytokeratin (CK) 7 and CK20 may also be useful in differentiating primary versus metastatic adenocarcinoma [1702]. Most pulmonary adenocarcinomas have a CK7 positive, CK20 negative immunophenotype. One exception is mucinous BAC, which is usually positive for CK20 and negative with TTF-1. The differentiation of mucinous BAC from metastatic colonic adenocarcinoma, which is also typically CK20 positive, is aided with positive staining for the CDX2 homebox gene [110,2124]. Prostate specific antigen, prostatic acid phosphatase and gross cystic disease fluid protein 15 may identify metastatic adenocarcinomas of prostate and breast origin, respectively [403,1780]. Differentiation between pulmonary adenocarcinoma and epithelioid malignant

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**Fig. 1.34** A Mucinous ("colloid") adenocarcinoma. This subpleural tumor has a lobulated gelatinous tan-white surface. B Mucinous ("colloid") adenocarcinoma. The tumor consists of pools of mucin flooding airspaces and spreading in a permeative fashion into adjacent alveolar tissue. At low power microscopy the neoplastic cells are difficult to discern. C Mucinous ("colloid") adenocarcinoma. There is abundant mucin within alveolar spaces. Scattered clusters of tumour cells are present within the pools of mucin. Columnar mucinous epithelial cells line fibrotically thickened alveolar walls. D Signet ring adenocarcinoma. Tumour cells contain abundant cytoplasmic mucin that pushes the nucleus to the periphery. Stromal invasion adjacent to bronchial cartilage (left). From Travis et al. (2024).
mesothelioma should include clinical, macroscopic and microscopic, as well as immunohistochemical and/or electron microscopic analysis. This is addressed in detail in the pleural chapter. A typical workup should include a mucin stain, pan cytokeratin, and at least 2 general adenocarcinoma markers (e.g. CEA, CD15, or MOC 31), a marker specific for pulmonary adenocarcinoma (TTF-1) and 2 mesothelioma markers (e.g. calretinin, cytokeratin 5/6) [286,395]. When examined under the electron microscope, microvilli of malignant mesothelioma are more slender than those of pulmonary adenocarcinoma. In malignant mesothelioma, the ratio of length to diameter often exceeds 10 [2107].

The separation of a small peripheral nonmucinous BAC from AAH may be difficult. No single criterion suffices and this distinction must be based on a constellation of features. Nonmucinous bronchioloalveolar carcinoma is typically >5 mm. size with marked cellular stratification, high cell density and marked overlapping of nuclei, coarse nuclear chromatin and the presence of nucleoli, columnar cell change with cellular crowding, and micropapillary tufting. AAH usually shows no more than one of these features. Marked pneumocyte atypia may be encountered adjacent to lung scars and associated with organizing alveolar injury. In the latter situation a history of pneumonia or prior chemotherapy or radiation is very helpful. In both situations the presence of a heterogeneous population of metaplastic cells, including ciliated cells, and a relative lack of cellular crowding and cytologic monotony (which favor adenocarcinoma) are important.

Prominent bronchiolar metaplasia in fibrotic lesions such as usual interstitial pneumonia may be confused with adenocarcinoma. The presence of papillary or invasive growth and abundant intracytoplasmic mucin favors adenocarcinoma.

**Grading**

Histological grading is a qualitative assessment of tumour differentiation and is an important component of the pathology report. Grading of pulmonary adenocarcinomas is based on conventional histological criteria, including the extent to which the architectural pattern of the tumour resembles normal lung tissue, and cytologic atypia. The amount of each component should be considered.

Typically, three grades are used. Well (grade 1), moderate (grade 2), and poorly differentiated (grade 3) tumours are recognized among acinar and papillary adenocarcinomas. The bronchioloalveolar pattern is virtually always well or moderately differentiated, whereas solid adenocarcinomas are poorly differentiated. If there is evidence of more than one grade of differentiation in a tumour, the least differentiated component should be recorded as the histological grade.

**Histogenesis**

Attempts to identify the cell of origin for lung adenocarcinomas has been frustrated by the diversity of epithelial cell types lining the airways, the propensity of lung adenocarcinomas to undergo phenotypic shifts during tumour progression, and the consequent morphologic heterogeneity among different lung adenocarcinomas and even within individual tumours. The phenotypic expression is influenced by anatomic location. Centrally located tumours arising from the large bronchi typically consist of a combination of columnar cells and mucinous cells. These central adenocarcinomas likely arise from the bronchial epithelium or bronchial glands. The absence of a recognized preinvasive lesion for these central adenocarcinomas has handicapped efforts to trace their origin to a specific progenitor cell.

Most adenocarcinomas develop in the lung periphery. By light microscopy, electron microscopy, immunohistochemistry and gene expression analysis, these peripheral adenocarcinomas are composed of cells that closely resemble type II pneumocytes and Clara cells [163,481,661,800] and these cells are identified as the likely cells of origin [1021,1377,1521]. AAH is recognized as a preinvasive lesion for peripheral lung adenocarcinomas (particularly non-mucinous bronchioloalveolar carcinomas) [2125]. In AAH, the epithelial cells consist mostly of type II pneumocytes; Clara cells are more likely to be seen in bronchioloalveolar carcinomas than in AAH [481,800,1022].

**Somatic genetics**

**Cytogenetics and CGH**

Lung adenocarcinoma may be near diploid with only simple numerical chromosome changes, in particular loss of the Y chromosome and gains of autosomes 1 and 7. Alternatively, they may be hyperdiploid but also, even less commonly, hypodiploid, particularly the latter state being associated with extensive
Numerical and structural aberrations. The mean chromosome number is near the triploid range {104,1330}. The most frequent chromosomal imbalance is 1q overrepresentation {1582}. It is probably responsible for the inherent higher capacity of adenocarcinoma for hematogenous dissemination compared to squamous cell cancer because gain of the centromeric 1q region is also associated with metastasis formation {698}. Other frequently observed imbalances are deletions on chromosomes 3p, 4q, 5q, 6q, 8p, 13q and gains on 5p, 8q, 20q {104,125,698,898;1301,1330,1582}. The CGH pattern can be helpful in the differentiation from squamous cell carcinoma {1582} and in particular mesothelioma {178,1075}.

**Molecular genetics**

The genetic alterations in adenocarcinoma include point mutations of dominant oncogenes, such as the K-ras gene, and tumour suppressor genes such as p53 and p16Ink4. K-ras mutations occur in approximately 30% of adenocarcinomas {1837} but are rare in other lung cancers. Most mutations are in codon 12, with smaller numbers in codon 13 and rarely in codon 61. They are more common in cancers arising in smokers. Mutations result in constant downstream signaling resulting in proliferative stimuli. Mutations have also been described in the putative precursor lesion, atypical adenomatous hyperplasia. p53 mutations are also a negative prognostic factor for limited stage adenocarcinoma {432,1331}. Increased expression of p27, one of the cell cycle regulators, correlates with better tumour differentiation and more favourable prognosis {2200}. p16Ink4 inactivation by multiple mechanisms occurs frequently in adenocarcinomas and may be smoking related {1300}. LKB1/STK11, the gene responsible for Peutz-Jeghers syndrome, is reported to be frequently inactivated in adenocarcinoma of the lung {1733}. Other important changes frequent in adenocarcinomas, but also present in smaller numbers of other non-small cell carcinomas, are over-expression of the HER2/Neu and COX-2 genes.

**Expression profiles**

Recently, using the microarray technique, several genome-wide analyses have been reported. For example, using gene expression profiling, lung carcinomas have been subdivided into several groups and it has been possible to discriminate primary cancers from metastases of extrapulmonary origin {163,661,1332,1638,2147}. The abnormal expression of genes involved in maintaining the mitotic spindle checkpoint and genomic stability contributes to the molecular pathogenesis and tumour progression of tobacco smoke-induced adenocarcinoma of the lung {1332}. Alterations in cell cycle genes have also been identified in lung adenocarcinoma using gene expression profiling {1830}.

Gene expression profiles revealed by microarray analyses have been found to be of prognostic significance in adenocarcinomas. Two studies have focused on classifying lung adenocarcinomas {163,661} using hierarchical clustering (535) to identify sub-classes in an unbiased fashion. Two of these subclasses are highlighted below. One adenocarcinoma subgroup is comprised of tumours that express neuroendocrine markers, such as l-aromatic amino acid decarboxylase, the human achaete-scute homolog 1 (hASH1), and insulinoma-associated 1. This expression pattern was associated with a significant decrease in patient survival when compared to other adenocarcinomas {163}. Adenocarcinoma group 1 of the cDNA microarray expression study {661} shared significant patterns of relatively high-level gene expression with adenocarcinoma group C4 in the oligonucleotide array study {163}. These studies identified a subset of adenocarcinoma that appeared to express markers of alveolar type II pneumocytes {661}. High relative expression levels of surfactant protein genes and several other shared genes, including BENE, cytochrome b5, and selenium-binding protein 1, characterize these two groups. These samples were often diagnosed as bronchioloalveolar carcinomas {163} and appear to form a clear and distinct branch within the adenocarcinomas. More recently, a risk index compiling the relative expression of 50 genes was developed to identify high or low risk groups of Stage I adenocarcinomas that correlated inversely with patient survival {133} Using an independent, non-selective gene expression analysis method, serial analysis of gene expression or SAGE {623,1420} demonstrated that lung adenocarcinoma exhibits distinct molecular characteristics as observed by the oligonucleotide microarray {163}. Furthermore, SAGE analyses also identified the down regulation of several p53 regulated genes and the over expression of immuno-related genes in lung adenocarcinoma {1420}.

Matrix-assisted laser desorption/ionisation mass spectrometry has been utilized to classify lung tumors based on their proteomic profile. In one study, proteomic spectra were obtained for 79 lung tumors and 14 normal lung tissues {2194}. More than 1600 protein peaks were detected from histologically selected 1 mm diameter regions of single frozen sections from each tissue. Classification models based on differentially expressed peaks enabled the classification of lung cancer histologies, distinction between primary tumors and metastases to the lung from other sites, and classification of nodal involvement with 85% accuracy {2194}.

**Prognostic and predictive factors**

Radiologic features

Lesions with a component of ground glass opacity found in the context of CT screening, when resected, were found to be 1) atypical adenomatous hyperplasia, if very small, and when larger either 2) bronchioloalveolar carcinoma or 3) mixed adenocarcinoma with BAC and other patterns {819,1324,1425}. Kodama et al. {1039} showed that the ground-glass component correlates with the bronchioloalveolar carcinoma component in the histologic specimen. CT screening which started in 1993 in Japan, showed long-term survival of patients with nodules to be associated with ground glass opacity {1038,1039,2112,2192}. All of these studies show a more favourable prognosis for patients with tumours having a larger ground-glass component than a solid component, with long-term survival rates of up to 100%. Suzuki {1926} showed that none of the 69 cases of lung cancer found in sub-solid nodules had lymph node metastases and all were alive with a median follow-up time of 35 months. Takashima et al found that the presence of air bronchograms was an independent predictor of prognosis {1951}.

Histopathological criteria

Histological grading has prognostic implications. In general, patients with Adenocarcinoma 43
poorly differentiated adenocarcinomas have more local recurrences and lymph node metastases than patients with well or moderately differentiated tumours [371]. However, histological grade may not be of prognostic importance in peripheral T1 adenocarcinoma [408]. The papillary pattern, including cases with a micropapillary pattern, appears to represent an unfavorable prognostic finding [1335, 1484, 1825]. Histologic parameters that correlate with unfavourable prognosis include high histologic grade and vascular invasion [391]. Also considered promising, as unfavourable prognostic indicators are increased mitotic activity, relatively few tumour infiltrating lymphoid cells, and extensive tumour necrosis [391, 1934]. Histologic assessment that relates to stage (pleural invasion, evaluation of resection margins, assessment of sampled lymph nodes, search for intrapulmonary metastases) are all important and should be carefully evaluated in each case. The diagnosis of bronchioloalveolar adenocarcinoma (BAC) is restricted to cases showing no pleural, vascular, or stromal invasion. In some series this applies to up to 20% of resected adenocarcinomas [1993]. The 5-year survival for localized resected BAC is 100% [1484, 1929, 1993, 2208]. Recent studies [1929, 1993, 2208] suggest that adenocarcinomas with a predominant BAC pattern and central scarring less than 0.5 cm in tumours of 3 cm or less in diameter or p-T1 tumours, (regardless of the issue of invasion) have a similar, very favourable prognosis. Up to 30% of resected adenocarcinomas may be in this category [1993]. In a study by Maeshima et al small adenocarcinomas (less than 2.0 cm) showing a bronchioloalveolar pattern without a central desmoplastic reaction showed 100% survival at ten years. The prognostic effect of the stromal reaction in small adenocarcinomas is important. Cases with central scars less than 0.5 cm in diameter (even if stromal invasion is present in this focus) have a very favourable prognosis [1222, 1929, 1993, 2208].

These data, the radiologic studies above [1038, 1039, 1952, 2112, 2192], and other recent studies [912] suggest that limited resection (eg. wedge resection) may be reasonable for small (< 2 cm., with good CT correlation, and entirely sectioned histologically) noninvasive peripheral tumours lacking active central fibrosis. Additional prospective confirmatory studies are necessary. This approach would render the distinction between AAH and BAC less critical for small lesions that have been entirely removed. Ishiwa et al. [912] showed that 13 of 54 patients (24%) with adenocarcinomas <2 cm. lacking fibroblastic proliferation and invasion (BAC) had no lymph node metastases on routine sectioning and with cytokeratin staining looking for micrometastases. Bronchioloalveolar differentiation and never-smoking history predicts sensitivity to IRESSA in advanced non-small cell lung carcinoma [1321].

Genetic predictive factors
There are no universally accepted genetic factors predictive of prognosis that have become part of routine clinical practice at the present time. Some promising preliminary studies have appeared. K-ras oncogene activation by point mutation correlates with poor survival and is also associated with the effect of chemotherapy at advanced stage (1670). Another important prognostic factor is p53 gene mutation. The negative prognostic effect of p53 alteration is highly significant especially in adenocarcinoma both at the protein and DNA level [1331]. Also predictive of poor survival is the overexpression of p185neu (c-erbB2 oncogene-encoded protein) [1451]. Mutations in the EGFR gene have been found in patients who respond to the inhibitor of the EGFR signaling pathway IRESSA (gefitinib) [1217, 1530]. Testing 3 molecular markers — c-Ki-ras, p53, and c-erbB2 — appears to improve the estimation of prognosis [1767]. In addition to these gene alterations, prognostic significance has been reported in many genes, although this is still controversial. For example, while expression of p21WAF1 is associated with favourable prognosis, expressions of cyclin D and p16 genes are associated with poor prognosis [589, 1012, 1479, 2092].

Several studies using gene expression profiling have begun to identify prognostically significant subsets of lung adenocarcinoma [163, 661, 715]. Loss of heterozygosity at chromosomes 2q, 9p, 18q, and 22q occurs frequently in advanced non-small cell lung carcinoma (NSCLC) plays an important role in the progression of NSCLC and predicts poor survival [1813]. Although reports of functional losses of the repair genes in adenocarcinoma have been infrequent, there have been reports that allelic imbalances at 9p and 22q with p53 alteration correlates with shortened survival [2011].
Large cell carcinoma

Definition
Large cell carcinoma is an undifferentiated non-small cell carcinoma that lacks the cytologic and architectural features of small cell carcinoma and glandular or squamous differentiation.

ICD-O codes
Large cell carcinoma 8012/3
Large cell neuroendocrine carcinoma 8013/3
Combined large cell neuroendocrine carcinoma 8013/3
Basaloid carcinoma 8123/3
Lymphoepithelioma-like carcinoma 8082/3
Clear cell carcinoma 8310/3
Large cell carcinoma with rhabdoid phenotype 8014/3

Synonyms
Large cell carcinoma has previously been called large cell anaplastic carcinoma and large cell undifferentiated carcinoma. Before the description of large cell neuroendocrine carcinoma terms such as large cell neuroendocrine tumour (769), neuroendocrine carcinoma with intermediate differentiation (2109), atypical endocrine tumour of the lung (1283), and large cell carcinoma of the lung with neuroendocrine differentiation (2135) were used for tumours that we now call large cell carcinoma with neuroendocrine differentiation. LCNEC was described in 1991 (216); basaloid carcinoma was described in 1992 (216) and both tumours were recognized as distinct clinicopathological entities by the WHO in the 1999 classification (2024).

Epidemiology
Large cell carcinoma accounts for approximately 9% of all lung cancers (2029) in most studies (916, 1957). Large cell neuroendocrine carcinoma accounts for about 3% of lung cancer (916). All types predominate in smokers, except lymphoepithelioma-like carcinoma. Average age at diagnosis is about 60 and most patients are male (216, 916, 1390, 2026). Lymphoepithelioma-like carcinoma (LELC) is a very rare tumour, but represents 1% of lung tumours in China, affects younger, mostly female patients (mean age 57) and only 40% are smokers (324, 331, 340, 770, 771, 2168).

Clinical features
Signs and symptoms
Symptoms are common with those of other NSCLC. Most tumours are peripheral except basaloid carcinoma. Ectopic hormone production is uncommon in LCNEC (475).

Relevant diagnostic procedures
Large cell carcinomas have no particular distinguishing radiological features. The appearance depends on the site of the tumour (614). Large cell carcinomas, except basaloid carcinoma, occur preferentially in the lung periphery, so that tumours may be accessible by transthoracic fine needle aspiration biopsy as well as bronchoscopy. Specific diagnosis of LCC and variants can only be reliably achieved on surgical material.

Cytology
Most cases of LCC do not have specific discriminating cytologic features. Most cytologic samples show cellular aggregates; less often cells are dispersed. Cellular borders are indistinct so syncytia form haphazardly (673, 936, 1826). Nuclei vary from round to extremely irregular (255) with irregular chromatin distribution. Nucleoli are generally very prominent. Cytoplasm is basophilic, usually scant with a high nuclear-to-cytoplasmic (N/C) ratio.

LCNEC shows neuroendocrine features (nuclear palisading and molding), but are distinguished from SCLC by the presence of prominent nucleoli and
nuclei larger than 3 times the diameter of a small resting lymphocyte. Basaloid carcinoma in smears consists of both individual tumour cells and cohesive aggregates. Well developed nuclear palisading can be discerned at the periphery of some cellular aggregates. Lymphoepithelioma-like carcinomas show cohesive flat syncytia. Spindle-shaped tumour cells have solitary large nuclei with huge nucleoli, intimately admixed with numerous small lymphocytes.

**Macroscopy and localization**
Large cell carcinomas typically present as large, peripheral masses, frequently identified on chest radiographs, but which may also involve subsegmental or large bronchi. The tumour often invades visceral pleura, chest wall, or adjacent structures. Sectioning reveals a soft, pink-tan tumour with frequent necrosis, occasional hemorrhage and rarely, cavi
tation. Large cell neuroendocrine carcinomas are often peripheral. In contrast basaloid carcinomas characteristically show exo
ychatic bronchial growth.

**Tumour spread and staging**
The pattern of spread of large cell carcinoma is similar to other non-small cell lung carcinomas. Metastases occur most frequently to hilar or mediastinal nodes followed by metastases to the pleura, liver, bone, brain, abdominal lymph nodes and pericardium. Micrometastases detected in hilar nodes have no significant impact on prognosis in otherwise stage I tumours. Specific subtypes of large cell carcinoma differ in their pattern of spread, response to therapy and ultimate prognosis. Large cell neuroendocrine carcinoma combined large cell neuroendocrine carcinoma and basaloid carcinoma have a worse prognosis than classic large cell carcinoma. Recent studies have report

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**Fig. 1.39** Large cell neuroendocrine carcinoma. A Note numerous rosettes. B Palisading at the periphery of the nests of tumour cells and rosettes can be seen. Necrosis is present and mitoses are numerous. C High magnification shows details of rosettes and nuclei with vesicular chromatin. D Palisading and rosette-like formations. Numerous mitoses. The nuclear chromatin is vesicular and many cells have prominent nucleoli. From Travis et al. (2024).

**Fig. 1.40** A Ultrastructural aspect of neuroendocrine cells in a large cell neuroendocrine carcinoma. Numerous dense core neurosecretory granules are present in the cytoplasm. B Ultrastructural features in a combined large neuroendocrine carcinoma showing within the same cell acinus formation with apical microvilli and typical neurosecretory granules.

**Fig. 1.41** Large cell neuroendocrine carcinoma. A Chromogranin immunostaining shows a granular cytoplasmic pattern. B NCAM (CD56) immunostaining with typical membrane pattern. C TTF1 (thyroid transcription factor one) immunoreactivity with a typical nuclear pattern.
ed both a better prognosis and better response by lymphoepithelial like carcinoma to both chemotherapy and radiation therapy (302,324,331,340,770). The clinical behavior of clear cell carcinoma is similar to typical large cell carcinomas (971).

Stage distribution for LCC at diagnosis is as seen in other NSCLC. Large cell neuroendocrine carcinomas are often stage III-IV at diagnosis. Basaloid carcinoma is frequently operable at presentation but prognosis is worse than that of other NSCLC and brain metastases are more frequent (1390).

**Histopathology**

**Large cell carcinomas**

These are, by definition, poorly differentiated tumours. It is a diagnosis of exclusion made after ruling out the presence of a component of squamous cell carcinoma, adenocarcinoma or small cell carcinoma. They consist of sheets or nests of large polygonal cells with vesicular nuclei with prominent nucleoli, and a moderate amount of cytoplasm. Ultrastructurally minimal squamous or glandular differentiation is common.

**Large cell neuroendocrine carcinoma**

Large cell neuroendocrine carcinoma (LCNEC) shows histological features such as organoid nesting, trabecular growth, rosettes and perilobular palisading patterns, suggesting neuroendocrine differentiation (2024,2026). The tumour cells are generally large, with moderate to abundant cytoplasm. Nucleoli are frequent, prominent and their presence facilitates separation from small cell carcinoma. Mitotic counts are typically 11 or more (average 75) per 2 mm² of viable tumour. Large zones of necrosis are common. Confirmation of neuroendocrine differentiation is required using immunohistochemical markers such as chromogranin, synaptophysin and NCAM (CD56) (1128). One positive marker is enough if the staining is clearcut. Around 50% of LCNEC express TTF-1 (1216,1892,1894), but expression of CK 1, 5, 10, 14, 20 (34ßE12) is uncommon (1892,1893).

**Combined large cell neuroendocrine carcinoma**

A large cell neuroendocrine carcinoma with components of adenocarcinoma, squamous cell carcinoma, giant cell carcinoma and/or spindle cell carcinoma. Like small cell carcinoma, a small percentage of large cell neuroendocrine carcinomas are histologically heterogeneous. In view of the many shared clinical, epidemiologic, survival, and neuroendocrine properties between large cell neuroendocrine carcinoma and small cell carcinoma, we have arbitrarily chosen to classify these tumours as combined large cell neuroendocrine car-

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**Fig. 1.42** This large cell neuroendocrine carcinoma is combined with an acinar adenocarcinoma. From Travis et al. (2024).

**Fig. 1.43** Combined large neuroendocrine carcinoma. A NCAM (CD56) immunostaining in the large cell neuroendocrine component. Note the typical cell membrane pattern. B Combined large neuroendocrine carcinoma associated with an adenocarcinoma. The large neuroendocrine carcinoma is immunostained with chromogranin antibody.
cinoma until future studies better define their biologic behavior. Combinations with small cell carcinoma also occur, but such tumors are classified as combined variants of small cell carcinoma.

**Basaloid carcinoma**
This tumor shows a solid nodular or anastomotic trabecular invasive growth pattern, with peripheral palisading. Tumour cells are relatively small, monomorphic, cuboidal fusiform, with moderately hyperchromatic nuclei, finely granular chromatin and absent or focal nucleoli. Cytoplasm is scant but nuclear molding is absent. Mitotic rate is high (15-50 per 2 mm²). Squamous differentiation is absent. Most basaloid carcinoma have hyalin or mucoid degeneration in the stroma. Frequent small cystic spaces are seen. Comedo type necrosis is common. Rosettes are seen in one third of cases. Immunohistochemical stains for neuroendocrine markers are generally negative. In 10% of cases, one neuroendocrine marker may be positive in less than 20% of tumour cells. Cytokeratin expression is as seen in NSCLC, and includes CK 1, 5, 10, and 14 (34ßE12), markers. Basaloid carcinoma does not express TTF-1 (1892).

**Lymphoepithelioma-like carcinoma**
Pulmonary lymphoepithelial-like carcinoma is characterized by a syncytial growth pattern, large vesicular nuclei, prominent eosinophilic nucleoli, and heavy lymphocytic infiltration (302,324, 331,340,770) It has predominantly pushing border, infiltrating in the form of diffuse sheets. The prominent lymphoid reaction consists of mature lymphocytes often admixed with plasma cells and histiocytes with occasional neutrophils or eosinophils. The lymphoid component is seen even in metastatic sites. In rare cases, there is intratumoural amyloid deposition. EBER-1 RNA is present in the nuclei of the large undifferentiated neoplastic cells.

**Clear cell carcinoma**
Clear cell carcinomas have large polygonal tumour cells with water-clear or foamy cytoplasm. Tumour cells may or may not contain glycogen.

**Large cell carcinoma with rhabdoid phenotype**
In large cell carcinoma with rhabdoid phenotype, at least 10% of the tumour cell population must consist of rhabdoid cells, characterized by eosinophilic cytoplasmic globules (304), consisting of intermediate filaments, which may be positive for vimentin and cytokeratin (304,1803). Pure large cell carcinomas with a rhabdoid phenotype are very rare. Small foci of adenocarcinoma (1803), and positive neuroendocrine markers may be seen. Ultrastructurally the eosinophilic inclusions are composed of aggregates of large intra cytoplasmic paranuclear intermediate filaments. Cells with rhabdoid features may be seen focally in other poorly differentiated NSCLC.

**Differential diagnosis**
The differential diagnosis of large cell carcinoma (NOS) includes poorly differentiated squamous cell carcinoma in which foci of keratinization and/or intercellular bridges are present and solid type adenocarcinoma, where a minimum of 5 mucinous droplets are present in at least 2 high power fields. The major differential diagnosis for LCNEC is atypical carcinoid (AC) and basaloid carcinoma. LCNEC is distinguished from atypical carcinoid primarily by a higher mitotic index (11 or more per 2mm²) and usually more extensive necrosis. Differential diagnosis between LCNEC and basaloid carcinoma is more difficult on H&E morphology alone and is usually achieved using neuroendocrine markers, since both tumours disclose palisading and one third of basaloid carcinoma show rosettes. Cytokeratins 1, 5, 10, 14 are
expressed (34ßE12) in other NSCLC but are typically negative in LCNEC (1892,1893). Basaloid carcinoma must be distinguished from poorly differentiated squamous carcinoma. Although initially described with 2 forms, one pure and one mixed, the latter is now considered as the basaloid variant of squamous cell carcinoma. Occurrence of even focal squamous differentiation favors the diagnosis of basaloid variant of squamous carcinoma. Small cell carcinoma enters the differential diagnosis of basaloid carcinoma due to their small cell size and high mitotic rate, but nuclear to cytoplasmic ratio is higher in SCLC and nuclear chromatin is vesicular rather than finely granular. The prominent inflammatory cell infiltrate, which characterises lymphoepithelioma-like carcinoma, may lead to consideration of inflammatory pseudotumour, malignant lymphoma (1262), or primary lymphoid hyperplasia of the lung. A panel of immunohistochemical stains allows recognition of the malignant epithelial cells, characteristically patchy in distribution, as well as CD8+ expression by the lymphocytic infiltrate.

Clear cell carcinoma of the lung resembles metastatic clear cell carcinomas arising in organs such as the kidney, thyroid and salivary gland. If squamous or glandular differentiation is seen, the tumour is classified as a clear cell variant of squamous cell or adenocarcinoma, respectively.

Precursor lesions
There is no precursor lesion identified for large cell carcinoma except for basaloid carcinoma. Adjacent squamous dysplasia in one third of basaloid carcinoma, their pattern of infiltration, and both their immunophenotype and ultrastructure characteristic of bronchial reserve cells (216,222,1281), supports an origin from bronchial preneoplastic lesions. Lymphoepithelioma-like carcinoma is characterised by the presence of EBV viral sequences, reflecting viral (EBER1) dependent transformation of lung epithelial cells.

Histogenesis
These tumours originate from a common pluripotent progenitor cell capable of multidirectional differentiation (1282, 2024). Neuroendocrine differentiation in LCNEC does not imply origin from a specific neuroendocrine cell. In contrast to carcinoid tumours, LCNEC is not associated with diffuse neuroendocrine hyperplasia.
plasia, tumourlets or MEN1 mutations [464]. Cells of basaloid carcinoma display the immunohistochemical and ultrastructural phenotype of reserve suprabasal bronchial cells. [216,222, 1281]

Clear cell and rhabdoid variants of LCC probably reflect the pluripotent capacity of the LC progenitor cell.

**Somatic genetics**

**Cytogenetics and CGH**

Large cell carcinoma of the lung is mostly an aneuploid neoplasm with the highest mean chromosome number and DNA content of all lung cancer types being in the near triploid range or above [1581]. Accordingly, the karyotypes are complex and indicate a high chromosomal instability [1330] of which the major biological effect is probably the generation of DNA copy number changes. The CGH pattern of classical, non-neuroendocrine large cell carcinoma shows similarities to lung adenocarcinoma and squamous cell carcinoma like overrepresentations on 1q and 3q [178,898]. In particular, the tumours harbour imbalances that have been associated with progression and metastasis formation, e.g. amplifications of 1q21-q22, 8q and deletion of 3p12-p14, 4p, 8p22-p23, 21q. Large cell neuroendocrine carcinoma may carry very similar chromosomal imbalances as small cell lung carcinoma [898,2051, 2052].

**Molecular genetics**

Large cell carcinomas share the molecular and genetic alterations commonly seen in NSCLC, since it is a poorly differentiated tumour issued from the same stem cells, exposed to the same carcinogens. K-ras mutations, P53 mutations and Rb pathway alteration (loss of P16INK4, hyperexpression of cyclin D1 or E) occurs with the same frequency as in other NSCLC. Large cell neuroendocrine carcinomas have P53 and Rb mutational patterns in addition to inactivation pathways similar to SCLC [212, 215,217,1516,1622]: a high frequency of P53 mutation, of bcl2 overexpression, lack of bax expression [217], high telomerase activity, but lower frequency of Rb / P14ARF loss of protein, and of E2F1 overexpression than SCLC [549,550]. They display a low frequency of P16 loss, cyclin D1 and cyclin E overexpression, and lack MEN1 mutation and allelic deletion. Fas is downregulated but its ligand FasL is strongly upregulated [2083].

**Histopathological criteria**

It is controversial whether the presence of neuroendocrine differentiation demonstrated by immunohistochemistry has any prognostic significance in NSCLC (NSCLC-NED). Some studies indicate a worse prognosis [841,916,1566], others a better prognosis [289,1759] and others show no difference in survival [651,1833, 1905]. In addition studies have suggested NSCLC-NED have a better prognosis [735] or no difference in response to chemotherapy [1448].

**Genetic predictive factors**

The genetic predictive factors of large cell carcinoma should correspond to those of general primary lung carcinoma. However, one variant of large cell carcinoma – large cell neuroendocrine carcinoma (LCNEC) – has specific genetic characters similar to SCLC: allelic losses of 3p21, FHIT, 3p22-24, 5q21, 9p21, and the RB gene. All of these markers correlate with poor prognosis in neuroendocrine carcinoma including LCNEC. Both p53 gene loss and point mutation also correlate with poor survival [1516].

**Fig. 1.48** DNA copy number changes in 18 classical (non-neuroendocrine) large cell carcinomas detected by CGH. Areas on the left side of the chromosome ideogram reflect loss of genetic material, those on the right side to DNA gains. DNA changes with 99% significance are coloured in blue, additional changes with 95% significance are depicted in green. The proportion of pronounced DNA imbalances are visualised in red; they typically represent high copy amplifications or multiple copy deletions.

**Prognosis and predictive factors**

**Clinical criteria**

Clinical prognostic criteria are not different from other NSCLC. The major criterion is performance status at diagnosis and the disease extension reflected by the TNM and stage. Although most basaloid carcinomas present as stage I-II tumours, they bear a dismal prognosis in contrast with lymphoepithelioma-like carcinoma, which present at extended stage but have better prognosis than NSCLC. A direct correlation between larger tumour size and high stage and titre of EBV serology has been demonstrated in lymphoepithelioma-like carcinoma [331]. There is no significant difference in the prognosis between LCNEC and SCLC after stratification by stage. There is a significantly shorter survival for stage I LCNEC as compared with stage I NSCLC [1957] and stage I large cell carcinoma [916]. The outcome of carefully staged LCNEC may be better than previous studies have indicated [2229].

Clinical criteria
Adenosquamous carcinoma

**Definition**
A carcinoma showing components of both squamous cell carcinoma and adenocarcinoma with each comprising at least 10% of the tumour.

**ICD-O Code**
8560/3

**Clinical features**

**Signs and symptoms**
The frequency of adenosquamous carcinoma is between 0.4-4% of lung carcinomas (586,909,1445,1867,1950,2203). Their incidence might be rising parallel to the increase of adenocarcinoma (1868). The majority of patients are smokers. Clinical presentation and behavior is similar to adenocarcinoma.

**Imaging and relevant diagnostic procedures**
Since most tumours are peripheral their diagnosis can be assessed by bronchoscopy in segmental or subsegmental bronchi, or by transthoracic needle biopsy. However their recognition is sampling dependent, the likelihood of identifying both components in small samples is small, and diagnosis is more definitive on surgical samples. Radiographic features are not different from those of non-small cell carcinoma; peripheral tumours may show central scarring and indentation or puckering of the overlying pleura. Some may display a rim of ground glass opacity.

**Macroscopy and localization**
Adenosquamous carcinomas are usually located in the periphery of the lung and may contain a central scar. They are grossly similar to other non-small cell carcinomas.

**Tumour spread and staging**
Metastases usually show the same combination of squamous and glandular differentiation as the primary. The spread of adenosquamous carcinoma is similar to other non-small cell carcinomas. They show early metastases and a poor prognosis (84).

**Histopathology**
As there is a continuum of histological heterogeneity with both squamous cell and adenocarcinoma, the criterion of 10% for each component is arbitrary. Since some squamous cell carcinomas show focal mucin on histochemical stains the adenocarcinoma component is more easily defined if it shows an acinar, papillary or bronchioloalveolar pattern. Well-defined squamous cell carcinoma and adenocarcinoma are evident on light microscopy, the squamous cell carcinoma showing unequivocal keratin or intracellular bridges and the adenocarcinoma showing acini, tubules or papillary structures. The diagnosis of an adenocarcinoma component is difficult if it is confined to a solid pattern with mucin formation. More than 5 mucin droplets per high power field are then required for a diagnosis of adenocarcinoma. The two components may be separate or may merge and mingle. The squamous or the glandular component may be predominant or may be seen in equal proportion. The degree of differentiation of each component is not interdependent and is variable. A component of large cell carcinoma may be present in addition to the 2 other components but does not change the diagnosis. The same stromal features with or without inflammation occur as in other non-small cell lung carcinomas. Cases with amyloid-like stroma have been described (2217), as seen in salivary gland type neoplasms. Ultrastructural features are those of squamous carcinoma and adenocarcinoma. By electron microscopy features of both cell types are common but tumour classification is based on light microscopy. Immunohistochemical findings also recapitulate both squamous and adenocarcinoma characteristics. They express cytokeratins with a wide molecular weight range including AE1/AE3, CAM 5.2, KL1, and CK7 but usually not CK20. EMA is positive and TTF-1 positivity is confined to the adenocarcinoma component.

**Differential diagnosis**
The differential diagnosis includes entrapment of alveolar or bronchiolar acinar structures within a squamous cell

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Fig. 1.49 Adenosquamous carcinoma. The tumour consists of squamous cell carcinoma (left) and papillary adenocarcinoma (right). From Travis et al. (2024).
carcinoma. This should not be mistaken for glandular differentiation of the cancer. Similarly, adenocarcinoma may be associated with squamous metaplasia of entrapped bronchiolar structures. Mucoepidermoid carcinoma enters the differential diagnosis. Arising from bronchial glands, low-grade mucoepidermoid carcinoma are centrally located and show histologic features identical to their salivary gland counterpart, with mixture of mucinous glands, intermediate or squamoid cells, with no or mild atypia. High grade mucoepidermoid carcinoma is more difficult to differentiate from adenosquamous carcinoma. In favour of mucoepidermoid carcinoma is the characteristic admixture of mucinous and squamoid cells, a proximal exophytic endobronchial location, areas of classic low grade mucoepidermoid carcinoma, absence of keratinisation or squamous pearl formation without overlying in situ squamous cell carcinoma [2217,2221], or tubular, acinar, and papillary growth pattern. These two lung tumours cannot be distinguished reliably in all cases [1348].

**Histogenesis**
The cell of origin is believed to be a pluripotential bronchial reserve cell. It has been proposed that adenocarcinomas according to their central (bronchial) or peripheral (alveolar parenchyma) location arise from two distant stem cells, bronchial epithelial and Clara cell type respectively [402] with different mutational patterns. Since most adenocarcinomas have mixed patterns combining both central (acinar, solid) and peripheral (bronchioalveolar, papillary) adenocarcinoma patterns, it is likely they originate, like adenosquamous carcinoma, from a common intermediate bronchial-Clara type II cell type.

**Somatic genetics**
There is no information specifically available on adenosquamous carcinoma with regard to cytogenetics and CGH, expression profile and proteomics. The molecular genetic alterations of each component are those characteristic of squamous and adenocarcinoma respectively. They may display Ras mutations similar to peripheral adenocarcinoma.

**Prognosis and predictive factors**
The histologic criteria for the diagnosis in these studies vary, and should be kept in mind when comparing results. They have a poor prognosis with a 5-year survival rate after resection of 62.5% for localized disease and 35% for resectable cases [909]. The prognosis is poorer than that of stage I-II squamous carcinoma or adenocarcinoma, and this histological type was shown to be an independent prognostic determinant at limited stage. The SEER results report an overall 21% 5-year survival.

**Genetic predictive factors**
There are no specific studies reported for adenosquamous carcinoma, although they have been included in non-small cell lung carcinomas. Ras and P53 mutations might be an unfavorable prognostic factor in stage I tumours.

**Fig. 1.50** Adenosquamous carcinoma showing a squamous cell lobule on the left, adjacent to an acinar adenocarcinoma on the right.
Sarcomatoid carcinoma

Definition
Sarcomatoid carcinomas are a group of poorly differentiated non-small cell lung carcinomas that contain a component of sarcoma or sarcoma-like (spindle and/or giant cell) differentiation. Five subgroups representing a morphologic continuum are currently recognized: Pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma.

ICD-O codes
- Pleomorphic carcinoma: 8022/3
- Spindle cell carcinoma: 8032/3
- Giant cell carcinoma: 8031/3
- Carcinosarcoma: 8980/3
- Pulmonary blastoma: 8972/3

Synonyms
An alternative classification recognizing monophasic and biphasic varieties with the latter further classified as homologous or heterologous is not currently recommended.

Epidemiology
These tumours are rare, accounting for approximately only 0.3-1.3% of all lung malignancies. The average age at diagnosis is 60 years, and the male to female ratio is almost 4 to 1. Biphasic blastomas are exceptional in that they afflict men and women equally with an average age in the fourth decade.

Etiology
The factors implicated in the etiology of sarcomatoid carcinomas are similar to those involved in conventional histotypes. Tobacco smoking is the major factor; more than 90% of patients with pleomorphic carcinoma are heavy cigarette smokers. Some cases may be related to asbestos exposure.

Localization
Sarcomatoid carcinomas can arise in the central or peripheral lung. A predilection for the upper lobes has been reported. Pleomorphic carcinomas are often large peripheral tumours with a tendency to invade the chest wall.

Clinical features
Signs and symptoms
Signs and symptoms are related to tumour localization. Since central endobronchial tumours tend to protrude into the lumina of large airways, patients often present with cough, haemoptysis, and progressive dyspnoea or fever due to recurrent pneumonia. Peripheral tumours, especially pleomorphic carcinoma, grow to large sizes and often present with chest pain due to pleural or chest wall invasion.

Relevant diagnostic procedures
Due to sampling issues and histologic heterogeneity, the diagnosis of virtually all sarcomatoid carcinomas requires a surgical specimen. Based on cytology or a small biopsy specimens one might rarely suspect a diagnosis of pleomorphic, spindle cell or giant cell carcinoma, however it would be impossible to make a definitive diagnosis.

Cytology
Pleomorphic carcinoma consists of malignant giant and/or spindle cells and epithelial components such as squamous or adenocarcinoma in smears. The spindle and/or giant cells occur as cohesive aggregates of tumour cells, generally lacking any glandular or squamous differentiation. The neoplastic spindle cells are pleomorphic and elongated, singly or in loose clusters, bundles or tissue fragments. Nuclei are solitary, large and spindled, with prominent nucleoli. Nuclear-to-cytoplasmic ratios are high. Fragments of myxoid matrix

Fig. 1.51 Pleomorphic and sarcomatous carcinoma. A Huge individual neoplastic cells some of which have ovoid nuclei and one or two tails of basophilic cytoplasm. Several cells are multinucleated. Note the abnormal mitotic figure. Cohesion is distinctly lacking (Diff-Quik stain). B Solitary, huge multinucleated tumour giant cell in an aspiration biopsy of a giant cell carcinoma. The cell has multiple fused nuclei with coarse chromatin and distinct nucleoli (Diff-Quik stain).
material may also be identified, as may malignant tumour giant cells. Both cell types are usually positive for cytokeratins in cell blocks.

Spindle cell carcinoma features malignant spindle cells with nuclear hyperchromasia and irregular, distinct nucleoli. Cohesion is generally better preserved than with true sarcomas, but isolated spindled epithelial cells may also be seen.

Giant cell carcinoma is cellular in cytological preparations and is characterized by a marked lack of intercellular cohesion [420,1489]. Accordingly, numerous individual multinucleated neoplastic giant cells are present. The nuclei vary from round and smooth to highly irregular with large nucleoli, which are often multiple, and coarse darkly stained chromatin granules. Cytoplasm may be abundant in these cells. Another characteristic feature is the smear background, which includes granular necrotic material and neutrophil leukocytes. Neutrophil emperipolesis is also characteristic. When the malignant epithelial component is not evident within the smears, it could be difficult or impossible to distinguish a spindle cell or a giant cell carcinoma from a primary or metastatic spindle cell or pleomorphic sarcoma, respectively, based solely on cytomorphology [626,2182]. Here, immunocytochemistry performed on the smears or cell blocks, or obtaining an additional sample may be helpful.

In carcinosarcoma, and blastoma the cytologic smears contain heterologous sarcomatous elements, such as malignant cartilage, bone, or skeletal muscle, in addition to obvious carcinoma.

**Macroscopy**

Peripheral tumours are usually greater than 5 cm, well circumscribed and feature grey, yellow or tan creamy, gritty, mucoid and/or hemorrhagic cut surfaces with significant necrosis. Sessile or pedunculated endobronchial tumours are smaller and often infiltrate underlying lung parenchyma [265,584,1213,1430,1440,1442,1695]. Peripheral pulmonary blastomas are significantly larger than most NSCLC with a mean diameter of 10 cm.

**Tumour spread and staging**

These very aggressive tumours metastasize widely to the same sites as NSCLC, including unusual sites such as the esophagus, jejunum, rectum and kidney [154,265,330,584,1430]. Peripheral tumours usually present at a more advanced stage than central lesions. In general, stage at diagnosis is similar to that reported for the other non-small cell lung cancers [443,584,1213,1430,1440,1695].
Histopathology

Pleomorphic carcinoma

A poorly differentiated non-small cell carcinoma, namely squamous cell carcinoma, adenocarcinoma or large cell carcinoma containing spindle cells and/or giant cells or, a carcinoma consisting only of spindle and giant cells. The spindle or giant cell component should comprise at least 10% of the tumour and while the presence of adenocarcinoma or squamous cell carcinoma should be documented, foci of large cell carcinoma need not be mentioned. Histologic sections demonstrate conventional non-small cell carcinoma, namely adeno-, squamous cell or large cell subtypes, intimately associated with at least 10% malignant spindle cells and/or giant cells. Mitotically active spindle cells arranged haphazardly in a fascicular or storiform growth pattern have varying morphologic appearances ranging from epithelioid to mesenchymal sometimes with occasional smooth muscle features. The stroma may be fibrous or myxoid. Dyscohesive malignant giant cells are polygonal, uni- or multinucleated, and have dense eosinophilic cytoplasm and pleomorphic nuclei. Emperipolesis is often present and large vessel invasion along with extensive necrosis are commonly seen. Rarely squamous cell carcinomas have an angiosarcomatoid component that has been called pseudoangiosarcomatous carcinoma. This is characterized by anastomosing channels lined by anaplastic, epithelioid cells focally aggregated in pseudopapillae and forming spaces filled with erythrocytes [1441,1442,1662].

Spindle cell carcinoma

This variant is defined as a non-small cell carcinoma consisting of only spindle-shaped tumour cells. Identical to the spindle cell component of pleomorphic carcinoma, cohesive nests and irregular fascicles of overtly malignant cells feature nuclear hyperchromasia and distinct nucleoli. Specific patterns of adenocarcinoma, squamous cell, giant cell or large cell carcinoma are not seen. Scattered and focally dense lymphoplasmacytic infiltrates surround and percolate through the tumoural mass. Rare cases with prominent inflammatory infiltrates may resemble inflammatory myofibroblastic tumour.

Giant cell carcinoma

A non-small cell carcinoma composed of highly pleomorphic multi- and/or mononucleated tumour giant cells. Identical to the giant cell component of pleomorphic carcinoma, this tumour is composed entirely of giant cells and does not have specific patterns of either adenocarcinoma, squamous cell or large cell carcinoma. This tumour consists of very large, multinucleated and bizarre cells. Nuclei are pleomorphic, and often multilobed. The tumour cells are discohesive and tend to dissociate from each other [19,20,88,218,584,686,1695,2023, 2024]. There is generally a rich inflammatory infiltrate, usually of neutrophils, which frequently invade the tumour cells. This phenomenon was initially thought to represent phagocytosis by the tumour cells, but more probably reflects emperipolesis (active penetration of the leukocytes into the tumour cells) [934]. By electron microscopy, aggregates of paranuclear filaments and tonofibrils may be observed both in spindle cell and giant cell carcinomas [19,20,124,337, 584,1440,1664,1909,2023]. In giant cell
carcinoma, only very occasional desmosomes are seen.

**Carcinosarcoma**
This variant is defined as a malignant tumour with a mixture of carcinoma and sarcoma containing differentiated sarcomatous elements, such as malignant cartilage, bone or skeletal muscle. The tumour is histologically biphasic, with a mixture of a conventional non-small cell lung carcinoma and true sarcoma containing differentiated elements. The carcinomatous component is most often squamous cell carcinoma (45-70%), followed by adenocarcinoma (20-31%), and large cell carcinoma (10%) [1061]. An epithelial component resembling so-called high grade fetal adenocarcinoma can occur in nearly 20% of cases, but the blastematosus stroma of pulmonary blastoma is lacking [1061, 1436]. The malignant stroma often forms the bulk of carcinomas, and only small foci of carcinoma may be seen. A significant component of these sarcomas is often poorly differentiated “spindle cell” sarcoma, but a careful search always shows areas of more specific sarcomatous differentiation, most often rhabdomyosarcoma, followed by osteosarcoma or chondrosarcoma or combinations of osteosarcoma and chondrosarcoma [1061]. More than one differentiated stromal component can be present. While metastatic foci usually feature both epithelial and mesenchymal components, lesions may contain only one pattern.

**Pulmonary blastoma**
This is a biphasic tumour containing a primitive epithelial component that may resemble well-differentiated fetal adenocarcinoma and a primitive mesenchymal stroma, which occasionally has foci of osteosarcoma, chondrosarcoma or rhabdomyosarcoma [2024]. Pulmonary blastoma shows histologically a biphasic pattern with malignant gland growing in tubules that resemble fetal bronchioles, embedded in a sarcomatous embryonic-appearing mesenchyme (1857). The glycogen-rich, non-ciliated tubules and primitive stroma resemble that seen in fetal lung between 10-16 weeks gestation (the pseudoglandular stage of lung development) [2225]. The tubules can be well differentiated, resembling those reported in well-differentiated fetal adenocarcinomas, but they are usually less abundant. The tubules may also resemble a high-grade fetal adenocarcinoma. These tubules are lined by pseudostratified, non-ciliated columnar cells that have clear or lightly eosinophilic cytoplasm. The nuclei of the epithelial cells are oval or round and fairly uniform, but there can be cytologic atypia in the form of large multinucleated cells [2225]. The glands often have subnuclear or supranuclear vacuoles, producing an endometrioid appearance. The cytoplasmic vacuoles are due to abundant glycogen, readily demonstrated in periodic acid-Schiff stains. There may be small amounts of mucin within the glandular
lumens, but intracellular mucin is unusual. Similar to fetal adenocarcinomas, morular structures consisting of squamoid nests may be seen [605,917,1064,1435,2225]. Stromal cells generally have a blastemalike configuration. There is condensation of small oval and spindle cells in a myxoid stroma around neoplastic glands, similar to the appearance of Wilm’s tumour of the kidney. Small foci of adult-type spindle cell sarcoma (most commonly showing a fascicular or storiform pattern) can be present. Foci of differentiated sarcomatous elements such as rhabdomyosarcoma, chondrosarcoma or osteosarcoma may be found [605,1064].

Immunohistochemistry

**Pleomorphic, spindle and or giant cell carcinoma**
Expression of epithelial markers in the spindle and/or giant cell component of a pleomorphic carcinoma is not required for the diagnosis so long as there is a component of squamous cell carcinoma, adenocarcinoma, or large cell carcinoma [218,584,1430,1695,2023,2024]. Since these are poorly differentiated tumours, in some cases, multiple keratin antibodies and EMA are necessary to demonstrate epithelial differentiation in the sarcomatoid component. When pure spindle cell carcinomas fail to stain with any epithelial marker, separation from sarcoma may be difficult. The tumour cells often co-express cytokeratin, vimentin, carcinoembryonic antigen, and smooth muscle markers [20,88,337,584,1695]. TTF-1 may be positive in giant cell carcinomas.

**Carcinosarcoma**
The epithelial component of carcinosarcomas may stain with keratin antibodies. Chondrosarcoma will stain with S-100 protein and rhabdomyosarcoma with muscle markers.

**Pulmonary blastoma**
The fetal adenocarcinoma component of pulmonary blastomas will stain for epithelial markers (keratin, EMA and CEA) and it may be positive for neuroendocrine markers such as chromogranin A as well in both morular and glandular cells [1064,1435]. The tumour cells can also express specific hormones, such as calcitonin, gastrin-releasing peptide, bombesin, leucine and methionine enkephalin, somatostatin and serotonin. This type of staining mimics that seen in developing fetal lung tubes [2225]. The epithelial component of blastomas diffusely stains with antibodies to epithelial markers, such as cytokeratin, carcinoembryonic antigen, and epithelial membrane antigen. Pulmonary blastomas rarely stain with alpha-fetoprotein [1824]. Both Clara cell antigen and surfactant apoprotein are expressed in epithelial cells and particularly in morules [1435,2225]. Of interest, these antigens can also be seen in developing fetal lung tubules, which show differentiation towards Clara cells beginning at 13 weeks of gestation and towards Type II pneumocytes at 22 weeks [2225].

Fig. 1.59 Pulmonary blastoma. A Biphasic appearance, with a fetal-type gland and embryonic stroma. B Solid nests of epithelial cells and glands adjacent to an area of poorly differentiated spindle cell sarcoma. C The tumour consists of a spindle cell (left) and malignant glandular component (right). The glandular component resembles a well-differentiated fetal adenocarcinoma with endometrioid morphology. D Glandular pattern of a well-differentiated fetal adenocarcinoma with palisading of nuclei and abundant clear cytoplasm. The spindle cell component has a primitive malignant mesenchymal pattern. From Travis et al. (2024).
Stromal cells of blastomas contain vimentin and muscle-specific actin. Desmin and myoglobin or S-100 protein can be seen when there is striated muscle or cartilage respectively. There is generally restriction of vimentin and cytokeratin to mesenchymal and epithelial tissues respectively [1064], but vimentin can occur in glands and stromal cells can occasionally express cytokeratin [2225].

Differential diagnosis
The differential diagnosis for pleomorphic carcinoma includes other tumours in this section as well as both primary and metastatic sarcomas. Identification of areas of non-small cell carcinoma and immunohistochemical confirmation of epithelial differentiation aid in the distinction.

Pleomorphic carcinoma may be difficult to distinguish from reactive processes and sarcomas [390,391,1440,2139]. A generous sampling (at least one section per centimeter of tumour diameter) to disclose a clear-cut carcinomatous component may be helpful in pleomorphic carcinomas, together with the use of ancillary techniques. It should be kept in mind that, although spindle cell carcinomas are rare, they are more common than primary sarcomas of the lung [1440, 2138]. Separation of spindle cell carcinoma from cytokeratin-positive sarcomas, particularly synovial sarcoma may be difficult [546,957,2236]. However, synovial sarcoma has a characteristic morphology, it tends to be only weakly or focally positive for keratin and demonstration of the X:18 translocation can be helpful. Spindle cell carcinomas may show a marked inflammatory infiltrate and therefore may be confused with an inflammatory myofibroblastic tumour or a localized area of organizing pneumonia; such a tumour with particularly bland neoplastic cells has been referred to as an inflammatory sarcomatoid carcinoma [390,391, 1440,2139]. Features favouring carcinoma include nuclear atypia coupled with brisk mitotic activity, vascular invasion, and positive immunostaining for cytokeratins, epithelial membrane antigen and thyroid transcription factor-1.

The differential diagnosis of giant cell carcinoma includes not only other types of lung carcinomas, but also primary and metastatic sarcomas including pleomorphic rhabdomyosarcoma, metastatic adrenocortical carcinoma, metastatic choriodacarcinoma and other pleomorphic malignant tumours, most of which can be distinguished by their own distinctive markers. Beta-HCG staining can be seen in up to 20-93% of non-small cell carcinomas [207] and thus does not indicate a diagnosis of metastatic choriodacarcinoma, even if serum beta-HCG is elevated. Benign osteoclast-like giant cells can populate non-small cell carcinomas, but these rare tumours should not be mistaken for giant cell carcinoma [187]. The differential diagnosis of carcinosarcoma includes other tumours considered in this section as well as metastatic lesions including teratomas arising from the female gynaecologic tract and male genital tract. Biphasic blastoma should be distinguished from a fetal adenocarcinoma, pleuropulmonary blastoma as well as primary and metastatic sarcomas including synovial sarcoma. Immunohistochemical and molecular studies in addition to morphologic features should differentiate these tumours.

Histogenesis
Sarcomatoid carcinomas represent malignant epithelial neoplasms that have undergone divergent connective tissue differentiation (“tumour metaplasia” or “divergence hypothesis”) and not “collision” tumours (multiclonal hypothesis) [431, 866,1078,1440,1738,2002]. The light microscopic finding of transition between epithelial and spindle cell components of most tumours, the finding of carcinoma in-situ in some, and the immunohistochemical and ultrastructural identification of epithelial differentiation in the spindle cell components support this theory [745]. P53 mutational genotyping of a small number of pleomorphic carcinomas, carcinosarcomas and blastomas demonstrated identical mutations in spindle cells and epithelium, supporting the contention that both epithelial and mesenchymal components originate from a single clone [189,866].

Somatic genetics
Molecular studies have established that the epithelial and sarcomatoid components of pleomorphic carcinoma have identical molecular profiles, including equivalent patterns of acquired allelic loss [431], p53 mutation profile [866] and X chromosome inactivation [2002]. A high percentage of pleomorphic carcinomas were reported to have variant CYP1A12 [1624]. The molecular profiles of these tumours are not unlike those of other non-small cell tumours. Mutations in beta-catenin were recently shown in blastomas [1779,1801].

Prognosis and predictive factors
Clinical criteria
Clinical outcome is stage dependent but these tumours have a worse prognosis than conventional non-small cell carcinomas [330,584,1261,1430,1695,1976]. Despite the fact that one half of patients present with stage I disease, the 5-year survival is only 20% [218,584,1430,1695,2023,2029]. Adjuvant chemotherapy and radiotherapy do not appear helpful [330, 443,584,1430,1440,1664,1695,1741,1870].
Carcinoid tumour

Definitions
Carcinoid tumours are characterized by growth patterns (organoid, trabecular, insular, palisading, ribbon, rosette-like arrangements) that suggest neuroendocrine differentiation. Tumour cells have uniform cytologic features with moderate eosinophilic, finely granular cytoplasm, and nuclei with a finely granular chromatin pattern.

Typical carcinoid (TC): A carcinoid tumour with fewer than 2 mitoses per 2 mm² and lacking necrosis.

Atypical carcinoid (AC): A carcinoid tumour with 2-10 mitoses per 2 mm² and/or foci of necrosis.

ICD-O codes
Carcinoid 8240/3
Typical carcinoid 8240/3
Atypical carcinoid 8249/3

Synonyms
The following synonyms have been used, but are no longer recommended.

Typical carcinoid: Well differentiated neuroendocrine carcinoma, Kulchitsky cell carcinoma – grade 1, mature carcinoid.

Atypical carcinoid: Malignant carcinoid, moderately differentiated neuroendocrine carcinoma, grade 2 neuroendocrine carcinoma.

Localization
TC is uniformly distributed throughout the lungs [391,2026] whereas AC is more commonly peripheral [128].

Clinical features

Signs and symptoms
Up to half of all bronchopulmonary carcinoids identified as an incidental radiographic finding [580]. The most common symptoms cough and haemoptysis typically relate to bronchial obstruction. Cushing’s syndrome due to ectopic ACTH production is uncommon [2026]. The carcinoid syndrome is rare and only occurs when there are widespread metastases [580]. MEN1 syndrome is another rare association [1439].

Imaging
Carcinoid tumours are seen as well defined pulmonary nodules [613]. Calcification is often seen. Cavitation and irregular margins are rare and pleural effusions are uncommon. Endobronchial tumours can sometimes be directly demonstrated on CT and obstructive atelectasis or consolidation and mucoid impaction may be evident distal to the mass. Because of their vascularity, carcinoid tumours often show intense contrast enhancement. PET scanning may be negative. TC and AC tumours are indistinguishable radiographically.

Diagnostic procedures
Carcinoid tumours can be diagnosed reliably by cytology of fine needle aspiration or bronchoscopic specimens, but sputum samples are often hypocellular [53,673,936,1329,1457,1940]. In most cases the diagnosis can be made by bronchoscopic biopsy. However, separation of TC from AC usually requires examination of a resected specimen unless mitoses and/or necrosis are seen on a bronchoscopic biopsy.

Fig. 1.60 Bronchoscopic image of a typical carcinoid, presenting as a polypoid endobronchial mass.

Fig. 1.61 Carcinoid. A Loose aggregates of slightly irregular small sized tumor cells. Delicate, capillaries with loosely attached radiating tumor cells. Round or oval nuclei with a irregular ‘salt and pepper’ chromatin pattern. B Aspiration biopsy showing the classic association of carcinoid tumor cells with arborizing delicate capillaries. Note the striking uniformity of the neoplastic elements. Diff-Quik stain.
Cytology
Carcinoid tumours are generally identifiable in cytological specimens although haemorrhage may dilute brush samples (53,673,936,1329,1457,1940). The neoplastic cells are generally present both individually and in cohesive aggregates. The latter include acini, flat sheets, trabeculae, and vascularized connective tissue fragments; the latter typically present solely in aspiration smears [1329]. There is a striking uniformity of the neoplastic cells. These are small and may be difficult to distinguish from plasma cells, especially in aspiration specimens. Usually, they are oval with moderate amounts of cytoplasm. The latter is basophilic and occasionally granular. The nuclei are uniformly round or ovoid. Finely stippled chromatin granules give the nucleus a characteristic “salt and pepper” pattern. Nucleoli are small and inconspicuous. Isolated tumour cells have more peripheral nuclei. Infrequently, carcinoids are composed of spindle cells [421,566]. In most cytologic specimens, the smear background is clean but in aspiration biopsies it often contains abundant basophilic granular material. In AC, the neoplastic cells may be more pleomorphic and larger [619,942,1940] and the nuclei show slightly greater chromatin staining.

Macroscopy
TC and AC both form firm, well demarcated, tan to yellow tumours. TC in particular is typically associated with bronchi and are frequently endobronchial. The overlying mucosa may be intact or ulcerated. Squamous metaplasia may be seen. Other bronchial carcinoids push down into the adjacent lung parenchyma. Association with an airway may not be readily evident in peripheral tumours (391,1844).

Histopathology
Carcinoid tumours are classically composed of uniform polygonal cells with finely granular chromatin, inconspicuous nucleoli and scant to moderate amounts of eosinophilic cytoplasm (1844). Oncocytic tumours have abundant eosinophilic cytoplasm (391,2026). Rarely the tumour cell cytoplasm is clear or it may contain melanin [647,653]. Intracytoplasmic mucus is very unusual. Nuclear atypia and pleomorphism may be quite marked, even in TC, but these features are unreliable criteria for distinguishing TC from AC [2028]. Prominent nucleoli may be observed [1844,2026]. A variety of growth patterns are encountered frequently within one tumour. The most common patterns are the organoid and trabecular, in which the tumour cells are respectively arranged in nests or cords. Other patterns include spindle
cell, papillary, pseudoglandular, rosette formation and follicular (391,1246,2026). True gland formation is rare. There is generally a highly vascularized fibrovascular stroma, but in some tumours the stroma is hyalinized, or it shows cartilage or bone formation (391). Stromal amyloid is rare (35,537). The adjacent airway epithelium may show neuroendocrine cell hyperplasia, sometimes associated with airway fibrosis, as described in diffuse idiopathic neuroendocrine cell hyperplasia (29,1317). This is seen most often in association with peripheral carcinoids. In rare cases there are also multiple tumourlets or multiple carcinoid tumours (1314). AC shows either focal necrosis or mitoses numbering between 2-10/2mm² (2026,2028). AC may exhibit all of the growth patterns and cytologic features listed above for TC.

**Immunohistochemistry**

Most carcinoid tumours stain for cytokeratin but up to 20% may be keratin negative (128,272,2026). Neuroendocrine markers such as chromogranin, synaptophysin, Leu-7 (CD57) and N-CAM (CD56) are typically strongly positive, particularly in TC (600,2026,2028).

However, in AC, staining for these markers may be patchy or focal. S-100 protein may highlight the presence of sustentacular cells (108,718). Varying results are published for TTF-1 with some indicating TC and AC are usually negative (1894) but others finding approximately a third of TC and most AC are positive (600, 1513,2134). The explanation for this discrepancy is not known. CD99, is also positive in many carcinoids (1565,2134). Ki 67 is more often positive in AC than TC and is related to survival (416). EM demonstrates desmosomes and dense core neurosecretory granules (2110).

**Differential diagnosis**

The differential diagnosis of carcinoid tumours includes separation from other neuroendocrine tumours, and a wide variety of other tumours depending on the cytology or pattern of the carcinoid. It may be difficult to address the diagnostic differential based on small specimens obtained by bronchoscopy or fine needle aspiration. Carcinoid tumourlets resemble TC and are only distinguished by size, being less than 5 mm in diameter (373). TC and AC are distinguished by the criteria outlined above and this distinction usually requires a surgical specimen. The high-grade neuroendocrine tumours, large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC) are distinguished by having a mitotic rate greater than 10 / 2mm². Ordinarily the rate is much higher than this, making these two tumours easily distinguishable from AC. The presence of large areas of necrosis is also against the diagnosis of AC (128, 2026,2028). Pseudoglandular or gland-like patterns in carcinoid tumours can be mistaken with adenocarcinoma, mucocoeplidemoid carcinoma, and adenoid cystic carcinoma. Adenocarcinomas usually show more cytologic atypia, mucin production and less staining for neuroendocrine markers than carcinoids. Mucocoeplidemoid carcinomas are negative for neuroendocrine markers and they produce mucin. The solid component of adenoid cystic carcinomas may be mistaken for carcinoid, but these cells are negative for neuroendocrine markers (1368). The organoid nesting pattern of carcinoid tumours can be confused with paragangliomas, which are very rare in the lung. The presence of S-100 positive sustentacular cells in some carcinoids may also cause confusion (108,718). A key discriminating feature is the lack of cytokeratin staining in paraganglioma, which is frequently positive in carcinoids (391). Glomus tumour may also resemble carcinoid but it is positive for smooth muscle actin and negative for neuroendocrine markers (645). Spindle cell carcinoids may be confused with various mesenchymal tumours, particularly smooth muscle tumours; recognition of the finely granular nuclear chromatin and organoid nesting pattern this can generally be resolved morphologically and with appropriate immunohistochemical stains. Carcinoids with a prominent papillary pattern may be confused with sclerosing hemangioma but this tumour is negative with neuroendocrine stains (488). The epithelial pattern of a carcinoid can be mimicked by metastatic breast or prostate carcinoma. Although the architecture may be the same, the nuclei in the latter have a more vesicular chromatin pattern. In addition, immunohistochemistry is helpful for the distinction since PSA is positive in prostate carcinoma, while neuroendocrine markers and TTF1 are negative (61,391).

**Grading**

Carcinoid tumours are divided into the low grade TC and intermediate grade AC based on the criteria outlined above.

**Histogenesis**

Pulmonary carcinoid tumours are derived from neuroendocrine cells known to exist in normal airways. In fetal lung, neuroendocrine cells are numerous and are known to play an important role in lung development (539,761,1141). They are less common in the lungs of adults, but various stimuli result in neuroendocrine cell hyperplasia (28,719,720). However, none of these stimuli is recognized to be
of importance of carcinoid tumours. The very rare condition of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is recognized to be a preinvasive lesion for carcinoids [29, 2024].

**Somatic genetics**  
**Cytogenetics and CGH**  
Unbalanced chromosomal aberrations as observed by comparative genomic hybridization (CGH) are rare in carcinoids except underrepresentation of 11q material including MEN1 gene in 0-50% of typical carcinoids and 50-70% of atypical carcinoids [2052,2097]. Atypical carcinoids but not typical carcinoids may show 10q and 13q underrepresentation [2097].

**Molecular genetics**  
Carcinoids have features of neuroendocrine cells, in common with small cell lung cancer and also share some genetic alterations. In general, atypical carcinoids (AC) have more extensive changes than typical carcinoids. A distinctive feature of carcinoids not found in other lung cancers is the frequent presence of mutations of the MEN1 gene and absence of its protein product, menin [463,1516], even though virtually all bronchial carcinoids are sporadic and not familial tumours. The mutations are accompanied by allelic loss at the MEN1 locus at 11p13. These features are also found in gastrointestinal carcinoids. Loss of heterozygosity (LOH) at 3p, 13q, 9p21 and 17p is rare in TC but present in AC at frequencies lower than in SCLC [1516].

LOH at 3p (3p14.3-21.3) at has been found in 40% of AC, which is significantly lower than other NSCLC including the high-grade neuroendocrine tumours LCNEC and SCLC (p<0.001). LOH at Rb locus (13p14) and retinoblastoma gene pathway inhibitor (Rb) is rare in typical carcinoids [127,269,726,727] but present in 20% of AC [127]. Similarly, Rb expression is normal in typical carcinoids but lost in 21% of atypical carcinoids. Cyclin D1 is overexpressed in 6% of TC [127] LOH is at 9p21 (P16) is observed in a few (20%) AC and TC [1516]. In contrast to smoking associated lung cancers that often show G:T transversions, AC show P53 point mutation of an unusual type (G:C to A:T transitions or nonsense mutations) [1516]. The p53 pathway is infrequently affected and inactivated in carcinoids, and is extremely rare in TC. Accordingly P53 aberrant stabilization is not seen in TC and seen in rare cases of AC [217,1622]. Other proteins of Rb/P53 pathways such as E2F1 are rarely affected in TC but more often in AC. P14ARF protein loss occurs in 6% of TC and 43% of AC [549,669]. Methylation of tumour suppressor genes is infrequently seen in TC and AC [1814,2019]. Methylation index was lower in carcinoids than in SCLC There was no difference in methylation frequencies and index between TC and AC except for RASSF1A methylation (a gene with functions similar to Ras), which is observed in 71% of AC (as frequently as in SCLC) and in 45% of TC [2019]. Caspase 8 promoter methylation occurs in 18% of carcinoids [1814]. Except for this important proapoptotic molecule, methylation and silencing of tumour suppressor genes is relatively rare in carcinoids compared to other lung cancers [1814,2017,2019].

**Expression profiles**  
Limited expression data are available for carcinoid tumours. Those data, which are available, indicate that carcinoid tumours are more similar to neuronal tumours than to normal bronchial epithelial cells or small cell carcinoma [52].

**Prognosis and predictive factors**  
**Clinical and histopathological criteria**  
The overall 5- and 10-year survival rates are worse for AC (61-73% and 35-59%) than TC (90-98% and 82-95%, p<0.001) [128,1844,2028]. After separation of TC from AC, stage is the most important prognostic factor [128,2028]. However, even with lymph node metastasis, TC carries an excellent prognosis [1999]. With AC size over 3.5 cm also conveys a worse prognosis [128]. Further histopathological prognostic criteria (beyond necrosis and mitoses) include vascular invasion and nuclear pleomorphism [2028]. Negative predictors of prognosis in AC include mitotic rate, pleomorphism, and aerogenous spread, whereas palisading, papillary formation, and pseudo-glandular patterns are favourable prognostic features [128].

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**Fig. 1.65 Atypical carcinoid. A Small necrotic focus. B A single mitosis is present in this high power field. The tumour cells show carcinoid morphology with moderate eosinophilic cytoplasm and finely granular nuclear chromatin. From Travis et al. [2024].**
Mucoepidermoid carcinoma

Definition
A malignant epithelial tumour characterized by the presence of squamoid cells, mucin-secreting cells and cells of intermediate type. It is histologically identical to the salivary gland tumour of the same name.

ICD-O code
Mucoepidermoid carcinoma 8430/3

Synonyms
Mucoepidermoid tumour.

Epidemiology
Mucoepidermoid tumours comprise less than 1% of all lung tumours [732,2040, 2221]. They have an equal sex distribution with a slight predilection for men and have an age range of 3-78 years with 50% of tumours occurring in individuals less than 30 years, and most patients presenting in the third and fourth decade [811,2221]. There is a suggestion of predilection for Caucasians over Blacks. They form a significant proportion of pediatric endobronchial tumours.

Etiology
There appears to be no association with cigarette smoking or other risk factors.

Localization
The majority arise from bronchial glands in the central airways. Tumours with this histology that are encountered in the peripheral lung should raise the question of metastatic tumour or adenosquamous carcinoma.

Clinical features
Signs and symptoms
Signs and symptoms are related to the polypoid endobronchial growth of this tumour and tracheal and large airway irritation [398,1011,1646]. Wheeze, haemoptysis, and recurrent pneumonia with post-obstructive changes are most often noted, although up to 25% of patients may be asymptomatic.

Imaging
Chest radiographs and CT scans demonstrate a well-circumscribed oval or lobulated mass arising within the bronchus [612]. Calcification is occasionally seen. Post-obstructive pulmonary infiltrates are often noted, occasionally with cavitation.

Macroscopy
Grossly, these tumours usually occur in the main, lobar or segmental bronchi, ranging in size from 0.5-6 cm with an average size of approximately 2.2 cm [811,2221]. They are soft, polypoid, and pink-tan in colour often with cystic appearance. Extension between bronchial cartilaginous plates is occasionally noted. Distal obstructive / cholesterol pneumonia may be seen. High-grade lesions are usually more infiltrative.

Tumour spread and staging
Low-grade mucoepidermoid tumours spread to regional lymph nodes by local growth in less than 5% of cases, although distant spread rarely occurs. High-grade tumours involve not only regional nodes but may metastasize to liver, bones, adrenal gland, and brain.

Histopathology
On the basis of morphological and cytological features, tumours are divided into low and high-grade types. In low-grade tumours, cystic changes often dominate and solid areas typically comprise mucin secreting and columnar epithelium forming small glands, tubules, and cysts. Necrosis is inconspicuous. These cysts often contain inspissated mucus, which has a colloid-like appearance and frequently is calcified. The lining cells are cytologically bland with round to oval nuclei, abundant eosinophilic, mucin-rich cytoplasm, and infrequent mitotic figures. Often, intimately admixed with this mucinous epithelium are non-keratinizing squamoid cells that grow in a sheet-like pattern with intercellular bridges. The third cellular component is an intermediate or transitional cell that is oval in shape, has a round nucleus and faint eosinophilic cytoplasm. The accompanying stroma is often oedematous with foci of dense stromal hyalinization, particularly around the glandular elements, that may have an amyloid-like appearance. Stromal calcification and ossification, with a granulomatous reaction is seen around areas of mucus extravasation. High-grade mucoepidermoid carcinomas are rare and have histologic features that overlap with adenosquamous carcinoma [811,1445,2221]. They consist largely of intermediate and squamoid cells with a minor component of mucin secreting elements. They demonstrate nuclear atypia with hyperchromatism, pleomorphism, brisk mitotic activity and a high nuclear to cytoplasmic ratio. These lesions often invade the pulmonary parenchyma and may be associated with positive regional lymph nodes. Controversy exists in their separation from adenosquamous carcinoma. Criteria more typical of high grade mucoepidermoid tumours include: (1) exophytic endobronchial growth, (2) surface epithelium lacking changes of in situ carcinoma, (3) absence of individual cell keratinization and squamous pearl formation, (4) transitional areas to low grade mucoepidermoid carcinoma.

Histogenesis
Mucoepidermoid carcinomas are histologically similar to their counterparts in the salivary glands and it has been pre-
assumed that they are derived from primitive cells differentiating within the tracheobronchial mucous glands.

**Somatic genetics**
No consistent cytogenetic abnormalities have been noted with mucoepidermoid carcinomas of the tracheobronchial tree.

**Genetic susceptibility**
No genetic susceptibilities are noted with mucoepidermoid tumours. It should be noted, however, that the pediatric population comprises a significant percentage of patients with this lesion.

**Prognosis and predictive factors**
Low-grade mucoepidermoid tumours have a much better prognosis than high-grade tumours, the latter being similar to non-small cell carcinomas \(732,811,2221\). Low-grade tumours rarely metastasize with less than 5% of reported cases metastasizing to regional lymph nodes. Children have a particularly benign clinical course. Low-grade tumours are often treated with bronchoplastic procedures such as sleeve resection.

High-grade mucoepidermoid carcinomas are generally treated similar to non-small cell carcinomas. Their prognosis is much more guarded as they tend to behave as non-small cell carcinomas. Diagnostic features, which indicate a high likelihood of recurrence, metastasis, or death include constitutional signs and symptoms including pain, weight loss, malaise. Positive margins of resection; positive hilar lymph nodes and local aggressive behaviour, such as chest wall invasion are also adverse factors \(398,732,2221\).
Adenoid cystic carcinoma

Definition
Adenoid cystic carcinoma is a malignant epithelial neoplasm, recapitulating its counterpart in the salivary glands, with a distinctive histologic pattern of growth of the epithelial cells in cribriform, tubular and glandular arrays orientated around and associated with a variably mucinous and hyalinized basement membrane-rich extracellular matrix, with the cells showing differentiation characteristics of duct lining and myoepithelial cells.

ICD-O code 8200/3

Synonyms
Cylindroma and adenocystic carcinoma.

Epidemiology
Adenoid cystic carcinoma of the lung and bronchus comprises less than 1% of all lung tumours (809,2029). It has an equal sex distribution and tends to occur in the fourth and fifth decades of life (1368). In the majority of cases adenoid cystic carcinoma behaves in an insidious and indolent fashion with multiple local recurrences preceding metastases.

Etiology
There appears to be no association with cigarette smoking or other risk factor(s).

Localization
90% of cases originate intraluminally within trachea, main stem or lobar bronchi (1621).

Clinical features
Presentation reflects proximal airway obstruction with shortness of breath, cough, wheeze, chest pain and haemoptysis described [833,1271,1487,1560, 2014]. Radiographs show a centrally located mass that may have an endobronchial component or may form plaques or annular lesions in the wall of bronchi (1271). Extension into the pulmonary parenchyma is often present and occasionally into mediastinal fat.

Macroscopy
Adenoid cystic carcinoma typically forms gray-white or tan polypoid lesions thickening the submucosa of the bronchus, sometimes with no alteration of the surface mucosa. It also may form diffuse infiltrative plaques that extend in a longitudinal and/or circumferential fashion beneath the submucosa. Size ranges from 1–4 cm with an average of 2 cm (1368). A distinctive feature is that it has deceptively infiltrative margins, which extend far beyond the localized nodule noted grossly and therefore sampling of peribronchial soft tissue is worthwhile.

Tumour spread and staging
Staging of adenoid cystic carcinomas is performed according to the AJCC and UICC TNM staging system. Adenoid cystic carcinoma is predisposed to recur within the lung parenchyma, the pleura, chest wall, and mediastinum before metastasizing late to liver, brain, bone, spleen, kidney, and adrenal glands. Regional lymph node metastases are seen in approximately 20% of cases and systemic metastases in approximately 40%.

Histopathology
Architecturally, adenoid cystic carcinoma often breaches the cartilaginous plate extending into the pulmonary parenchyma, hilar and mediastinal soft tissues. Its growth pattern is typically heterogeneous, with neoplastic cells arranged in cribriform arrays, tubules or solid nests. The most characteristic cribriform pattern shows cells surrounding cylinders in a sclerotic acid mucopolysaccharide-rich basement membrane-like material. The neoplastic cells are small with scant cytoplasm and dark hyperchromatic nuclei.
nuclei that are oval to angulated, and show infrequent mitotic figures. Occasionally, these cells form tubules lined by two to three cells, with the luminal cells having a low cuboidal appearance and the peripheral cells forming a myoepithelial layer. Perineural invasion is seen in 40% of cases and extension along vascular structures, bronchi and bronchioles, and lymphatics is characteristic.

Immunoperoxidase stains show that the neoplastic cells have a variable ductal and myoepithelial phenotype, the cells expressing cytokeratin but also vimentin, smooth muscle actin, calponin, S-100 protein, p63, and GFAP. The surrounding matrix recapitulates a basement membrane like material in that it stains positive with antibodies directed at Type IV collagen, laminin, and heparin sulfate.

**Histogenesis**

Adenoid cystic carcinoma is derived from a primitive cell, presumably of tracheobronchial gland origin, which shows differentiation characteristics of ductal and myoepithelial cells.

**Prognosis and predictive factors**

The behavior of adenoid cystic carcinoma is one of multiple recurrences with late metastases and survival needs to be analyzed over a prolonged period (10-15 years) [398,1271,1560,1621]. Patients are prone to develop local recurrence because of difficulty obtaining clear margins and it is recommended that margins of resection be analyzed by frozen section at the time of primary surgery. Primary treatment is surgery with supplemental radiation, especially by linear accelerator. Poor prognosis is related to stage of the tumor at the time of diagnosis, the presence of positive margins, and a solid cellular growth pattern.

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Fig. 1.70 Adenoid cystic carcinoma.  
A Adenoid cystic carcinoma was historically termed cylindroma: neoplastic cells typically form cylinders of basophilic mucoid and basement membrane-like material surrounded by hyperchromatic angulated epithelial cells.  
B Cylinders are surrounded by small hyperchromatic cells with dense oval nuclei having scant eosinophilic cytoplasm. Occasional tubular differentiation is noted.  
The tracheobronchial tree may be the site of origin for a wide variety of salivary gland tumours [1187,1364,1563,1883,1883]. These include epithelial-myoepithelial carcinoma, acinic cell carcinoma, carcinoma ex pleomorphic adenoma and malignant endobronchial myxoid tumour. Of these only epithelial-myoepithelial carcinomas have been analysed in significant numbers.

**Definition**
Epithelial-myoepithelial carcinomas consist of myoepithelial cells with spindle cell, clear cell or plasmacytoid morphology and varying amounts of duct-forming epithelium.

**ICD-O code**  8562/3

**Synonyms**
Adenomyoepithelioma, myoepithelioma, epithelial-myoepithelial carcinoma, epithelial-myoepithelial tumour, epithelial-myoepithelial carcinoma, epithelial-myoepithelial tumour of unproven malignant potential and malignant mixed tumour comprising epithelial and myoepithelial cells.

**Epidemiology**
Age ranges from 33 to 71 years with no sex predominance.

**Etiology**
There appears to be no association with cigarette smoking or other risk factor(s).

**Localization**
The tumors are nearly all endobronchial in location.

**Clinical features**
Presenting symptoms and imaging reflect airway obstruction [639,1480,2037].

**Macroscopy**
The cut surface ranges from solid to gelatinous in texture and white to gray in colour [639,1480,2037].

**Histopathology**
Tumours comprise myoepithelial cells that are spindled or rounded and contain eosinophilic or clear cell cytoplasm, plus a variable proportion of duct-forming epithelium [639,1480,2037]. Occasional purely myoepitheliomatous tumours are described. Ducts are typically lined by a dual layer of cells, comprising an inner layer of cuboidal cells with eosinophilic cytoplasm and an outer layer of cells with predominantly clear cytoplasm. Mitotic activity is generally low. Generally, the inner layer of ducts stains for MNF116 and EMA and the outer layer plus solid components stain for SMA and S-100, although there may be some overlap.

**Prognosis and predictive factors**
Surgical resection is the treatment of choice and usually curative, although late recurrence may occur [639,1480,2037].
Tumours of the lung  - Preinvasive epithelial lesions

Definition
A precursor lesion of squamous cell carcinoma arising in the bronchial epithelium. Squamous dysplasia and carcinoma in situ are a continuum of recognizable histologic changes in the large airways. They can occur as single or multifocal lesions throughout the tracheobronchial tree. Dysplasia or carcinoma in situ may exist as an isolated finding or as a bronchial surface lesion accompanying invasive carcinoma.

ICD-O code
Squamous cell carcinoma in situ 8070/2

Synonyms and historical annotation
Squamous atypia, angiogenic squamous dysplasia, bronchial premalignancy, preinvasive squamous lesion, high-grade intraepithelial neoplasia, early non-invasive cancer.

The existence of central airway squamous lesions regarded as progenitors of squamous carcinoma has been recognized for decades [93]. They were initially graded according to complicated descriptive criteria including the loss of cilia, thickness (number of cell layers) of the epithelium, the degree of atypia and the percentage of atypical cells [94,95], but a manageable and reproducible classification was recently published [1465,2024].

Clinical features
Squamous dysplasia is nearly always asymptomatic but occurs in individuals with heavy tobacco exposure (more than 30 pack years of cigarette smoking) and with obstructive airway disease [849, 1389]. Pre-invasive squamous bronchial lesions are found more frequently in men than in women [1118].

Relevant diagnostic procedures
Sputum cytology examination
Currently, the only non-invasive test that can detect pre-invasive lesions is sputum cytology examination [620,993].

20% of patients with greater than a 30 pack year history of smoking, airway obstruction with forced expiratory volume 1 (FEV1) <70% of expected have moderate dysplasia or worse by fluorescence bronchoscopy [1533]. Of those with moderate atypia on sputum cytology, at least 55% have dysplasia detectable by fluorescence bronchoscopy. Sputum atypia as an independent variable in predicting dysplasia at fluorescence bronchoscopy has not yet been tested in a controlled trial evaluating high-risk smokers with airway obstruction.

White-light bronchoscopy
Approximately 40% of cases of carcinoma in situ can be detected by white-light reflectance bronchoscopy. About 75% of detected carcinoma in situ lesions

Fig. 1.72 Carcinoma in situ at the bronchus bifurcation. Note the plaque-like greyish lesions resembling leukoplakia.

Fig. 1.73 Bronchoscopy images of squamous dysplasia and carcinoma in situ. A Nodular carcinoma in-situ of the left lower lobe. White-light image. B Carcinoma in situ right upper lobe with focal thickening of the bronchial bifurcation and slight irregularity of the bronchial mucosa. C Carcinoma in situ upper divisional bronchus, left upper lobe. Focal increase in vascularity was observed under white-light bronchoscopy. D Carcinoma in situ left upper lobe. The lesion is visible as an area of reddish-brown fluorescence under autofluorescence bronchoscopy [1117,1120], using the LIFE-Lung Device. E Severe dysplasia left upper lobe. No abnormality under white-light bronchoscopy. F Same case as E. The dysplastic lesion is visible as an area of reddish fluorescence under autofluorescence bronchoscopy [1117,1120], using the Onco-LIFE Device (Xillix Technologies Inc. Vancouver, Canada).
appear as superficial or flat lesions; the remaining 25% have a nodular or polypoid appearance [967,1423]. Because nodular/polypoid lesions are elevated from the adjacent normal mucosa, lesions as small as 1-2 mm in diameter can be seen. Flat or superficially spreading lesions greater than 1-2 cm in surface diameter are generally visible as areas of focal thickening, increase in vascularity or marked irregularity of the mucosa. Flat lesions 5-10 mm in diameter usually produce non-specific thickening, redness, fine roughening, loss of luster or a slight increase in granularity which are difficult to distinguish from inflammation or squamous metaplasia [2057]. Lesions <5 mm are usually invisible on white light bronchoscopy. Bronchial dysplasia usually presents as non-specific mucosal swelling or thickening at a bronchial bifurcation.

**Autofluorescence bronchoscopy**

Pre-invasive lesions that have subtle or no visible findings on white-light bronchoscopy can be localized by autofluorescence imaging using a violet or blue light for illumination instead of white-light and special imaging sensors attached to a fiberoptic bronchoscope for detection of the abnormal autofluorescence [1117, 1120]. Dysplastic and malignant tissues have a significant decrease in the green autofluorescence intensity relative to the red autofluorescence. These pre-invasive lesions are identified by their brown or brownish-red autofluorescence. Lesions as small as 0.5 mm can be localized by this method.

**Cytology**

Sputum cytological classification schemes for preneoplastic lesions have been published by Saccomanno [1717] and Frost [621] and consist of gradations of microscopic abnormality similar to those observed in histological sections from lower airways of smokers. Squamous metaplasia presents in sputum smears as individual cells, but mostly as flat loosely cohesive clusters. The cytologic manifestations of dysplasia occur as increasingly severe cellular changes, ranging from mild, moderate, and severe atypia to carcinoma in situ (CIS) [1717]. There are progressive alterations including increasing variability in cellular and nuclear sizes, increasingly variable nuclear-to-cytoplasmic ratios, increasing proportions of cells with cytoplasmic eosinophilia (orangeophilia), increasing coarseness of chromatin granularity until a pyknotic-like pattern is reached in CIS, increasing irregularity in the distribution of chromatin granules, and increasing irregularities in the outlines of nuclear membranes [844,1717, 1718]. This last feature first appears in moderate atypia [1717]. According to Koprowska et al [1055], it is this deviation from smooth nuclear outlines that is most strongly associated with the presence of carcinoma.

**Localization and macroscopy**

Foci of carcinoma in situ usually arise near bifurcations in the segmental bronchi, subsequently extending proximally into the adjacent lobar bronchus and distally into subsegmental branches.

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**Fig. 1.74** Carcinoma in situ. The bronchial mucosa is replaced with atypical squamous cells extending from the surface to the base of the epithelial. Note the severe nuclear polymorphism, hyperchromasia and enlarged nuclei.
The lesions are less frequent in the trachea. Bronchoscopically and grossly there is often no macroscopical alteration. When gross abnormalities are present, focal or multi-focal plaque-like greyish lesions resembling leukoplakia, nonspecific erythema and even nodular or polypoid lesions may be seen.

**Histopathology**

A variety of bronchial epithelial hyperplasias and metaplasias may occur that are not regarded as preneoplastic including goblet cell hyperplasia, basal cell (reserve cell) hyperplasia, immature squamous metaplasia, and squamous metaplasia. The term preinvasive does not imply that progression to invasion will necessarily occur. These lesions represent a continuum of cytologic and histologic changes that may show some overlap between defined categories. Squamous dysplasia does not invade the stroma. The basement membrane remains intact and is variably thickened. There may be vascular budding into the epithelium, termed angiogenic squamous dysplasia [986]. The latter lesion has also been previously reported as micropapillomatosis [724, 1407].

**Immunohistochemistry**

A series of immunohistochemical changes accompany squamous dysplasia. These include increased expression of EGFR [607,1101,1710], HER2/neu [608], p53 [145,211,1251], MCM2 [1966], Ki-67 [607,1149,1966], cytokeratin 5/6 [54], bcl-2 [211], VEGF [602,1126], maldistribution of MUC1, and loss of several proteins including FHIT [1855], folate binding protein [609,676], and p16 [213,1122]. A linear progression of proliferative activity, assessed with immunohistochemical staining for the proliferation marker Ki-67 (MIB-1), correlates with the extent and grade of the preneoplasia [1966]. Loss of RAR-beta expression is very frequent in the bronchial epithelium of smokers [1252,2017]. Type IV collagen staining highlights discontinuities in basement membranes that increase from basal cell hyperplasia to dysplasia, progressing to destruction in carcinoma in situ and invasive carcinoma [657]. Changes also occur in matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP) expression corresponding to progression in severity of dysplasia, in situ carcinoma and invasive carcinoma [657].

**Electron microscopy**

There is an increase in atypical basal cells with loss of polarity. The nuclei show considerable hyperchromasia, and variations in shape with numerous invaginations. The number of nucleoli is increased, and so-called pseudoinclusion bodies may be seen within the nuclei. Some cells exhibit atypical development via an atypical array of organelles [711,712,1407]. A special feature is seen in the basement membrane in CIS. It is subdivided by multiple tentacle-like cytoplasmic protrusions, which vary considerably in shape and size but are always directed towards and between the fibrous structures of the basement membrane [711,712,1407].

**Histogenesis**

The stem cell for the squamous epithelium of the proximal airway is not certain, but it is presumed that the basal cells represent a relatively quiescent zone that is the precursor for preneoplastic epithelium. It is of interest that these cells express a different cytokeratin profile with high levels of cytokeratin 5/6 and are the only cells in the normal respiratory mucosa and express significant levels of epidermal growth factor receptor. In the earliest preinvasive lesions, this basal zone is expanded with phenotypic changes that mirror the quiescent basal zone in normal epithelium including the overexpression of EGFR, transformation from cytokeratin 5/6 negative to positive, and increased proliferative activity with high expression of Ki-67 and MCM2. It is widely supposed that low grade changes such as basal cell hyperplasia and squamous metaplasia may (with or without micropapillomatosis) progress through mild, moderate and severe dysplasia up to carcinoma in situ [392,994,2022] to invasive carcinoma. However, such a progression is rarely observed in individual subjects and the predictive power of specific grades of premalignant change for the future development of invasive carcinoma is still under investigation.

**Somatic genetics**

**Cytogenetics and CGH**

Relatively few cytogenetic studies have been performed on preneoplastic lesions because of their small size and because of the difficulty of identifying them [1449, 1854]. Classic cytogenetic studies are further limited by the necessity for short-term cultures and the inability to identify the cell of origin of metaphase spreads. For these reasons most analyses have utilized fluorescence in situ hybridization (FISH) for detection of chromosomal or numerical changes in bronchial epithelial cells. As part of the field effect resulting from widespread smoking damage to the entire upper aerodigestive tract, cytoge-
Mildly increased
between the sequential changes leading
cated similarities and differences
{844,2161}. These studies have also indi-
observed in other epithelial cancers
molecular changes similar to that
such lesions has provided a sequence of
followed by molecular genetic analysis of
Precise microdissection of epithelial cells
Molecular genetics
change {813}.
chromosome 3 were the most frequent
and found that numerical alterations of
preneoplastic lesions as well as histo-
changes of chromosme 7 are frequent
grade lesions. Small foci of allelic loss
commencing at the central (3p21) region
were detected at the carcinoma in situ
stage, and P53 mutations appear at vari-
able times [1900,2157,2162]. Chromo-
some 3p losses in normal epithelium,
basal cell hyperplasia and squamous
metaplasia are small and multifocal,
commencing at the central (3p21) region
of the chromosomal arm, while in later
lesions such as carcinoma in situ, allelic
loss is present along nearly all of the
short arm of chromosome 3p [2157,
2158]. The clonal patches of bronchial
epithelium having molecular changes
(allelic loss and genetic instability) are
usually small, and have been estimated
to be approximately 40,000 to 360,000
cells [1549]. p16INK4a methylation has
also been detected at early stages of
squamous preinvasive lesions with fre-
quency increasing during histopatholog-
ic progression from basal cell hyperpla-
netic changes may be detected both in
preneoplastic lesions as well as histolog-
ically normal appearing cells. Numerical
changes of chromosome 7 are frequent
and may predict risk for cancer develop-
ment {1147,2245}. Only one study to
date has performed comparative genom-
ic hybridization on preneoplastic lesions
and found that numerical alterations of
chromosome 3 were the most frequent
change [813].

**Molecular genetics**
Precise microdissection of epithelial cells
followed by molecular genetic analysis of
such lesions has provided a sequence of
molecular changes similar to that
observed in other epithelial cancers
{844,2161}. These studies have also indi-
cated similarities and differences
between the sequential changes leading
to central and peripheral tumours. The
histological changes preceding squa-
mous cell carcinomas are well docu-
mented because of accessibility of these
lesions, and the developmental sequence of molecular changes is non-
random. DNA aneuploidy is frequent in
dysplastic lesions particularly in high-
grade lesions. Small foci of allelic loss
are common at multiple sites in the
bronchial epithelium and persist long
after smoking cessation {1549}.
LOH occurs at one or more chromosome
3p regions and 9p21 early in neoplastic
development, commencing in histologi-
cally normal epithelium. Later changes
include 8p21-23, 13q14 (RB) and 17p13
(P53) being detected frequently in histo-
logically normal epithelium {1236,2157,
2158,2162}. In contrast, allele loss at
5q21 (APC-MCC region) mutations has
been detected at the carcinoma in situ
stage, and P53 mutations appear at vari-
able times [1900,2157,2162]. Chromo-
some 3p losses in normal epithelium,
basal cell hyperplasia and squamous
metaplasia are small and multifocal,
commencing at the central (3p21) region
of the chromosomal arm, while in later
lesions such as carcinoma in situ, allelic
loss is present along nearly all of the
short arm of chromosome 3p [2157,
2158]. The clonal patches of bronchial
epithelium having molecular changes
(allelic loss and genetic instability) are
usually small, and have been estimated
to be approximately 40,000 to 360,000
cells [1549]. p16INK4a methylation has
also been detected at early stages of
squamous preinvasive lesions with fre-
quency increasing during histopatholog-
ic progression from basal cell hyperpla-

### Table 1.11
Microscopic features of the squamous dysplasia and carcinoma *in situ*

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Thickness</th>
<th>Cell size</th>
<th>Maturation/orientation</th>
<th>Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild Dysplasia</strong></td>
<td>Mildly increased</td>
<td>Mildly increased</td>
<td>Continuous progression of maturation from base to luminal surface</td>
<td>Mild variation of N/C ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild anisocytosis, Pleomorphism</td>
<td>Basilar zone expanded with cellular crowding in lower third</td>
<td>Finely granular chromatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distinct intermediate (prickle cell) zone present</td>
<td>Minimal angulation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Superficial flattening of epithelial cells</td>
<td>Nucleoli inconspicuous or absent</td>
</tr>
<tr>
<td><strong>Moderate Dysplasia</strong></td>
<td>Moderately</td>
<td>Mild increase in cell size; cells often small</td>
<td>Partial progression of maturation from base to luminal surface</td>
<td>Moderate variation of N/C ratio</td>
</tr>
<tr>
<td></td>
<td>increased</td>
<td></td>
<td>Basilar zone expanded with cellular crowding in lower two thirds of epithelium</td>
<td>Finely granular chromatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate zone confined to upper third of epithelium</td>
<td>Angulations, grooves and lobulations present</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Superficial flattening of epithelial cells</td>
<td>Nucleoli inconspicuous or absent</td>
</tr>
<tr>
<td><strong>Severe Dysplasia</strong></td>
<td>Markedly</td>
<td>Markedly increased</td>
<td>Little progression of maturation from base to luminal surface</td>
<td>N/C ratio often high and variable</td>
</tr>
<tr>
<td></td>
<td>increased</td>
<td></td>
<td>Basilar zone expanded with cellular crowding well into upper third</td>
<td>Chromatin coarse and uneven</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate zone greatly attenuated</td>
<td>Nuclear angulations and folding prominent</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Superficial flattening of epithelial cells</td>
<td>Nucleoli frequently present and conspicuous</td>
</tr>
<tr>
<td><strong>Carcinoma in situ</strong></td>
<td>May or may not</td>
<td>May be markedly increased</td>
<td>No progression of maturation from base to luminal surface; epithelium could be inver-</td>
<td>N/C ratio often high and variable</td>
</tr>
<tr>
<td></td>
<td>be increased</td>
<td></td>
<td>ted with little change in appearance</td>
<td>Chromatin coarse and uneven</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Basilar zone expanded with cellular crowding throughout epithelium</td>
<td>Nuclear angulations and folding prominent</td>
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<td></td>
<td></td>
<td></td>
<td>Intermediate zone absent</td>
<td>Nucleoli may be present or inconspicuous</td>
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<td></td>
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<td></td>
<td>Surface flattening confined to the most superfiical cells</td>
<td>No consistent orientation of nuclei in relation to ep-</td>
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<td></td>
<td>thelium surface</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Mitotic figures present through full thickness</td>
</tr>
</tbody>
</table>

Squamous dysplasia and carcinoma in situ 71
Preinvasive epithelial lesions

From squamous metaplasia to carcinoma in situ (140). Detection of such changes in sputum samples may be of predictive value in identifying smokers at increased risk of developing lung cancer (141). Similar changes have been detected in telomerase activation (2199). While weak telomerase RNA expression is detected in basal layers of normal and hyperplastic epithelium, dysregulation of telomerase expression increases with tumour progression with moderate to strong expression throughout the multi-layers of the epithelium in squamous metaplasia, dysplasia and carcinoma in situ.

While specific preneoplastic changes associated with SCLC have not been identified, extensive genetic damage occurs in the accompanying normal and hyperplastic bronchial epithelium and is characteristic of SCLC tumours (2160). These changes are much more extensive than changes accompanying similar epithelia from lung resections of patients with squamous cell carcinoma or adenocarcinoma. These findings suggest major differences in the pathogenesis of the three major lung cancer types.

Our knowledge of the changes preceding peripheral tumours is much more limited, mainly because of the inability to identify and have access to such lesions. However, careful examination of lung cancer resections indicates that peripheral tumours, especially adenocarcinoma, may be accompanied by specific morphologic changes known as atypical adenomatous hyperplasia (AAH). The advent of CT scans for the detection of early lung cancers has greatly increased the identification of such lesions, both in smokers with and without lung cancer (844,2078). Inflation of the lungs prior to fixation greatly enhances the ability to detect these lesions. Multiple molecular changes have been described in these lesions (1021) including aneuploidy, ras gene mutations, COX-2 over expression, active proliferation, 3p and 9p deletions, K-ras codon 12 mutations, and disruption of the cell cycle control, but p53 gene aberrations are rare and telomerase activation is absent.

**Prognostic factors**

Carcinoma in situ, being a preneoplastic lesion, is classified as “Stage 0 disease.” Resection of specific lesions at this stage means 100% curability, although frequent multifocality means that other foci are liable to present elsewhere in the airways. In general, higher grades of dysplasia are more closely associated with synchronous invasive carcinomas, although the prognostic significance of identifying dysplasia in isolation is uncertain. Currently, there are no recommendations to screen asymptomatic individuals with a history of dysplasia for development of invasive lesions (1119,1408, 1860). There are no data to allow prediction of progression to invasive disease, depending on grade of dysplasia. It is likely that severe dysplasia/CIS carries a high risk. Progression of disease, from the early stages, probably takes many years.

**Genetic predictive factors**

There is a general consensus that numerous genetic and molecular abnormalities occur in very early stages of lung carcinogenesis including hyperplasia and metaplasia and even in normal appearing bronchial epithelium in smokers (1236,2162). None of these isolated molecular abnormalities have been shown to predict progression to cancer, but their cumulative rate may be associated with the risk of cancer in the bronchial tree (926).
Atypical adenomatous hyperplasia

 Definition
 Atypical adenomatous hyperplasia (AAH) is a localised proliferation of mild to moderately atypical cells lining involved alveoli and, sometimes, respiratory bronchioles, resulting in focal lesions in peripheral alveolated lung, usually less than 5mm in diameter and generally in the absence of underlying interstitial inflammation and fibrosis.

 Synonyms
 Atypical alveolar cuboidal cell hyperplasia {1807}, alveolar epithelial hyperplasia {1434}, atypical alveolar hyperplasia {288}, atypical bronchioloalveolar cell hyperplasia {2123}, bronchioloalveolar cell adenoma {1316}.

 Background
 AAH is a putative precursor of peripheral pulmonary adenocarcinoma, including bronchioloalveolar carcinoma (BAC) {1807}; the ‘adenoma’ in an adenocarcinoma sequence in the peripheral lung {1318}. Epidemiological, morphological, morphometric, cytofluorometric and genetic evidence support this hypothesis {392,994,1021,1378,2022}. AAH is most frequently found as an incidental histologic finding in lungs already bearing primary cancer, especially adenocarcinoma. Lungs with very high numbers of AAH (>40) have been reported in conjunction with multiple synchronous peripheral primary adenocarcinomas or BAC {51,333,1316,1434,1928,2123}. Autopsy studies have reported AAH in 2-4% of non-cancer bearing patients {1879,2206,2207}.

 AAH has been reported in up to 19% of women and 9.3% of men with lung cancer and up to 30.2% and 18.8%, respectively, in women and men with pulmonary adenocarcinoma {333}. In Japan, this gender relationship is inconsistent {1429,2123}. Almost all Caucasians reported with AAH have been smokers, while in Japan, an association is not clear. Data on the association of AAH with either a personal or family history of malignancy are conflicting {334,1429,1960}.

 Clinical features
 Signs and symptoms
 There are no clinical signs or symptoms directly referable to AAH. The lesions are usually encountered as incidental findings at gross or, more often, microscopic examination of lung.

 Imaging
 Radiological experience of AAH is largely confined to screening studies using High Resolution CT scanning (HRCT) {979,1108}, though some have been described during follow-up of patients with lung cancer {1038,1198}. In this context, small non-solid nodules, also described as localised areas of pure ground glass opacity (GGO), may be identified as areas of increased opacification with distinct borders, not completely obscuring the underlying lung parenchyma on CT scan, measuring 2-24mm in diameter, and typically not visualized on chest radiographs. Resection of GGOs has shown a range of pathology including benign disease in up to 30%, AAH in 10-77%, BAC in up to 50% and invasive adenocarcinoma in 10-25% of cases {979,1038,1108,1431}.

 Relevant diagnostic procedures
 AAH may rarely be visualised radiologically and a presumptive diagnosis made. Most likely as part of an HRCT screening

Table 1.12
AAH in lung cancer resection specimens.
From references: {33,1041,1316,1387,1434,2123}

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All primary lung cancer</td>
<td>9 - 21%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16 - 35%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3 - 11%</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>10 - 25%</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>4 - 10%</td>
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</tbody>
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Fig. 1.76 Atypical adenomatous hyperplasia. A Unusually prominent AAH lesion. Alveolar spaces are visible within the lesion. B AAH (center) detected incidentally in a lung resected for mucinous adenocarcinoma, present on the left.
programme for lung cancer, any detected lesion, which necessitates further investigation, can be sampled by fine needle aspiration or local resection.

**Cytology**
A diagnosis of AAH cannot be made on a cytology specimen. This issue is discussed further in the chapter on adenocarcinoma.

**Macroscopy and localization**
Most lesions are only incidentally found at microscopy but AAH may be visible on the cut surface of lung as discrete, grey to yellow foci ranging from less than 1mm to, rarely, over 10mm (408,994). Most are less than 3mm. AAH is easier to see by flooding the lung surface with water, or after tissue fixation with Bouin’s fluid (1316). Occasionally the alveolar spaces within the lesion create a stippled pattern of depressions. AAH lesions are more often found close to the pleura (1434) and in the upper lobes (1429). It is likely that most occur as multiple lesions.

**Histopathology**
AAH is a discrete parenchymal lesion arising often in the centriacinar region, close to respiratory bronchioles. The alveoli are lined by rounded, cuboidal, low columnar or ‘peg’ cells, which have round or oval nuclei. Up to 25% of the cells show intranuclear inclusions (1434) and many have light microscopic (1434) and ultrastructural (1022) features of Clara cells and type II pneumocytes. Ciliated and mucus cells are never seen. Double nuclei are common; mitoses are extremely rare. There is some blending with normal alveolar lining cells peripherally, but most lesions are well defined. The alveolar walls may be thickened by collagen, occasional fibroblasts and lymphocytes. Lesions with these components in abundance are unusual. These interstitial changes do not extend beyond the limits of the lesion, as defined by the epithelial cell population. Cellularity and cytological atypia vary. Many lesions show a discontinuous lining of cells with small nuclei and minimal nuclear atypia. Fewer show a more continuous single cell layer with moderate atypia. Pseudopapillae and tufts may be present. Some authors separate lesions into low and high grades: LGAAH and HGAAH (1023,1040). This practice is not universally accepted, has no known clinical significance, its reproducibility is untested, and this panel does not recommend it. The features of AAH fall short of those accepted as BAC. This issue is addressed in the discussion on BAC. The postulated progression of disease, apparent from the increasingly atypical morphology, is supported by numerous morphometric and cytfluorometric studies (1375,1379,1438). AAH and non-mucinous BAC generally represent a continuum of progression of pulmonary alveolar intraepithelial neoplasia. AAH must be distinguished from reactive hyperplasia, secondary to parenchymal inflammation or fibrosis, where the alveolar lining cells are not the dominant feature and are more diffusely distributed. Generally, AAH cannot be identified in the presence of inflammatory or fibrosing disease. Distinction between more cellular and atypical AAH and BAC is difficult. BAC is generally >10mm in size, has a more pleomorphic, homogeneous columnar cell population, which is densely packed with greater cell-cell contact, overlap, mild stratification, and, usually, a less graded, more abrupt transition to adjacent alveolar lining cells. True papillae suggest papillary adenocarcinoma.

**Immunohistochemistry**
AAH expresses SPA, CEA (1640), MMPs (1084), E-cadherin, β-catenin, CD44v6 and TTF-1. The expression of oncogene and tumour suppressor gene products (TP53, C-ERB2, RB, MST1(p16), WAF1/CIP1 (p21) and FHIT) essentially reflects neoplastic progression from AAH to BAC and invasive adenocarcinomas (802,995,1021,1100). In contrast to the data on TP53 mutations, TP53 protein accumulation seems to occur early in the proposed sequence of events (995).

**Histogenesis**
The origin of AAH cells is still unknown but the differentiation phenotype derived from immunohistochemical and ultrastructural features suggests an alveolar origin. Surfactant apoprotein (1041), and Clara cell specific 10kDd protein (1021, 1379) are expressed in almost all AAH lesions. Ultrastructurally, cytoplasmic lamellar bodies and nuclear branching microtubules, both typical of type II pneumocytes, are common (1021,1316,1521). AAH may be derived from a progenitor cell with the potential for both type II pneumocyte and Clara cell differentiation.

**Somatic genetics**
KRAS. Mutations of the K-ras gene, particularly at codon 12, are specific for peripheral lung adenocarcinomas, as opposed to bronchogenic carcinoma, suggesting an alternative pathway of peripheral lung tumourigenesis (287, 74).
K-ras codon 12 mutations are reported in 15-39% of AAH lesions, and up to 42% of concurrent adenocarcinomas. Most of the time, the K-ras mutations are different. One study found K-ras codon 12 mutations in 15% of AAH, 33% of ‘early’ BAC and 24% of ‘advanced’ BAC. {1021}, suggesting that K-ras mutation is a very early event in the development of peripheral adenocarcinoma {1021,2126}.

**TP53.** Abnormalities of the P53 gene (17p), with impaired protein function, promote neoplastic transformation in affected cells. Many lung adenocarcinomas show missense mutations of the P53 gene with abnormal nuclear protein accumulation. LOH and mutations of the P53 gene are very rare in AAH compared with adenocarcinoma; however p53 protein overexpression is frequent in AAH {1021}. P53 mutation has been demonstrated with increasing frequency in the progression from AAH, through BAC to early invasive adenocarcinoma {1836}. 

**LOH.** Allelic-specific losses at 3p and 9p loci have been detected in AAH {1044,2187}. Some AAH lesions have shown LOH in 9q {51} and both 17q {2187} and 17p {51} LOH in the 3p and 9p loci probably occurs at a very early stage and may represent the earliest and crucial event in neoplastic transformation, with 17p events occurring later.

**FHIT.** The fragile histidine triad (FHIT) gene (3p) is deleted in many lung carcinomas {1856}.

**p16INK4.** Loss and inactivation plays an important role in the pathogenesis of lung carcinoma. However, loss of expression of p16INK4 is relatively rare in both AAH and adenocarcinoma {1021}.

**TSC.** A recent study on lung adenocarcinoma with concurrent multiple AAH lesions showed frequent LOH of tuberous sclerosis complex (TSC)-associated regions (TSC1 at 9q and TSC2 in 16p), suggesting that these are candidate loci for tumour suppressor genes in peripheral lung adenocarcinoma {1949}.

**Aneuploidy.** FISH studies of AAH have shown frequent aneuploidy of chromosome 7. The percentages of aneuploid cells and mean chromosome copy number increased from AAH to invasive adenocarcinomas, suggesting increasing polyploidy during malignant change {2245}. Some cases of AAH have been shown to be monoclonal, suggesting that it is a true preneoplastic lesion {1475}.

**Prognosis and predictive factors**

Assuming that AAH is always multifocal, several studies have compared post-operative survival in groups of patients with, and without AAH {333,1198,1927,1960}. None showed any difference in outcome. There is no indication for surgical or medical therapy in patients without cancer who are incidentally found to have AAH. In such a clinical setting, careful followup is warranted.
**Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia**

**Definition**
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a generalised proliferation of scattered single cells, small nodules (neuroendocrine bodies), or linear proliferations of pulmonary neuroendocrine cells (PNCs) that may be confined to the bronchial and bronchiolar epithelium, include local extraluminal proliferation in the form of tumourlets, or extend to the development of carcinoid tumours. It is sometimes accompanied by intra- and extraluminal fibrosis of involved airways, but other pathology that might induce reactive PNC proliferation is absent.

**Synonyms**
The entity of DIPNECH was not fully recognised and named until 1992, but cases with its clinical and pathological features appear in the literature from the early 1950s.

**Clinical features**
**Signs and symptoms**
DIPNECH may occur at any age, but presents typically in the fifth or sixth decades, and is perhaps commoner in women. The history is one of a very slowly worsening dry cough and breathlessness, often over many years, sometimes misdiagnosed as mild bronchial asthma. Physical examination usually reveals no signs, but pulmonary function tests show an obstructive or mixed obstructive/restrictive pattern of impairment with reduced diffusing capacity.

**Imaging**
Plain thoracic radiography is often normal, but tomographic scanning reveals a mosaic pattern of air trapping, sometimes with nodules and thickened bronchial and bronchiolar walls. Multiple nodules corresponding to tumourlets or carcinoid tumours may be present.

**Macroscopy and localization**
The early lesions of DIPNECH are invisible to the naked eye, but tumourlets and microcarcinoids, when present, can be just discerned as small, gray-white nodules, the latter often well-demarcated and resembling ‘miliary bodies’. Larger carcinoid tumours are firm, homogeneous, well-defined, grey or yellow-white masses. The lesions of DIPNECH usually affect one or both lungs uniformly.

**Histopathology**
Histopathological examination reveals widespread proliferation of PNCs. The earliest lesions comprise increased numbers of individual cells, small groups, or larger, nodular aggregates, confined to the bronchial or bronchiolar epithelium, the larger lesions bulging into the lumen, but not breaching the subepithelial basement membrane. The bronchiolar wall sometimes is fibrotically thickened. Bronchiolar occlusion may occur due to fibrosis and/or PNC proliferation. These are sufficient for the diagnosis of DIPNECH providing other defining criteria are met. In particular inflammatory or fibrous lesions that might cause secondary PNC hyperplasia are not seen. However, more advanced lesions are often present. These develop when the proliferating PNCs break through the basement membrane to invade locally, developing a conspicuous fibrous stroma to form small (2-5 mm) aggregates traditionally known as ‘tumourlets’. This proliferation of PNCs is sometimes accompanied by intra- and extramural fibrosis of the involved airways that often obliterates them, but the surrounding lung is otherwise unremarkable. Once PNCs reach a size of 5mm or greater, they are classified as carcinoids.

**Differential diagnosis**
Clinically and on imaging, DIPNECH may be indistinguishable from other diffuse lung diseases characterised by cough,
breathlessness, mixed obstructive/restrictive pulmonary impairment and a nodular pattern of pulmonary infiltration, so that the diagnosis is usually impossible to make without recourse to biopsy. Histopathologically, DIPNECH must be distinguished from the PNC proliferation that may accompany a variety of pulmonary conditions, particularly chronic inflammatory diseases such as bronchiectasis and chronic lung abscess (717); in the latter situation, progression of the proliferation to carcinoid tumours does not occur. DIPNECH must also be distinguished from the proliferation of PNCs not uncommonly seen adjacent to peripheral carcinoids (29,1317).

**Histogenesis**

As with neuroendocrine neoplasms arising in the lungs, the origin of the proliferating PNCs that characterize DIPNECH is likely to be a yet-to-be-defined uncommitted precursor cell that is stimulated by unknown influences to differentiate along a neuroendocrine line. However, the PNCs that proliferate in DIPNECH are found in normal lungs of adults (719, 1141).

**Somatic genetics**

There are no genetic markers of DIPNECH such that it might be possible to distinguish it genetically from the limited, reactive, reversible proliferative response of PNCs that occurs after pulmonary injury. It is of interest, however, that allelic imbalance at the 11q13 region that closely approximates to the MEN1 tumour suppressor gene appears to be rare in tumourlets, but is present in the majority of carcinoid tumours (581).

**Prognosis and predictive factors**

DIPNECH is a slowly progressive condition with a benign course spanning many years. Associated carcinoid tumours are indolent and atypical features have not been described. There are no predictive histologic or genetic data for DIPNECH.
Definition
A papillary tumour consisting of delicate connective tissue fronds with a squamous epithelial surface. Squamous papillomas can be solitary or multiple and can be exophytic or inverted.

ICD-O codes
Squamous cell papilloma 8052/0
Exophytic 8052/0
Inverted 8053/0

Epidemiology
Solitary squamous papillomas are very rare representing less than 0.50% of lung tumours at one large institution [1612]. Exophytic lesions far outnumber the inverted growth pattern [592]. Solitary squamous papillomas are seen predominantly in men, with a median age of 54 years [592]. Juvenile and adult laryngotracheal papillomatosis rarely involve the lower respiratory tract are always related to laryngotracheal papillomatosis [1223].

Etiology
An association with human papilloma virus (HPV) subtypes 6 and 11 suggests a possible pathogenetic role for the virus [592]. Human papilloma virus subtypes 16,18 and 31/33/35 in squamous papillomas associated with carcinomas and in squamous cell carcinomas have been reported, suggesting that HPV infection might be related to tumoural progression [139,1611,1612]. More than half of patients are tobacco smokers, but an etiologic role has not been established [592,1937].

Localization
Papillomas are endobronchial.

Clinical features
While up to one-third of lesions are incidental radiographic findings, patients most often present with obstructive symptoms. Computed tomography scans demonstrate a small endobronchial protuberance or nodular airway thickening. Involvement of distal airways may lead to nodular opacities and/or thin-walled cavity nodules [2213]. An endobronchial biopsy may be diagnostic, but distinction from well-differentiated squamous cell carcinoma can be difficult, especially with superficial tissue fragments. Bronchoscopic cytologic specimens will only demonstrate the squamous nature of the lesion. Parakeratotic cells, cytologic atypia and viral cytopathic effect should not be misinterpreted as invasive carcinoma [1677].

Tumour spread and staging
Squamous papillomas may recur at their original site and laryngotracheal papillomatosis can spread into the lower respiratory tract. It has been suggested that electrical or laser fulguration is responsible for alveolar parenchymal seeding.

Histopathology
Squamous papillomas are composed of a loose fibrovascular core covered by stratified squamous epithelium. Exophytic lesions feature orderly squamous maturation from the basal layer to the superficial flattened and oftentimes keratinized cells. Acanthosis may be prominent. While non-keratinized epithelium may resemble transitional epithelium, the squamous nature of these cells has been demonstrated ultrastructurally and use of this term is discouraged. Over 20% of solitary squamous papillomas feature wrinkled nuclei, binucleate forms and perinuclear halos, i.e., koilocytosis related to HPV infection [592]. Scattered

Fig. 1.81 Exophytic squamous papilloma. Mature squamous epithelial cells are growing in an exophytic papillary pattern on the surface of thin fibrovascular cores. The papilloma is attached to the underlying bronchial wall by a stalk. ..
dyskeratotic cells, large atypical cells and occasional mitotic figures above the basal layer can be seen. Dysplasia should be graded according to the World Health Organization classification (2024). Squamous cell carcinoma infrequently arises in solitary squamous papillomas (1611,1612).

Inverted lesions feature both exophytic and random invaginations of squamous epithelium. The basal lamina investing the endophytic nests is continuous with the basal lamina underlying the surface epithelium. Basal cells are perpendicular to the basement membrane while central cells are parallel and whirling. Tumour can involve adjacent seromucinous glands.

Alveolar parenchymal involvement manifests as either well circumscribed solid intraalveolar nests of cytologically bland non-keratinizing squamous cells surrounded by hyperplastic type II pneumocytes or large cysts lined by similar benign epithelium. Lower respiratory tract involvement with laryngotracheal papillomatosis is morphologically similar with the exception that virtually all lesions feature viral cytopathic effect. Neither immunohistochemical nor in situ hybridization studies are helpful in diagnosis.

**Differential diagnosis**

Inflammatory endobronchial polyps may show focal squamous metaplasia but generally have voluminous granulation tissue-like stroma and subepithelial dense lymphoplasmacytic infiltrates with a lack of continuous proliferative epithelial surface. Well-differentiated squamous cell carcinoma can be entirely papillary and endobronchial, but usually demonstrates malignant cytologic features if not also stromal invasion and/or angiolympathic invasion. Entrapped glands within the papillary stalk of a benign papilloma should not be mistaken for invasion. Inverted papillomas with even minimal cytologic atypia may be indistinguishable from invasive squamous cell carcinoma. Parenchymal destruction, cellular pleomorphism, loss of maturation, prominent dyskeratosis and hyperkeratosis favour a diagnosis of carcinoma.

**Precursor lesions-Histogenesis**

Squamous papillomas most likely arise from metaplastic respiratory epithelium.

**Prognosis and predictive factors**

While solitary squamous papillomas are considered benign lesions, the presence of focal cytologic atypia, a recurrence rate approaching 20% and reports of squamous cell carcinomas arising at papilloma excision sites indicate a low malignant potential. Thus, lesions should be completely excised when feasible. Human papilloma virus subtyping may be prognostically significant as condylomatous papillomas have malignant potential (1611,1612,1937,2030). Solitary papillomas may progress to papillomatosis, but lower respiratory tract involvement usually represents spread of juvenile or rarely adult laryngotracheal papillomatosis. Papillomatosis may be lethal even in the absence of malignant transformation owing to obstructive complications. Increased topoisomerase alpha II and p53 expression along with reduced RB gene protein product and p21 expression may serve as markers of transformation to so-called invasive papillomatosis and squamous cell carcinoma (753).
Glandular papilloma

Definition
A papillary tumour lined by ciliated or non-ciliated columnar cells, with varying numbers of cuboidal cells and goblet cells.

ICD-O code 8260/0

Synonym
Columnar cell papilloma

Epidemiology
Glandular papillomas are exceedingly rare. An equal sex distribution and median age of 68 years are established based on the few reported cases [85,118,592,1858].

Etiology
No specific etiologies have been implicated in the evolution of glandular papillomas.

Localization
Endobronchial

Clinical features and diagnostic procedures
Individuals present with obstructive symptoms including wheezing or haemoptysis [592]: a minority are asymptomatic and radiographic studies demonstrate either a small endobronchial protuberance or nodular airway thickening. While bronchoscopic biopsy can identify a central lesion, complete excision is necessary for definitive diagnosis.

Macroscopy
Glandular papillomas are white to tan endobronchial polyps that measure from 0.7-1.5 cm. Bronchiolar lesions can appear solid without obvious papillary fronds.

Histopathology
Central lesions have relatively non-inflamed thick arborizing stromal stalks with prominent thin-walled blood vessels or hyalinization covered by glandular epithelium. Necrosis is absent. Pseudostratified or columnar epithelium lacks micropapillary tufts and cellular desquamation. Epithelium can be non-ciliated or ciliated, cuboidal or columnar or a mixture and interspersed mucin-rich cells can be seen. The cytoplasm can be clear and the nuclei lack atypia and mitoses. Peripheral lesions demonstrate attachment to bronchiolar mucosa and contain scattered ciliated cells.

Differential diagnosis
Primary and metastatic papillary adenocarcinomas feature epithelial crowding, malignant cytologic features and often show bronchial wall invasion. Inflammatory polyps and the papillary variant of mucus gland adenoma lack true fibrovascular stromal cores and inflammatory polyps lack a proliferative epithelial component. Papillary adenomas are parenchymal lesions without attachment to airways and usually demonstrate type II pneumocyte differentiation.

Prognosis and predictive factors
Glandular papillomas are benign tumours that may recur following incomplete resection, but neither extension into alveolar parenchyma nor malignant transformation has been reported [85,118,592,1858].

Fig. 1.83 Glandular papilloma. Columnar epithelial cells proliferate in a papillary fashion along the surface of fibrovascular cores From Flieder et al. (592) and Travis et al. (2024).
Mixed squamous cell and glandular papilloma

Definition
Mixed squamous and glandular papilloma is an endobronchial papillary tumour showing a mixture of squamous and glandular epithelium. One-third of the epithelium should be composed of the second epithelial type.

ICD-O code
8560/0

Synonyms
These tumours were formerly called transitional papillomas (1072).

Epidemiology
Mixed papillomas are exceedingly rare with seven cases reported in the world literature. An equal sex distribution and median age of 64 years are compiled from the few reported cases (592,1858).

Etiology
No specific etiologies have been implicated in the evolution of mixed papillomas. Human papilloma virus has not been detected in the few cases studied. 60% of patients are tobacco smokers, but an etiologic role has not been established (592).

Clinical features and diagnostic procedures
Individuals present with obstructive symptoms (592,1858). While endobronchial biopsy can demonstrate the neoplastic nature of a central lesion, complete excision is necessary for definitive diagnosis.

Macroscopy
Endobronchial lesions are tan to red, polypoid and measure from 0.2-2.5 cm. A lobar preference is not seen.

Histopathology
Endobronchial lesions are composed of fibrovascular cores with scattered lymphoplasmacytic infiltrates lined by squamous and glandular epithelium. Pseudostratified ciliated and nonciliated cuboidal to columnar cells with occasional mucin-filled cells are distinct from acanthotic and focally keratinizing squamous epithelium. Squamous atypia ranging from mild to severe dysplasia can be seen but viral cytopathic change has not been reported. Glandular atypia and necrosis are not seen.

Differential diagnosis
This is the same as for pure squamous and glandular papillomas.

Prognosis and predictive factors
Complete resection appears to be curative (592).
Alveolar adenoma

Definition
A solitary well-circumscribed peripheral lung tumour consisting of a network of spaces lined by a simple low cuboidal epithelium associated with a variably thin and inconspicuous to thick spindle cell-rich stroma, sometimes with a myxoid matrix.

ICD-O code 8251/0

Synonyms
This tumour has been mistakenly reported under the term lymphangioma.

Epidemiology
This tumour is very rare. The age range is 39-74 years (mean, 53 years), with a slight female predominance (194,252,624,792,1054,1297,1464,1514,1782,1811,1822,2219).

Localization
Alveolar adenoma has been reported in all five lobes with a predilection for the left lower lobe (1116). Most tumours are intraparenchymal peripheral or subpleural although a hilar location has been noted.

Clinical features
Patients are usually asymptomatic and the tumour is an incidental radiographic finding. (1116). Chest X-ray and CT appearances are those of a well-circumscribed, homogenous, non-calcified, solitary mass, although one report, unconfirmed histologically, raises the possibility of multifocality (624). Contrast enhancement on CT and MRI displays cystic spaces with central fluid and rim enhancement (624).

Macroscopy
Tumours measure from 0.7-6.0 cm and feature well demarcated smooth, lobulated, multicystic, soft to firm and pale yellow to tan cut surfaces (252).

Histopathology
Alveolar adenomas are well-circumscribed unencapsulated multicystic masses with ectatic spaces filled with eosinophilic granular material. Spaces are lined by cytologically bland flattened, cuboidal and hobnail cells. Cystic spaces are usually larger in the centre of the lesion and squamous metaplasia can be seen. The myxoid and collagenous interstitium varies in thickness and contains scattered to dense groups of cytologically bland spindle cells.

Immunohistochemistry
Epithelial lining cells are type 2 pneumocytes that stain for broad-spectrum keratin, CEA, surfactant protein and TTF-1 while stromal cells show focal positivity for smooth-muscle actin and muscle-specific actin and negativity for desmin, TTF-1, proSPB, proSPC and CC10 (252). Low proliferation indices in both the epithelial and mesenchymal cells have been reported (194,1297).

Electron microscopy
By electron microscopy, lining cells contain lamellar bodies, blunt surface microvilli and cell junctions of the zonula adherens type.

Differential diagnosis
Lymphangioma, sclerosing haemangioma, and adenocarcinoma including bronchioloalveolar carcinoma comprise the differential diagnosis. Cytokeratin positivity of cells lining the cystic spaces differentiates this lesion from a lymphangioma (252). The single architectural growth pattern, large ectatic spaces lacking blood and stromal cell negativity for TTF-1 discern the tumour from a sclerosing haemangioma (252,1464). The well-circumscribed growth pattern, lack of lepidic growth and cytologic atypia discern alveolar adenoma from bronchioloalveolar carcinoma (252). Primary and metastatic spindle cell tumours may

Fig. 1.85 Alveolar adenoma. A This tumour nodule is circumscribed, but not encapsulated. There are large cysts and smaller spaces resembling alveoli. From Burke et al. (252) and Travis et al (2024). B This whole-mount section demonstrates the well circumscribed nature of the multicystic neoplasm.
also become cystic, with foci resembling alveolar adenoma.

**Histogenesis**
This lesion appears to represent a combined proliferation of alveolar pneumocytes and septal mesenchyme (252, 1514).

**Somatic genetics**
The neoplastic nature of alveolar adenoma was demonstrated in a cytogenetic study of one tumour. A pseudodiploid karyotype, 46,XX, add (16) (q24), was described and fluorescence in situ hybridization studies revealed the add (16) (q24) to be a der(16)t(10;16) (q23;q24) (1682).

**Prognosis and predictive factors**
Alveolar adenomas are benign tumours and surgical excision is curative.

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Fig. 1.86 Alveolar adenoma. A Cystic spaces of varying sizes are filled with eosinophilic fluid and PAS-positive granular material. Intervening stroma is focally prominent. B Alveolus-like spaces are lined by flat or cuboidal pneumocytes on the surface of a thin layer of vascular connective tissue resembling an alveolar wall. A few macrophages are present within the alveolar-like spaces. From Burke et al. (252) and Travis et al. (2024).
**Definition**

Papillary adenoma is a circumscribed papillary neoplasm consisting of cytologically bland cuboidal to columnar cells lining the surface of a fibrovascular stroma.

**ICD-O code**

8260/0

**Synonyms**

Bronchiolar adenoma, papillary adenoma of type II pneumocytes, type II pneumocyte adenoma, adenoma of type II pneumocytes, peripheral papillary tumour of type II pneumocytes.

**Epidemiology**

The papillary adenoma is a rare tumour with less than 20 cases reported. Individuals range in age from 7-60 years (mean 32 years) and males predominate {484,555,579,635,808,1103,1376,1483,1858,2185}.

**Etiology**

The etiology in humans is unknown but a similar lesion can be chemically induced in mice [974].

**Localization**

The tumour has no lobar predilection and involves alveolar parenchyma but not airways {484,555,579,635,808,1103,1376,1483,1858,2185}.

**Clinical features**

Individuals are usually asymptomatic and the tumour is incidentally noted on chest radiographs as a well-defined pulmonary nodule {484,555,579,635,808,1376,1483,1858,2185}.

**Macroscopy**

Grossly, the tumour is a well defined, sometimes encapsulated, soft, spongy to firm mass with a granular gray white/brown cut surface measuring from 1.0-4.0 cm {484,555,579,635,808,1376,1483,1858,2185}. Although generally separate from the airways, protrusion into the lumen of a small bronchiole can occur {1483}.

**Histopathology**

Papillary adenomas are generally well circumscribed but infiltrative growth has been described. The tumour has a papillary growth pattern sometimes mixed with more solid areas. Focally inflamed fibrovascular cores are lined with cuboidal to columnar epithelial cells with round to oval nuclei. Ciliated {635,1376} and oxyphilic cells {555,579} can be seen. Occasional eosinophilic intranuclear inclusions are noted but nuclear atypia and mitosis are rare to absent. Intracellular mucin is not present.

**Immunohistochemistry and electron microscopy**

Both type II and Clara cells can be found in papillary adenomas resulting in positive staining for broad-spectrum cytokeratin, Clara cell protein, TTF-1 and surfactant apoprotein as well as CEA. Neuroendocrine markers are negative {484,555,579,635,808,1376,1483,1858,2185}. Ultrastructurally lamellar bodies, surface microvilli, with membrane bound electron dense deposits have been observed {635,2185}.

**Differential diagnosis**

Sclerosing haemangioma demonstrates varied architectural growth patterns including hemorrhagic, sclerotic and solid tumour cell growth {488}. Alveolar adenoma does not display a papillary growth pattern, Clara cells or ciliated cells {252}. Papillary adenocarcinomas including metastatic thyroid carcinoma and broncholoalveolar carcinoma have a greater degree of cellular proliferation with micropapillary tufts and nuclear pleomorphism. Papillary carcinoid tumour has granular cytoplasm and a finely granular chromatin pattern.

**Histogenesis**

Pulmonary papillary adenoma is thought to arise from a multipotential stem cell/immature bronchioloalveolar cell that differentiates towards type II pneumocytes, Clara cells or ciliated respiratory epithelial cells {555,635,1483,1858}.

**Prognosis and predictive factors**

Papillary adenoma is benign and surgical excision is curative. {484,555,635,808,1103,1376,1483,2185}.

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**Fig. 1.87 Papillary adenoma. Cuboidal epithelial cells line the surface of the fibrovascular cores. From Travis et al. (2024).**
Mucous gland adenoma

**Definition**
A benign predominantly exophytic tumour of the tracheobronchial seromucinous glands and ducts featuring mucus-filled cysts, tubules, glands and papillary formations lined by a spectrum of epithelium including tall columnar cells, flattened cuboidal cells, goblet cells, oncocytic cells and clear cells.

**ICD-O code** 8480/0

**Synonyms**
Bronchial cystadenoma, mucous cell adenoma, polyadenoma, bronchial adenoma arising in mucous glands

**Epidemiology**
The tumour is extremely rare \{1561\}. There is no sex predilection and tumours have been reported in both children and the elderly with a mean age of 52 years \{543,1077\}.

**Localization**
Most tumours are central but peripheral lesions have been described \{543,2117\}.

**Clinical features**
Individuals present with signs and symptoms of obstruction. Radiographic studies demonstrate a coin lesion. CT scans may show a well-defined intraluminal mass with air-meniscus sign \{1109\}. Excision is usually required for definitive diagnosis \{472\}.

**Macroscopy**
Grossly, white-pink to tan, smooth and shiny tumours with gelatinous mucoid solid and cystic cut surfaces measure from 0.7-7.5 cm (mean 2.3 cm) \{543\}.

**Histopathology**
Mucous gland adenomas are well-circumscribed, predominantly exophytic nodules above the cartilaginous plates of the bronchial wall. Tumours comprise numerous mucin-filled cystic spaces and non-dilated microacini, glands, tubules and papillae may also be seen. Neutral and acid-mucin filled cysts are lined by cytologically bland columnar, cuboidal or flattened mucus secreting cells. Oncocytic and clear cell change can also be seen as well as focal ciliated epithelium. Hyperchromasia, pleomorphism and mitoses are rare while squamous metaplasia only involves overlying surface respiratory epithelium. Bands of spindle cell-rich stroma may be hyalinized or with prominent lymphocytes and/or plasma cells.

**Immunohistochemistry and EM**
Immunohistochemistry demonstrates similar staining to non-neoplastic bronchial glands with epithelial cells positive for EMA, broad-spectrum cytokeratins and CEA. Focal stromal cell positivity for broad-spectrum keratins, smooth-muscle actin and S-100 protein indicate a myoepithelial component. Proliferating cell nuclear antigen and Ki-67 staining performed in several cases demonstrate rare tumour cell positivity \{543\}. Mucinous and myoepithelial cell types have been identified by electron microscopy \{543,804\}.

**Differential diagnosis**
Low-grade mucoepidermoid carcinoma including the papillary and cystic variants may closely mimic mucus gland adenoma. Despite architectural similarities, the presence of squamous and intermediate cells confirms mucoepidermoid carcinoma. Mucinous cystadenomas are located in the lung periphery and consist of a cystic lesion filled with mucus and lined by uniform, bland mucus cells. Adenocarcinomas are usually infiltrative and feature cytologic atypia, mitoses and necrosis.

**Histogenesis**
The tumour is postulated to arise from the mucus glands of the bronchus.

**Prognosis and predictive factors**
Mucous gland adenomas are benign and conservative lung-sparing bronchoscopic or sleeve resection is recommended \{543\}.

---

**Fig. 1.88** Mucous gland adenoma. A Endobronchial mass is comprised of numerous mucin-filled cystic spaces, microacini, glands, tubules and papillae. B Papillary fronds are a minor architectural pattern. C Neutral and acid-mucin filled cysts are lined by cytologically bland columnar, cuboidal or flattened mucus secreting cells. D Glands lined by columnar epithelium with small basally oriented nuclei and abundant apical mucinous cytoplasm. From Travis et al. (2024).
Pleomorphic adenoma

Definition
A tumour with both epithelial and connective tissue differentiation consisting of glands intermingled with myoepithelial cells in a myxoid and chondroid stroma.

ICD-O code
8940/0

Synonym
Benign mixed tumour

Epidemiology
Although rare, pulmonary pleomorphic adenoma has been reported in individuals ranging from 11-74 years, but most often affects those in their sixth and seventh decades of life. A gender predilection is not seen [803,1364,1727,1958].

Etiology
No specific etiologies have been implicated in the evolution of the tumour.

Localization
Most tumours are centrally located endobronchial polypoid masses but peripheral lesions occur [803,1364,1727,1958].

Clinical features
Tumours most often present with obstructive symptoms [1364]. A minority of lesions are incidental X-ray findings demonstrating either discrete endobronchial mass with minimal bronchial wall thickening or well-circumscribed peripheral nodules. Cytologic and bronchoscopic biopsy material can suggest the diagnosis but complete excision is required for a definitive diagnosis.

Macroscopy
Tumours range in size from 1.5-16 cm [803,1364,1727,1958]. Typically, endobronchial lesions are usually associated with a major or secondary bronchus and are polypoid, with some degree of luminal occlusion. Peripheral lesions are not intimately associated with airways. Tumours are circumscribed, unencapsulated with a gray-white, rubbery or myxoid cut surface.

Histopathology
Pulmonary pleomorphic adenomas are biphasic like their salivary gland counterpart, but do not often feature either a prominent glandular component or chondroid stroma. Rather, tumours exhibit features of the so-called “cellular mixed tumour” manifesting sheets, trabeculae or islands of epithelial and/or myoepithelial cells and a myxoid matrix. When present, ducts composed of an outer layer of myoepithelial cells and an inner layer of epithelial cells containing small amounts of periodic acid-Schiff (PAS)-positive luminal secretion. Mitotic activity, pleomorphism and necrosis are unusual.

Immunohistochemistry
Ductal and myoepithelial cells stain for both low-molecular weight and broad spectrum keratin while myoepithelial and stromal cells are positive for vimentin, smooth-muscle actin and glial fibrillary acidic protein. S-100 protein immunoreactivity can also be seen in both epithelial and myoepithelial cells [1364,1727].

Differential diagnosis
Pulmonary pleomorphic adenoma must be discerned from head and neck or even breast metastasis by thorough clinical history and examination. A solitary tumour associated with a cartilage-bearing airway suggests a pulmonary origin. The morphologic differential diagnosis includes hamartoma, pulmonary blastoma and carcinosarcoma. Hamartomas usually show cartilage and other mesenchymal elements while the latter tumours feature obviously malignant stroma and epithelium.

Histogenesis
This neoplasm with epithelial and connective tissue differentiation is regarded as arising from the submucosal bronchial gland epithelium. However, peripheral and subpleural locations unrelated to bronchi raise the possibility that the tumour may originate from a primitive stem cell.

Prognosis and predictive factors
Pleomorphic adenomas of the lung exhibit a spectrum of clinical behavior ranging from benign to malignant. On the basis of several studies, small well-circumscribed lesions are cured with lobectomy while larger, infiltrative or poorly circumscribed lesions tend to recur and metastasize. Tumours with greater than 5 mitoses per 10 high-power fields may be associated with aggressive behavior [1364], but in the absence of malignant cytology, necrosis and angiolymphatic invasion such lesions should be diagnosed as benign pleomorphic adenoma rather than carcinoma ex pleomorphic adenoma.

Other benign salivary gland-like tumours
Well-defined salivary gland tumours including monomorphic adenoma, oncocytoma, and myoepithelioma are extremely rare primary lung tumours [429,1812,1883,1977,2037]. Adenomyoepithelioma [2037] is discussed under epimyoepithelial carcinoma in the section on malignant salivary gland tumours. In the absence of known salivary gland primaries and exclusion of mimics such as metastatic and primary malignancies including typical carcinoid tumour, these solitary lesions in the lung can be diagnosed as primary lung neoplasms.
Mucinous cystadenoma

Definition
A localized cystic mass filled with mucin and surrounded by a fibrous wall lined by well-differentiated columnar mucinous epithelium.

ICD-O code 8470/0

Epidemiology
This exceedingly rare tumour is most often seen in both men and women in their sixth and seventh decades of life [730,1067,1068,1699]. Most reported cases occur in tobacco-smokers but no specific etiologies have been implicated in the evolution of the tumour [730,1067,1068].

Localization
These tumours are usually located in the peripheral lung.

Clinical features and diagnostic procedures
Mucinous cystadenoma are asymptomatic lesions that present as incidental rounded well demarcated masses on X-ray and CT scans [1067,1068]. Fine needle aspirates and transbronchial biopsies may sample mucin or goblet cells, but a definitive diagnosis requires surgical excision and complete histologic sampling.

Macroscopy
Grossly, unilocular mucous-filled cysts measure from less than 1.0-5.0 cm and are not associated with airways. Cyst walls are thin (0.1 cm) and lack mural nodules [1067,1068].

Tumour spread and staging
One instance of tumour seeding the parietal pleura (so-called pleural pseudomyxoma) has been reported [730].

Histopathology
Microscopically, the cystic lesion is filled with mucus and the fibrous connective tissue wall is lined by a discontinuous layer of low cuboidal to tall columnar, mucin-secreting epithelium. Lining cells feature basally located hyperchromatic nuclei and abundant cytoplasmic mucin. Focal cellular stratification, papillary infoldings and rare mitoses may be seen, but micropapillary fronds, necrosis and overt cytologic atypia are by definition absent. Foreign body giant cell reaction associated with extravasated mucus and stromal chronic inflammation are prominent adjacent to areas of denuded epithelium.

Immunohistochemistry
Lesional epithelium is broad-spectrum keratin positive, rarely CEA positive and surfactant-associated protein A negative [1067,1699]. Proliferating cell nuclear antigen and Ki-67 antibodies stain less than 10% and 5% of lesional cell nuclei, respectively [1699].

Differential diagnosis
Mucinous cystadenoma should not be confused with mucinous cystadenocarcinoma or the colloid mucinous variant of adenocarcinoma. Mucus extravasation, lepidic spread of epithelium beyond the fibrous capsule or into adjacent lung invasion or cytologic anaplasia indicates adenocarcinoma. Other considerations include mucinous bronchioloalveolar carcinoma, and non-neoplastic lesions, such as congenital cystic adenomatoid malformation as well as developmental and post-infectious bronchogenic cysts.

Prognosis and predictive factors
Mucinous cystadenomas are benign tumours. Complete excision is curative.

Fig. 1.90 Mucinous cystadenoma. A A subpleural cystic tumour is surrounded by a fibrous wall and contains abundant mucus. From Travis et al. (2024). B Columnar epithelial cells line the wall of the cyst. Most of the nuclei are basally oriented but there is focal nuclear pseudostratification. The apical cytoplasm is filled with abundant mucin. From Travis et al. (2024).
Marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type

**Definition**
Pulmonary marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is an extranodal lymphoma comprising morphologically heterogeneous small B-cells, cells resembling monocytoid cells, and/or small lymphocytes, with scattered immunoblasts and centroblasts-like cells. There is plasma cell differentiation in a proportion of the cases. The infiltrate is in the marginal zone of reactive B-cell follicles and extends into the interfollicular region. The neoplastic cells typically infiltrate the broncholar mucosal epithelium, forming lymphoepithelial lesions.

**ICD-O code** 9699/3

**Synonyms**
The term pseudolymphoma is considered obsolete, and lymphocytic interstitial pneumonia is now limited to inflammatory lesions. Terms such as BALT (bronchial associated lymphoid tissue) lymphoma and BALTOMA should now also be avoided.

**Historical annotation**
Primary pulmonary non-Hodgkin's lymphoma was originally defined as a lymphoma that presented primarily in the lungs, with or without hilar node involvement but without clinical evidence of disease elsewhere [1731]. Those tumours not fulfilling these criteria were classified as pseudolymphomas, but this term is now obsolete as most of these cases are now believed to be neoplastic and the rare localized reactive lesions are classified as nodular lymphoid hyperplasia. Early series of pulmonary lymphoma were categorised according to lymph node classifications [1063,2041], but it is now accepted that the majority of cases arise from bronchial mucosa-associated lymphoid tissue (MALT) [21,137,407,577,1104,1176,1467]. The REAL classification currently recommends the ‘Marginal Zone B-Cell Lymphoma of the Mucosa-Associated Lymphoid Tissue (MALT) Type’ for those with ‘low-grade’ features and ‘diffuse large B-cell non-Hodgkin’s lymphoma’ for those with ‘high-grade’ features.

**Epidemiology**
Approximately 70-90% of primary pulmonary lymphomas are marginal zone lymphomas of MALT type but they account for less than 0.5% of all primary lung neoplasms and a similarly low proportion of all lymphomas [21,1063,1176]. Patients tend to be in their fifth, sixth or seventh decades, with a slight male preponderance. Presentation in younger patients is rare without underlying immunosuppression [21,137,407,577,1176,1467].

**Etiology**
Pulmonary marginal zone B-cell lymphomas of MALT type are thought to arise in acquired MALT secondary to inflammatory or autoimmune processes. Bronchial MALT is not thought to be a normal constituent of the human bronchus, and it likely develops as a response to various antigenic stimuli, for example smoking [1659] and autoimmune disease [1469]. However, a common association, as seen between gastric lymphomas of MALT origin and Helicobacter pylori infection [2171], has not been found. The etiology of most cases of pulmonary MALT lymphoma is not known.

**Localization**
Tumours have no zonal or lobar predisposition, are typically peripheral in location, and range from solitary nodules to diffuse bilateral disease (the pattern that mimics lymphocytic interstitial pneumonia).

**Clinical features**
The most common presentation is a mass discovered on a chest radiograph in an asymptomatic patient, with symptomatic patients presenting with cough, dyspnoea, chest pain and haemoptysis. Previous or synchronous MALT lymphomas at other extranodal sites are not uncommon. A monoclonal gammopathy may be present, but if present may indicate pulmonary involvement by lymphoplasmacytic lymphoma in a patient with Waldenstrom macroglobulinemia. Rarely patients manifest systemic or ‘B’ symptoms.

Chest radiographs and high resolution computerized tomograph (HRCT) scanning show multiple, solitary masses or alveolar opacities with associated air bronchograms. HRCT scans may also show airway dilatation, positive angiogram signs and haloes of ground glass shadowing at lesion margins [1014].

Diagnosis can be made by bronchoscopic or transbronchial biopsy, although not infrequently a surgical lung biopsy will be required. Broncholaveolar lavage and fine-needle aspiration biopsy specimens can be diagnostic of lymphoma if a clonal B-cell population can be demonstrated, but the specific type of lymphoma can rarely be diagnosed by these techniques.

**Macroscopy**
Nodular areas of pulmonary involvement by pulmonary marginal zone B-cell lymphomas of MALT type typically show a consolidative mass that is yellow to cream in colour, not dissimilar in texture to the cut surface of a lymph node involved by lymphoma. Rarely, tumours are focally cystic.

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**Fig. 1.91 Marginal zone B-cell lymphoma of MALT.**

Macroscopy. A diffuse consolidation of the middle lobe with a solid cream-coloured cut surface that is similar in texture to the cut surface of a lymph node involved by lymphoma.
Histopathology
Pulmonary marginal zone B-cell lymphomas of MALT type generally appear as a diffuse infiltrate of small lymphoid cells, which surround reactive follicles that are typically smaller and less conspicuous than those arising in the stomach. Follicles, best seen when highlighted with a CD21 stain, may be overrun by tumour cells (follicular colonization). Tumours are composed of lymphocyte-like, lymphoplasmacytic-like, centrocyte-like (marginal zone), or monocytoid B cells, which are all thought to be variations of the same neoplastic cell [904, 1104]. Infiltration of bronchial, bronchiolar and alveolar epithelium (lymphoepithelial lesions) is characteristic but not pathognomonic, since this phenomenon can be seen in non-neoplastic pulmonary lymphoid infiltrates. Plasma cells may be numerous and may accumulate along bronchovascular bundles or interlobular septa and may or may not show light chain restriction. Scattered transformed large cells (centroblasts and immunoblasts) are typically seen, but these are in the minority. The term, marginal zone B-cell lymphoma of MALT type refers only to tumours with a predominance of small cells ('low grade'). Areas with sheets of large cells should receive a separate diagnosis of diffuse large B-cell lymphoma. Lymphoid cells often track along bronchovascular bundles and interlobular septa at the periphery of masses but alveolar parenchyma is destroyed towards their centres. Airways are often left intact, correlating with the presence of air bronchograms on HRCT. Central sclerosis may also be a feature. Giant lamellated bodies are seen in about 20% of cases, most likely reflecting the indolent nature of the neoplasm [1576]. Vascular infiltration, pleural involvement and granuloma formation are not uncommon, but have no prognostic significance. Necrosis is very rare. Amyloid deposition forming nodules with a ring of lymphoma cells can be seen.

Immunophenotype
The neoplastic cells are monoclonal B cells, and may be identified by CD20 or CD79a staining, with a variable reactive T-cell population in the background. Light chain restriction is present in all cases if studied in fresh tissue; it can be demonstrated in paraffin sections in a variable proportion of the cases depending on the laboratory. Cytoplasmic secretory immunoglobulin indicating plasmacytic differentiation is observed in about 30% of cases. The majority of the cases express mu heavy chain, but some express gamma or alpha. They are CD5-, CD10-, CD23-, BCL6-, and CD43 is expressed in some cases. The tumour cells are usually BCL2+ in contrast to reactive monocytoid B cells. Stains for follicular dendritic cells (FDC) such as CD21, CD23, and CD35 highlight reactive follicles and often demonstrate expanded meshworks associated with disrupted follicles overrun by tumour cells. The proliferation fraction (Ki67) is usually very low (<10%); residual follicles show numerous Ki67+ cells. Stains for cytokeratin highlight lymphoepithelial lesions.

Differential diagnosis
From the clinical and imaging aspect, the differential diagnosis includes sarcoidosis, bronchioloalveolar cell carcinoma, organizing pneumonia, infections and rarer alveolar filling disorders and amyloidosis. The histologic differential diagnosis includes lymphocytic interstitial pneumonia, nodular lymphoid hyperplasia, extrinsic allergic alveolitis, inflammatory myofibroblastic tumour and plasma cell granuloma. In relation to lymphocytic interstitial pneumonia, pulmonary marginal zone B-cell lymphomas of MALT type tend to infiltrate and destroy the alveolar architecture, with greater widening of alveolar septa by the lymphoid infiltrate. Lymphoepithelial lesions may be seen in reactive conditions, but are more prominent in the lymphomas. Using immunohistochemical stains, the presence of expanded infiltrates of B cells outside of follicles is characteristic of MALT lymphoma, while in reactive infiltrates B cells are present as small aggregates or follicles with a peribronchial and/or septal distribution. Demonstration of immunoglobulin light chain restriction is important in this differential diagnosis, but is optimally done on fresh frozen tissue; analysis of immunoglobulin heavy gene rearrangement by PCR can also be very helpful. Nodular lymphoid hyperplasia (NLH) refers to the rare occurrence of one or several pulmonary nodules consisting of reactive lymphoid cells [1066]. Patients have similar presentation and epidemiology to those with pulmonary marginal zone B-cell lymphomas of MALT type although associated lymphadenopathy and pleural effusions suggest the diagnosis of lymphoma [611].
Histologically, NLH comprises numerous reactive germinal centres with well-preserved mantle zones and interfollicular sheets of mature plasma cells, with varying degrees of interfollicular fibrosis. Plasma cells may show Russell bodies, but not Dutcher bodies. Invasion of the visceral pleura or invasion of bronchial cartilage are not found. Immunohistochemical stains demonstrate a reactive pattern of B cells and T cells. In particular, the germinal centers stain for the B-cell marker CD20, while interfollicular lymphocytes are immunoreactive for CD3, CD43 and CD5 {10}. Antibodies to CD45RA stain the mantle zone lymphocytes, but stains for bcl-1 and bcl-2 do not decorate the follicles. The CD20-positive lymphocytes do not co-express either CD43 or CD5. Staining for immunoglobulin light chains shows a polyclonal pattern among the plasma cells. Molecular genetic analysis has shown no rearrangement of the immunoglobulin heavy chain gene {10}. Assays for the chromosomal rearrangement t(14;18) have been negative. Pulmonary marginal zone B-cell lymphomas of MALT type may produce amyloid and must be distinguished from nodular amyloidomas {430}. The morphologic finding of a dense plasma cell infiltrate, light chain restriction in plasma cells, numerous B cells expressing CD20 and coexpression of CD43 by B cells have been shown to be useful in confirming the diagnosis of lymphoma. The differential diagnosis, particularly on small biopsy specimens, also includes other small B-cell lymphomas, such as follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (CLL) and lymphoplasmacytic lymphoma. Lack of CD5 is helpful in excluding small lymphocytic and mantle cell lymphoma, lack of cyclin D1 in excluding mantle cell lymphoma, and lack of CD10 and BCL6 in excluding follicular lymphoma. Distinction from lymphoplasmacytic lymphoma requires finding the characteristic morphologic features of pulmonary marginal zone B-cell lymphomas of MALT type (follicles and marginal zone differentiation) or the characteristic clinical features of lymphoplasmacytic lymphoma (disseminated disease with bone marrow involvement and macroglobulinemia).

**Histogenesis**

Lymphocytes within bronchial MALT.

**Somatic genetics**

Immunoglobulin genes are clonally rearranged. Rearrangements can be detected by Southern blot in all cases if fresh or frozen tissue is used. Amplification of the immunoglobulin heavy chain gene from paraffin sections with the polymerase chain reaction can detect monoclonality in 60% of marginal zone lymphomas {137,1467}. T(11;18)(q21;q21) translocation, is the most common genetic abnormality in pulmonary marginal zone B-cell lymphoma of MALT type (50-60% of cases). T(1;14) or trisomy 3 may also occur. The t(11;18) involves the API2 anti-apoptosis gene on chromosome 11 and a recently recognized gene called MLT on chromosome 18, and produces a fusion protein. Both the t(1;14) and the t(11;18) lead to nuclear Bcl-10 expression {1504}. One recent study has shown that t(11;18) and aneuploidy are primarily mutually exclusive events, especially in the lung, suggesting different pathogenetic pathways in the development of this type of lymphoma. Both abnormalities were associated with recurrent disease {1104}.

**Tumour spread and staging**

It has been recommended that cases with unilateral or bilateral pulmonary involvement be staged as IE, and cases with regional lymph node (hilar/mediastinal) involvement be staged as IIE {2053}. When distant spread occurs, there is preferential spread to other mucosal sites rather than to lymph nodes (just as other lymphomas of MALT origin may spread to the lung) {407,1467}.

**Prognosis and predictive factors**

In patients with resectable disease, surgery has resulted in prolonged remission {2053}, but for those with either bilateral or unresectable unilateral disease, treatment has been governed by the principles that apply to more advanced nodal lymphomas. Indeed, elderly patients with asymptomatic lesions may well be followed up without treatment. Five-year survival for marginal zone lymphomas of MALT origin is quoted at 84-94% {577,1176,1467}. A small percentage of MALT lymphomas progress to diffuse large B-cell lymphoma.
Primary pulmonary diffuse large B-cell lymphoma

**Definition**
Diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) is a diffuse proliferation of large neoplastic B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte. Primary pulmonary DLBCL is used for tumours that are localized to the lungs at presentation.

**ICD-O code** 9680/3

**Synonyms**
High-grade MALT lymphoma has been used for these tumours, but this term should no longer be used.

**Epidemiology**
DLBCL comprise about 5-20% of primary pulmonary lymphomas [21,407,577, 1063,1176,1467]. Patients usually present between 50-70 years of age, similar to patients with pulmonary marginal zone B-cell lymphoma of MALT type. There is no sex predisposition. Primary pulmonary DLBCL may occur as a complication of immunosuppression for allo-grafts.

**Etiology**
The etiology of most diffuse large B-cell lymphomas is not known. However, an association between diffuse large B-cell non-Hodgkin lymphomas arising in the lung and collagen vascular diseases, both with and without fibrosing alveolitis, has been reported [1469]. Other associations of B-cell lymphomas include AIDS and immunodeficiency conditions.

**Localization**
Tumours have no zonal or lobar predisposition, and are typically peripheral in location.

**Clinical features**
Patients are nearly always symptomatic and present with cough, haemoptysis and dyspnoea. Some patients complain of systemic (‘B’) symptoms. Imaging shows solid and often multiple masses.

**Macroscopy**
Nodules are typically solid and cream-coloured, and may also exhibit paler and softer areas that correlate with necrosis.

**Tumour spread and staging**
It has been recommended that cases with unilateral or bilateral pulmonary involvement be staged as IE, and cases with regional lymph node (hilar/mediastinal) involvement be staged as IIE [2053].

**Histopathology**
DLBCL of the lung are morphologically similar to DLBCL in other sites. Tumours consist of diffuse sheets of large, blastic lymphoid cells, 2-4 times the size of normal lymphocytes, infiltrating and destroying the lung parenchyma. Vascular infiltration and pleural involvement are commonly seen, but lymphoepithelial lesions are rare. Necrosis is common.

**Immunohistochemistry**
The neoplastic cells are of B-cell phenotype, expressing pan-B antigens (CD20, CD79a) with a variable reactive T-cell population in the background. Monotypic immunoglobulin light chain expression may be detected if frozen tissue is available.

**Somatic genetics**
Immunoglobulin genes are clonally rearranged. Evidence of monoclonality via amplification of the immunoglobulin heavy chain gene with the polymerase chain reaction can be demonstrated in about 25% of DLBCL [1467]. Little is known about genetic abnormalities in primary pulmonary DLBCL.

**Prognosis and predictive factors**
Patients may inadvertently undergo resection for localised disease, but are usually treated with combination chemotherapy as for DLBCL in other sites, often with high response rates to adriamycin-based regimens [1203, 1320]. Overall, five-year survival ranges from 0-60% [577,1176,1467].
Lymphomatoid granulomatosis

Definition
Lymphomatoid granulomatosis (LYG) is an extranodal angiocentric and angiodestructive lymphoproliferative disorder, composed of a polymorphous infiltrate of atypical appearing Epstein Barr virus-infected B cells and numerically more abundant admixed reactive T cells (752). Lymphomatoid granulomatosis shows a spectrum of histologic grade and clinical aggressiveness, which is related to the proportion of EBV positive large B cells. LYG may progress to an EBV positive diffuse large B-cell lymphoma.

ICD-O code 9766/1

Synonyms and historical annotation
These lesions were first described nearly 30 years ago by Averill Liebow, who could not decide whether they were a variant of Wegener’s granulomatosis or a malignant lymphoma - hence, the unusual name “lymphomatoid granulomatosis” (1182). More recently, the term “angiocentric immunoproliferative lesion” (AIL) was proposed, which included what we now know as nasal-type NK/T-cell lymphoma, and suggested that the disease is a lymphoproliferative disorder with the capability of evolving into lymphoma (919). Neoplasms of T or NK-cell origin with an angiocentric growth pattern should not be classified as LYG, but rather as extranodal peripheral T-cell lymphomas. The term LYG is currently preferred.

Epidemiology
LYG is rare. It typically presents in middle-aged adults (although both younger and older patients have been reported) (562,969,1062,1182,1603). The disease can occur as an apparently idiopathic lesion, but it more often occurs in patients who have been immunosuppressed. Examples include patients who have AIDS or Wiskott-Aldrich syndrome, those who have had organ transplants or who have been treated for acute lymphoblastic lymphoma or follicular lymphoma and those who have agnogenic myeloid metaplasia (1468). In patients without known prior immunodeficiency, anergy, impaired in vitro responsiveness to mitogens, diminished humoral and cell-mediated responsiveness to Epstein-Bar virus and decrease in total T cells, CD4 and CD8 lymphocytes, have all been reported (920,2154).

Etiology
LYG is an EBV-driven B-cell lymphoproliferative disorder, probably arising in a background of immunodeficiency in most cases.

Localization
Masses or nodules can involve a variety of organs, most often lung and central nervous system, and kidney; skin may be involved (in the form of ulcerated or non-ulcerated subcutaneous nodules, erythematous dermal papules or plaques) (131).

Clinical features
There is a complex array of symptoms, corresponding to the sites of involvement. Up to 70% of patients show bilateral, usually peripheral, lung nodules that measure up to 9 cm. in diameter (969, 1062,1603). Cavitation may or may not be present. Other radiographic patterns include diffuse reticulonodular or alveolar infiltrates, localized infiltrates or a solitary mass. The upper respiratory tract can be involved by ulcero-destructive lesions but lymphadenopathy is infrequent.

Macroscopy
The lungs usually show yellow-white well-demarcated masses that can have a solid or granular, cheesy appearance. They often have a “cannon ball” appearance. They may be cavitated. Similar masses can be found in other organs, such as the kidney or brain.

Histopathology
The lymphoid infiltrate often surrounds muscular pulmonary arteries and veins early in the course of the disease, and typically invades the walls of these vessels. Necrosis is a frequent, although not universal, feature of the disease and it can range from extensive in larger masses or high-grade lesions to minimal in low-grade lesions. LYG consists of small round lymphocytes, some of which may show slight cytologic atypia and variable numbers of atypical large mononuclear lymphoid cells in a background of histiocytes and occasional plasma cells (969,1062,
Lymphomatoid granulomatosis

Eosinophils and neutrophils are usually not conspicuous. The large cells resemble immunoblasts; some of the atypical cells may have double nuclei, suggesting Reed-Sternberg cells, but classic Reed-Sternberg cells are not seen. Despite the term “granulomatosis” in the name, epithelioid granulomas and giant cells are almost always absent. Sample size is important: Less than 30% of transbronchial biopsies are diagnostic, so a surgical lung biopsy will be necessary in most cases to achieve a diagnosis.

There is a histologic grading system for LYG that is based on the number of atypical large EBV-infected cells. Grade 1 lesions contain few or no EBV-infected cells (less than 5 per high-power field), usually lack necrosis, and are polymorphous. Grade 2 lesions have scattered EBV-infected cells (5-20 per high-power field) and foci of necrosis (extensive at times), but they remain polymorphous; this is the classic and most frequently encountered type of case. Grade 3 lesions show sheets of EBV-infected cells, necrosis, and cellular monomorphism, and are considered a subtype of diffuse large B-cell lymphoma.

**Immunophenotype**
LYG is a T-cell-rich, B-cell lymphoproliferative process, as shown by a number of studies, both in lung and in other sites, such as skin.

**Histogenesis**
EBV-infected peripheral B cell.

**Genetics and pathogenesis**
In grade 2 and 3 lesions, the B-cells are either clonal or oligoclonal by methods such as VJ-PCR and Southern blot and appear to be proliferating, at least by proliferation indices. The EBV sequences also are typically clonal. Different monoclonal B-cell clones can occur in different sites in the same patient. In grade 1 lesions, monoclonality can be more difficult to demonstrate, possibly because of the paucity of neoplastic B cells, or alternatively because some of these lesions may not be truly neoplastic. The T cells that are so abundant in LYG are polyclonal by molecular methods.

These results suggest that in most cases LYG is a T-cell-rich B-cell lymphoma. However, some grade 1 cases may be EBV driven polyclonal lymphoproliferations, and grade 2 cases may be similar to polymorphous, monoclonal post-transplant lymphoproliferative disorders (PTLD), in which some degree of immunodeficiency allows proliferation of clonal EBV+ B cells. These cases may evolve...
into an autonomous, monomorphic diffuse large B-cell lymphoma, analogous to the situation in PTLD (751,919,920). EBV in a partially immunocompetent host may explain the vascular damage that is a hallmark of the disease. Chemokines, such as IP-10 and Mig, elaborated as a result of the EBV infection may be responsible for vascular damage by promoting T-cell adhesion to endothelial cells (1994).

**Differential diagnosis**

Some lesions that are histologically similar to LYG do not show atypical EBV-infected B cells, but rather contain atypical cells that are CD3+ T cells (1382, 1417). These T-cell lesions are peripheral T-cell lymphomas, that, because they are angiocentric and polymorphous, are histologically similar to LYG (1382). Cases of enteropathy-associated T-cell lymphoma and of acute T-cell lymphoblastic leukemia have been confused as cases of LYG in some series (1468). T-cell lymphomas of other types, such as nasal-type CD56+ NK/T-cell lymphomas may also mimic LYG histologically. Immunophenotypic analysis to demonstrate the B or T/NK-cell nature of the large cells is important in distinguishing these entities. In many peripheral T-cell lymphomas the proliferation fraction of the T cells (Ki67+) is higher than that of the T cells in LYG. The diagnosis of LYG should be made only in cases in which the proliferating large cells are B cells. Cases of grade 1 LYG may lack EBV-positive B cells. Skin lesions also often have very few EBV-infected B cells and are subject to sampling problems (131). These cases give rise to a differential diagnosis of reactive inflammatory processes. Clinical correlation and biopsy of other sites may be necessary to establish the diagnosis.

**Prognosis and predictive factors**

Outcome is variable. Patients may show waxing and waning of their disease. When disease is confined to the lung, or skin, it may resolve without treatment (14-27% of patients) (919,920). Still, the most common result is death, with median survival of 2 years (919). The histologic grade of the lesion is correlated with outcome (969,1192). Most patients have grades 1 or 2 disease. Only one-third of patients with grade 1 lesions progress to malignant lymphoma (grade 3), whereas two-thirds of patients with grade 2 lesions develop lymphoma (all patients with grade 3 lesions have lymphoma by definition) (1192). It is less clear whether stage of disease correlates with outcome: one study reported a worse prognosis in patients with neurologic lesions, while another did not (969,1062). Lesions in the central nervous system are often of high histological grade. Long-term survival may occur even in untreated patients with grade 1 and 2 lesions, particularly those whose disease is restricted to lung (969,1062). Currently, grade 3 lesions are typically treated as diffuse large B cell lymphoma (1168) with aggressive chemotherapy; grade 1 and 2 lesions are often treated with interferon alpha 2b (920,2154).

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<td><strong>Immunoprofile of lymphomatoid granulomatosis. From references (776,1382,2154).</strong></td>
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| **B cells (immunoblasts)** |
| CD20+, CD79a+, CD30+ (EBV-induced), CD43+/−, CD15- EBV+ (by in situ hybridization for EBER 1/2 RNA or by immunohistochemistry for LMP) |

| **T cells** |
| CD3+, CD4+, CD8+ |
| Cytotoxic markers: TIA-1, granzyme B |
**Pulmonary Langerhans cell histiocytosis**

**Definition**
Pulmonary Langerhans cell histiocytosis (PLCH) is an interstitial lung disease caused by the proliferation of Langerhans cells and their associated changes in the lung. Most affected patients are adults and in most the lung is the sole site of involvement. Many Langerhans cell proliferation syndromes are considered clonal and neoplastic [919] but clonality studies on PLCH in adults suggest that this may represent a reactive proliferation of Langerhans cells [2218].

**ICD-O code** 9751/1

**Synonyms**
Pulmonary histiocytosis X, pulmonary eosinophilic granuloma, pulmonary Langerhans cell granulomatosis.

**Epidemiology**
PLCH is an uncommon form of interstitial lung disease [2025,2075,2076]. The sex predilection has varied in series; it is probably roughly equal. The mean age at diagnosis is approximately 40 years with a broad range (18-70 years) when children with disseminated LCH syndromes are excluded [2075,2076].

**Etiology**
95% or more of patients are current or former cigarette smokers [2075,2076].

**Localization**
Predominantly upper and mid zones with sparing of the costophrenic angles.

**Clinical features**

**Signs and symptoms**
Patients may be asymptomatic (15-25%), or may present with pulmonary symptoms (cough, dyspnoea, chest pain) or with systemic complaints (malaise, weight loss, fever) [2025,2075,2076]. Approximately 15% of adults with PLCH have extrapulmonary involvement [2075]. PLCH in adults may rarely be part of a systemic Langerhans cell histiocytosis or Langerhans cell sarcoma, which are best considered a neoplastic hematologic problem [919].

Pulmonary function studies are abnormal in most (85% or more) patients and include (in order of frequency) restrictive deficits, obstructive deficits, isolated decreased diffusing capacity, and mixed restrictive/obstructive deficits [2076].

**Imaging**
Chest radiographs show interstitial lung disease with predilection for the mid and upper lung zones [2025,2075,2076]. High-resolution CT scanning is distinctive, most typically showing nodules or nodules and cystic change with mid and upper lung zone predilection [2025, 2075,2076].

**Macroscopy**
The gross findings depend on the extent of involvement and the amount of scarring. Small nodules, generally 2-5 mm in size (rarely up to 2 cm), may be palpated [2025]. In progressive disease there is extensive interstitial fibrosis with or without associated emphysematous changes.

**Histopathology**
Histologically most cases of PLCH show concomitant changes of smoking including emphysema and respiratory bronchiolitis [2025,2075,2076]. The lesions of PLCH begin as cellular proliferations of Langerhans cells along small airways, primarily bronchioles and alveolar ducts. As the lesions enlarge, rounded or stellate nodules develop and the bronchiolcentricity is less easy to discern. The nodules undergo a natural history from cellular lesions rich in Langerhans cells to fibrotic lesions which, in their end-stage, are entirely devoid of identifiable Langerhans cells. In healed PLCH cases the diagnosis is possible based on the presence of stellate centriflobular scarring in the setting of typical HRCT changes.

Langerhans cells are recognized by their distinctive morphology with pale eosinophilic cytoplasm and delicate nuclei with prominent folding of the nuclear membranes [919,2025,2075, 2076]. Their presence may be confirmed with S-100 protein and/or CD1a staining.

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**Fig. 1.98** Pulmonary Langerhans cell histiocytosis. Multiple nodular interstitial infiltrates with focal central cavitation. The edge of the nodular infiltrates shows a stellate shape. From Travis et al. (2024).
The morphologic features are sufficiently characteristic that immunohistochemical staining is unnecessary for diagnosis in classic cases.

**Precursor lesions**
Langerhans cell hyperplasia in association with smoking [2075].

**Histogenesis**
Proliferation of Langerhans cells [2075].

**Somatic genetics**
Yousem et al used the X-linked polymorphic human androgen receptor assay (HUMARA) locus to assess clonality in female patients with pulmonary LCH and found that seven (29%) were clonal and 17 (71%) were nonclonal. A nonclonal population was found in three of six cases with multiple nodules. In one biopsy with five nodules, two nodules were clonal with one allele inactivated, one nodule was clonal with the other allele inactivated, and two nodules were nonclonal. These findings indicate that pulmonary LCH appears to be primarily a reactive process with clonal proliferation of Langerhans cells developing in the setting of nonclonal Langerhans cell hyperplasia, probably in response to antigens in cigarette smoke [2218].

**Treatment**
Steroids have been the mainstay therapy for PLCH [2075,2076]. With the recognition of the association of PLCH with cigarette smoking, smoking cessation is also important. Refractory cases may respond to immunosuppressive therapy. Some cases of PLCH clear spontaneously, making the effects of treatment difficult to determine.

**Prognosis and predictive factors**
Approximately 15% of patients have progressive respiratory disease that may be fatal or lead to lung transplantation [2076]. Progression may be slow, spanning decades and be dominated by clinical features of obstructive lung disease. Predictors of shorter survival include older age, lower forced expiratory volume in one second (FEV1), higher residual volume, lower ratio of FEV1 to forced vital capacity, and reduced carbon monoxide diffusing capacity [2076].

**Pulmonary involvement by other haematolymphoid malignancies**
The lung may rarely be the primary site of presentation of most types of lymphomas recognized in lymph nodes [391] including both non-Hodgkin lymphoma (follicle center cell lymphoma, mantle cell lymphoma, intravascular large B-cell lymphoma, anaplastic large-cell lymphoma, etc.) and Hodgkin lymphoma. Primary plasmacytomias are also recognized. The lung is also a very common site of relapse in patients who already carry a diagnosis of lymphoma. Similarly, virtually any leukaemia may affect the lung, either primarily (and be the initial site of presentation) or in patients with known disease [391].

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**Table 1.14**

<table>
<thead>
<tr>
<th>Classification of Langerhans cell histiocytosis in adults.</th>
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<tbody>
<tr>
<td><strong>Single-organ disease</strong></td>
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<tr>
<td>Lung (occurs in isolation in &gt; 85% of cases with lung involvement)</td>
</tr>
<tr>
<td>Bone</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Pituitary</td>
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<td>Lymph nodes</td>
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<tr>
<td>Other sites; thyroid, liver, spleen, brain</td>
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<tr>
<td><strong>Multisystem involvement</strong></td>
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<tr>
<td>Multiorgan disease with lung involvement (in 5-15% of cases with lung involvement)</td>
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<tr>
<td>Multiorgan disease without lung involvement</td>
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<tr>
<td>Multiorgan histiocytic disorder</td>
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</table>
**Definition**

Pulmonary epithelioid haemangioendothelioma (PEH) is a low-to-intermediate-grade vascular tumour composed of short cords and nests of epithelioid endothelial cells embedded in a myxohyaline matrix. The tumours are distinctive for their epithelioid character, sharply defined cytoplasmic vacuoles, intraalveolar and intravascular growth and central hyaline necrosis. High-grade epithelioid vascular tumours are called epithelioid angiosarcomas.

**ICD-O code**

Epithelioid haemangioendothelioma 9133/1
Angiosarcoma 9120/3

**Synonyms and historical annotation**

Epithelioid haemangioendothelioma was previously called intravascular ‘sclerosing’ bronchioloalveolar tumour (IVBAT) in the lung.

**Clinical features**

**Signs and symptoms**

Most patients with PEH are Caucasian, 80% are women. The mean age is 36 with a range of 12-61 years [435,533,2120]. The presentation is usually indolent and almost half of the patients are asymptomatic. Symptomatic patients may present with pleuritic chest pain, dyspnoea, mild nonproductive cough, haemoptysis, and clubbing. PEH may rarely present with alveolar hemorrhage [225,298] or as thromboembolic disease [2205]. Up to 15% of patients may have substantial liver involvement. PEH with histology similar to that seen in the lung occur in the liver, bone and soft tissue [510,536,1227,1453].

**Imaging**

CT scans or chest x-rays characteristically demonstrate multiple, bilateral, small nodules 1-2 cm in size. However, PEH may present as a solitary lung mass [1399]. The radiographic pattern of the multiple smaller lesions may mimic that of pulmonary Langerhans’ cell histiocytosis [1606]. Occasionally the lung nodules may appear calcified [1212]. The most common initial interpretation of the radiographic picture is that of metastatic tumour or old granulomatous disease.

**Macroscopy and localization**

The most common gross appearance of PEH is that of a 0.3-2.0 cm circumscribed mass of gray-white or gray-tan firm tissue with occasional yellow flecks [435,2081]. The center of the nodules may be calcified and the cut surface reveals a cartilaginous consistency. PEH may involve the pleura in a pattern resembling diffuse malignant mesothelioma [424,1184,2222,2239].

**Histopathology**

Low power histologic examination reveals round to oval-shaped nodules, which typically have a central sclerotic, hypocellular zone and a cellular peripheral zone. The necrotic center of the nodules sometimes can be calcified and ossified. The tumour typically spreads into adjacent bronchioles and alveolar spaces in a micropolypoid manner and can be seen passing through pores of Kohn in alveolar walls. Extensive lymphangitic spread may mimic metastatic carcinoma. The intercellular stroma consists of an abundant matrix that may appear chondroid, hyaline, mucinous or myxomatous. Intracellular vacuoles are common, sometimes creating a signet-ring appearance, and suggest an attempt to form unicellular vascular channels. The nuclei of the tumour cells are usually round to oval. Intranuclear cytoplasmic inclusions are common.

**Immunohistochemistry and electron microscopy**

Commonly used endothelial markers include CD31, CD34 and factor VIII (von Willebrand factor), and most PEH express these markers [462]. Recently, Fli1 (a member of the ETS family of DNA binding transcription factors) and FKBP12 (a cytosolic FK506 binding protein interacting with calcineurin) have been shown to be reliable endothelial markers [599,828]. In epithelioid haemangioendotheliomas, CD31, CD34 and Fli1 protein are more sensitive and reliable markers than von Willebrand factor. Vimentin is strongly positive and present in abundance in these tumour cells in

![Fig. 1.101 Epithelioid haemangioendothelioma. A Tumour nodule showing increased cellularity at the periphery and abundant eosinophilic stroma with focal necrosis in the center. B Abundant eosinophilic stroma; cells have prominent cytoplasmic vacuoles or intracytoplasmic lumina. From Travis et al. (2024). C CD31 stain. The tumour cells stain positively; several show prominent cytoplasmic vacuoles.](image-url)
comparison with normal endothelial cells. Focal cytokeratin expression is reported in 20-30% of cases. Angiosarcomas are also known to express endothelial markers such as von Willebrand factor, CD31, CD34 and Fli1 in the majority of cases. Among them, von Willebrand factor is more specific, but least sensitive. It is often present in a minority of cases with focal weak staining. CD31 is relatively specific and extremely sensitive, being positive in about 90% of the cases. Cytokeratin is expressed in about 30% of the cases, emphasizing the importance of antibody panels to distinguish these vascular tumours from carcinoma {1184,1308}. Electron microscopic studies reveal an external lamina or basement membrane surrounding the tumour cells and occasional tight junctions {409,1798,2122}. Pinocytotic vesicles may be seen. Conspicuous 100-150 µm thick cytoplasmic laminae are present. Weibel-Palade bodies have been described, but may not be detectable in every case. Intracytoplasmic lumens are characteristically present.

**Differential diagnosis**
The differential diagnosis of PEH includes a variety of benign non-neoplastic conditions such as old granulomatous disease, organizing infarcts, amyloid nodules; several benign neoplasms such as hamartomas, sclerosing haemangioma, and chemodectomas; and malignant neoplasms such as mesothelioma, adenocarcinoma (both primary and metastatic), angiosarcoma, chondrosarcoma, or leiomyosarcoma. Most of these considerations can be excluded by recognition of the characteristic architecture of the nodular lesions of PEH with a cellular periphery and a central zone, which is often necrotic. The possibility of lung metastases should be considered since EH can also arise in the liver, soft tissue, and bone. When these tumours metastasize to the lungs, they may present with histologic features identical to cases of PEH {510,536, 2081}. In the presence of a dominant mass in an extrapulmonary site, the lung involvement may represent metastatic disease. Some cases of multifocal bilateral pulmonary disease suggesting metastases, do not have extrathoracic tumours {435}. Grading: PEH are low or intermediate grade tumours. High grade epithelioid vascular tumours are called epithelioid angiosarcoma, and show more nuclear atypia (mitoses, nuclei, hyperchromatic chromatin) and less eosinophilic matrix and may have spindle cell foci. Epithelioid angiosarcomas also tend to present as large solitary masses.

**Histogenesis**
Epithelioid haemangioendotheliomas are derived from endothelial cells.

**Somatic genetics**
Little is known about the genetics of epithelioid haemangioendothelioma. In two cases an identical chromosomal translocation involving chromosomes 1 and 3 [t(1;3)(p36.3;q25)] was detected {1295}. In another case karyotyping revealed several clonal abnormalities: a complex unbalanced translocation [7;22] involving multiple breakpoints (confirmed by fluorescence in situ hybridization), a Robertsonian t(14;14), and loss of the Y chromosome {208}. Monosomy for chromosome 11 was noted in a subset of the tumour cells {208}.
Pleuropulmonary blastoma

Definition

Pleuropulmonary blastoma is a malignant tumour of infancy and early childhood arising as a cystic and/ or solid sarcomatous neoplasm, in the lung or less often from the parietal pleura (99,1231). The cystic component is lined by benign metaplastic epithelium that may be ciliated. This embryonic or dysontogenetic neoplasm of the lung and/or pleura is the nosologic counterpart to other like neoplasms of childhood including Wilms tumour, neuroblastoma, hepatoblastoma and retinoblastoma.

ICD-O code 8973/3

Synonyms

Rhabdomyosarcoma arising in congenital cystic adenomatoid malformation, pulmonary blastoma of childhood, pulmonary sarcoma arising in mesenchymal cystic hamartoma, embryonal rhabdomyosarcoma arising within congenital bronchogenic cyst, pulmonary blastoma associated with cystic lung disease, pleuropulmonary blastoma in congenital cystic adenomatoid malformation (565).

Epidemiology

Owing to the fact that the pleuropulmonary blastoma came to be recognized as a clinicopathologic entity in 1989, systematic data are not available on its incidence. There are presently over 100 cases registered with The Pleuropulmonary Blastoma Registry (www.ppbregistry.org). It is certainly less common than Wilms tumour, neuroblastoma and even hepatoblastoma. Approximately 25% of cases are accompanied by an apparent constitutional and heritable predisposition to dysplastic or neoplastic disease in keeping with a familial cancer syndrome (1620). Cystic nephroma, ovarian teratoma, multiple intestinal polyps, and a second pleuropulmonary blastoma have been observed in affected children (910, 1025,1115,1393,1593).

Age and sex distribution

The age at diagnosis ranges from one month to 12 years, with a median age of 2 years. Most are diagnosed at or before 4 years of age (1619). The male to female ratio is approximately equal.

Etiology

The origin of this tumour remains unknown, but it may represent the expression of the mesodermally derived thoracic splanchnopleural mesenchyme in the absence of any neoplastic epithelial elements, as in a classic pulmonary blastoma (1231 Since one type of pleuropulmonary blastoma is exclusively cystic, a controversial suggested origin is from congenital cystic adenomatoid malformation (1207).

Localization

Pleura and/or lung.

Clinical features

The clinical manifestations are variable and depend on age and pathologic type. Respiratory distress with or without pneumothorax is the most common presentation of the cystic pleuropulmonary blastoma in the first 12-18 months of life (892, 1619). Asymptomatic lesions may be incidental findings during investigation of seemingly unrelated clinical problems (1544,1545,1619). Fever, chest pain and cough are the presenting complaints in the 2-4 year old child with a cystic and solid or exclusively solid neoplasm, which may be suspected initially to be pneumonia or empyema.

Imaging

Unilateral, rarely bilateral, localized air-filled cysts are a common finding on images that have been obtained subsequent to the onset of respiratory distress (468,1207,1545,1619,1650). A pneumothorax is rarely present. Septal thickening or an intracystic mass(es) is another feature which should suggest the possibility of something other than a congenital adenomatoid malformation or congenital lobar emphysema. Other patterns of masses lesions and/ or cysts are described (99).

Macroscopy

Three basic pathologic types are currently recognized with associated gross and microscopic features (468,2173). The purely cystic pleuropulmonary blastoma is characterized as a filmy, thin-walled multicystic structure, which collapses after resection (321). Another pattern is a solid, firm to gelatinous creamy white, sometimes hemorrhagic tumour, measuring over 15 cm in greatest dimension and weighing over 500 g. The solid tumours may occupy an entire lobe or lung and in a minority of cases, the mass has arisen from the visceral or parietal pleura, including the dome of the diaphragm.

Histopathology

The purely cystic or type I pleuropulmonary blastoma is characterized by the presence of a multicystic structure lined by respiratory type epithelium beneath which is a population of small primitive malignant cells with or without apparent rhabdomyoblastic differentiation. The malignant cells may be identified as a continuous or discontinuous cambium layer-like zone, but may be difficult to find. Small nodules of fetal appearing cartilage or a hyalinized septal stroma are features which should prompt careful search for malignant cells, if they are not initially apparent. Type II pleuropulmonary blastoma shows partial or complete overgrowth of the septal stroma by sheets of primitive small cells without apparent differentiation, embryonal rhab-
domyosarcoma or fascicles of a spindle cell sarcoma with the formation of plaques or nodules. Other examples of type II tumours are those with a grossly visible solid component and microscopically identifiable type I foci. Type III tumours are solid. The solid areas of the types II and III neoplasms have mixed blastematous and sarcomatous features. Nodules of malignant appearing cartilage, small aggregates of anaplastic and pleomorphic appearing cells, fibrosarcoma-like areas, rhabdomyosarcomatous foci and condensed blastema-like islands separated by loosely arrayed short spindle cells may also be seen alone, or in combination. Foci of necrosis, haemorrhage and fibrosis are variably present. Though respiratory epithelium may be entrapped within a field of tumour, neoplastic epithelial elements have not been seen in this tumour type to date, in contrast to the classic pulmonary blastoma. The primitive small cell pattern with or without apparent rhabdomyoblastic differentiation is seen in the purely cystic lesion whereas a more complex mixed sarcomatous pattern is present in those neoplasms with a solid component.

**Immunohistochemistry**

Based upon the microscopic features, the immunophenotype is predictable in that most neoplastic cells are reactive for vimentin, and the only cytokeratin-positive cells are the respiratory-type cells lining the cysts and the entrapped small airspaces within solid areas of the tumour. Muscle specific actin and desmin are consistently expressed in cells identifiable histologically as rhabdomyoblastic and less consistently in the primitive small cells in the cambium layer-like subepithelial zones in the cystic areas [1619]. The nodules of cartilage express S-100 protein. Immunohistochemistry is useful in the differential diagnosis in those rare cases of a cystic synovial sarcoma of the lung and chest wall [546]. When the latter is a consideration, epithelial membrane antigen, cytokeratin and CD99 are useful since these three markers are not expressed in the pleuropulmonary blastoma.

**Histogenesis**

The cell of origin for pleuropulmonary blastoma is not known. However, it is probably derived from primitive mesenchymal cells in the lung and or pleura.

**Somatic genetics**

Several reports have documented gains in chromosome 8 detected by karyotyping and fluorescence in situ hybridization [111, 910, 991, 1035, 1107, 1492, 1620, 1773, 2073, 2196]. Though this finding appears to be consistent in these tumours, gains in chromosome 8 have been observed in infantile fibrosarcoma, desmoid fibromatosis and mesoblastic nephroma. It is interesting that the latter tumour has been reported on occasion in children who also have a pleuropulmonary blastoma. An unbalanced translocation between chromosomes 1 and X has been described resulting in addition copies of 1q and Xq and loss of part of Xp. Mutations in p53 are also reported.

**Prognosis and predictive factors**

The pure cystic or type I pleuropulmonary blastoma has a generally favourable prognosis of 80-90% 5-year disease-free survival, whereas the types II and III have a poorer outcome of less than 50% [1569, 1619]. The importance of recognizing this neoplasm in its cystic form has been emphasized in the recent literature [1545, 1941]. It would appear that the occult type II neoplasm with microscopic overgrowth of the septal areas, and without the formation of grossly visible masses or plaques, may have a similar favourable outcome as the type I pleuropulmonary blastoma. These tumours locally recur and have a predilection for metastasis to the brain-spinal cord and skeletal system [1619]. Ocular and pancreatic metastases have also been reported [494, 1115, 2100].
Chondroma

Definition
A benign tumour composed of hyaline or myxohyaline cartilage. It is usually found in Carney triad (gastric stromal sarcoma, pulmonary chondroma and paraganglioma).

ICD-O code
9220/0

Synonyms
Osteochondroma, chondroma

Clinical features
Signs, symptoms and imaging
These are usually asymptomatic tumours. Radiologically, they appear as circumscribed lesions with “pop-corn” calcification, usually multiple, and predominantly in young women [292,689, 2006].

Macroscopy and localization
These are peripheral solid lesions, which may be calcified and easily enucleated at surgery.

Histopathology
These lesions consist of encapsulated lobules of hypocellular neoplastic cartilaginous tissue. Features of malignancy are absent [292,689,2006].

Differential diagnosis
Pulmonary hamartoma (mesenchymoma), in the majority of cases, shows cleft-like spaces between cartilaginous lobules lined by a component of respiratory epithelium, with, less often, other differentiated mesenchymal elements. Metastatic chondrosarcoma may also be considered. Clinical history and cytological evidence of malignancy will aid distinction.

Prognostic factors
These patients are cured upon removal of their pulmonary chondroma. Clinical problems in these patients are more likely to relate to their gastric leiomyosarcomas or paragangliomas [294,1772].

Fig. 1.105 Chondroma. Circumscribed, bosselated tumour composed of white glistening, irregularly-shaped lobules, some with a bluish tinge.

Fig. 1.106 Chondroma. A Encapsulated, hypocellular (left) to moderately cellular (right) tumour with dispersed cells set in a chondromyxoid stroma. A fibrous capsule with spicules of mature bone containing marrow fat separates the tumour from the surrounding compressed pulmonary parenchyma. B Paucicellular tumour featuring elongated fusiform and stellate cells with eosinophilic cytoplasm and hyperchromatic, polymorphic nuclei set in a loose chondromyxoid matrix.
Congenital peribronchial myofibroblastic tumour

Definition
An interstitial and peribronchovascular proliferation of uniform, plump to more fusiform cells arranged in broad, interlacing fascicles; cellularity and mitotic activity may be marked. This spindle cell neoplasm is reminiscent of the congenital infantile fibrosarcoma.

ICD-O codes 8827/1

Synonyms
Congenital fibrosarcoma, congenital leiomyosarcoma, congenital bronchopulmonary leiomyosarcoma, congenital pulmonary myofibroblastic tumour, congenital mesenchymal malformation of lung, neonatal pulmonary hamartoma

Epidemiology
This rare neoplasm is documented in the literature as individual case studies with less than 15 cases to date [45,930,1001,1082,1284].

Etiology
This tumour occurs sporadically and has neither syndromic association nor relevant maternal history, at least to date.

Clinical features
As a congenital tumour, it is recognized shortly after birth although the pregnancy may be complicated by polydramnios and non-immune hydrops fetalis. However, its detection by prenatal ultrasonography should be anticipated [45,930,1001,1082,1284].

Macroscopy
The well-circumscribed, non-encapsulated mass has a smooth or multinodular surface with or without fine trabeculations. The cut surface has a tann-grey to yellow-tan fleshy appearance. Haemorrhage and necrosis are variable features. The maximum dimension varies from 5-10 cm and the tumour may weigh in excess of 100 gms. The bronchus is often distorted or totally obliterated.

Histopathology
The lung parenchyma is replaced by fascicles of uniform spindle cells [903], arranged in intersecting fascicles with or without a herringbone pattern. The nuclei are elongated and have finely dispersed chromatin, an absence of pleomorphism or anaplasia and variable mitotic activity. Atypical mitotic figures are not present. Bronchial invasion is often seen, and the peribronchial distribution is implicit in the name. The growth may diffusely obliterate the parenchyma or form islands and nodules of spindle cells with interposed foci of uninvolved parenchyma [930]. Tumour growth in septa or on the pleural surface may occur. In less cellular perivascular areas, the tumour cells appear less sarcomatous with a more fibromyxoid or myofibroblastic proliferation. Cystic foci of haemorrhage may be present.

Immunoprofile and electron microscopy
A myofibroblastic immunophenotype is not demonstrable in all cases. The spindle cells are consistently positive for vimentin whereas staining for desmin and smooth muscle actin is absent or restricted to isolated cells [1082,1284]. Ultrastructural studies suggest myofibroblastic differentiation [1284]. Muscle specific actin immunoreactivity is present in less than 5% of the cells and desmin reactivity may be observed on rare occasion. This tumour is considered to be identical with, or at least related to, the lesions reported as congenital leiomyosarcoma, fibrosarcoma, and fibro-leiomyosarcoma. Immunoprofiles in the tumours diagnosed as such are non-specific and have been reported to express neuron-specific enolase, alpha-smooth muscle actin, HHF 35 actin and muscle-specific actin (382). Desmin, S-100 protein, CD34, CD57, CD68, factor XIIIa, and CAM 5.2 are also occasionally expressed.

Fig. 1.107 Congenital peribronchial myofibroblastic tumour. A Plain view chest roentgenograph shows opacification of the right hemithorax of a 7-week-old female who presented with respiratory distress. B Computed tomogram reveals a well circumscribed mass lesion with a collage of high and low density foci, representing areas of tumour and compressed uninvolved parenchyma.

Fig. 1.108 Congenital peribronchial myofibroblastic tumour. The resected tumour required a pneumectomy in a 7-week-old female. The cross-section reveals a circumscribed, tan-grey, multinodular mass measuring 10 cm in greatest dimension.

W.D. Travis
L.P. Dehner
T. Manabe
H.D. Tazelaar
Imaging
A large mass lesion partially or totally opacifying the hemithorax is the usual appearance on a plain chest radiograph. Computed tomography reveals a well-circumscribed heterogeneous mass [45, 930, 1001, 1082, 1284].

Somatic genetics
One case has been reported with a complex karyotype which included a t(8;10) (p11.2;p15) translocation [45]. Although these tumours resemble congenital-infantile fibrosarcoma and congenital mesoblastic nephroma in their gross and microscopic features, there are no reports to date of the detection of t(12;15) (p13;q25-26) translocation in a congenital peribronchial myofibroblastic tumour [1734].

Prognosis and predictive factors
Surgical resection of the involved lobe or lung is the treatment of choice. However, the presence of fetal hydrops with its own associated morbidity and mortality may complicate the clinical outcome.

Fig. 1.109 Congenital peribronchial myofibroblastic tumour. A There is an extensive infiltrate of spindle cells along lymphatic routes: pleura, septa and bronchovascular bundles. B The spindle cells resemble smooth muscle cells and infiltrate around bronchial cartilage, epithelium and vessels. From Travis et al. (2024).
**Diffuse pulmonary lymphangiomatosis**

**K.O. Leslie**

**H.D. Tazelaar**

**Definition**
A diffuse proliferation of lymphatic vascular spaces and smooth muscle, distributed with the normal lymphatics of the lungs, pleura and mediastinum.

**Synonyms**
Lymphangiomatosis, lymphangiectasis, lymphatic dysplasia

**Clinical features**
The process affects children and young adults of both sexes who present with progressive symptoms of “asthma,” dyspnoea or haemoptysis [230,563,832,925,1319,1637,1933,1985,2039].

**Imaging**
Chest radiographs show increased interstitial markings. Computed tomography shows smooth thickening of the interlobular septa, major fissures, central airways and pleura.

**Macroscopy and localization**
There is prominence of the bronchovascular bundles and other structures, including pleura, interlobular pulmonary septa, and mediastinum, reflecting the lymphatic distribution of the disease.

**Histopathology**
Anastomosing endothelial-lined spaces of varying size are diffusely distributed along lymphatic routes in pleura, intralobular septa, and bronchovascular sheaths and often contain acellular, sometimes eosinophilic, material [230,563,832,925,1319,1637,1933,1985,2039]. Variable numbers of spindle cells with bland oval to cigar shaped nuclei are present between channels. Mass lesions and cysts are not identified. Intra-alveolar siderophages are often present in surrounding lung parenchyma.

**Immunophenotype and electron microscopy**
The immunophenotypic profile of the lining cells is compatible with endothelium (FVIIIrAg positive, vimentin positive, UEA positive) [1985]. The spindle cells commonly express vimentin, desmin, actin, and progesteron receptor but are negative for estrogen receptor, keratin, and HMB-45. Ultrastructurally, the spindle cells resemble smooth muscle cells.

**Differential diagnosis**
In lymphangiectasis the lymphatic vessels are not increased in number and do not anastomose [230,563,832,925,1319,1637,1933,1985,2039]. Lymphangioleiomyomatosis exhibits a more random distribution in association with cysts. Kaposi sarcoma does not exhibit the complex anastomosing lymphatic channels. In diffuse pulmonary haemangiomatosis vascular spaces are blood-filled and in interstitial emphysema spaces are airfilled and lack smooth muscle.
**Inflammatory myofibroblastic tumour**

**Definition**
Inflammatory myofibroblastic tumour is a subgroup of the broad category of “inflammatory pseudotumours” and is composed of a variable mixture of collagen, inflammatory cells, and usually cytologically bland spindle cells showing myofibroblastic differentiation.

**ICD-O code** 8825/1

**Synonyms**
Inflammatory myofibroblastic tumour has acquired a wide array of synonyms including the following: inflammatory pseudotumour, plasma cell granuloma, fibroxanthoma, fibrous histiocytoma, pseudosarcomatous myofibroblastic tumour, and invasive fibrous tumour of the tracheobronchial tree.

**Epidemiology**
Inflammatory myofibroblastic tumour has an equal sex distribution and occurs in all ages, though most occur in individuals less than 40 years. Inflammatory myofibroblastic tumour is the most common endobronchial mesenchymal lesion in childhood.

**Etiology**
Some believe inflammatory myofibroblastic tumour is a reactive inflammatory condition, others that it represents a low-grade mesenchymal malignancy. Pulmonary lesions have been associated with previous viral infections, and some reports have indicated an association with HHV8.

**Localization**
Chest radiographs show a solitary mass with regular borders in 80% of the cases. The mass may have a spiculated appearance and if endobronchial in location, may be accompanied by a post-obstructive pneumonia and atelectasis.

**Clinical features**
The clinical presentation of patients with inflammatory myofibroblastic tumour is protean, with signs and symptoms relating to the site of involvement. Endobronchial lesions present with complaints reflecting bronchial irritation, with cough, wheeze, haemoptysis, and chest pain. Constitutional symptoms are rare. Peripheral pulmonary parenchymal nodules are often asymptomatic although local invasion into the chest wall may elicit pleuritic or chest wall pain.

**Macroscopy**
These lesions are typically solitary round rubbery masses, which have a variable degree of a yellowish-gray discoloration reflecting the histiocytic component of the inflammatory infiltrate. The size range is wide (1-36 cm) with an average size of 3.0 cm. The lesions do not appear encapsulated and local involvement of hilar soft tissues or chest wall is seen in 5-10% of cases. Gritty calcification is occasionally noted. Cavitation is rare.

**Tumour spread and staging**
Inflammatory myofibroblastic tumour is usually localised. Involvement of the chest wall, mediastinum, or pleura is rare, as are recurrences and metastases.

**Histopathology**
Inflammatory myofibroblastic tumour contains a mixture of spindle cells showing fibroblastic and myofibroblastic differentiation arrayed in fascicles, or with storiform architecture. The spindle cells have oval nuclei, fine chromatin, inconspicuous nucleoli, and abundant bipolar lightly eosinophilic cytoplasm. Mitoses are infrequent. Cytologic atypia is not obvious. Admixed with the spindle proliferation, and often obscuring it, is an inflammatory infiltrate containing lymphocytes, plasma cells, and histiocytes, including Touton type giant cells. Plasma cells may be prominent and are often associated with lymphoid follicles. The spindle cells, in rare instances, will infiltrate blood vessels or the pleura.

**Immunohistochemistry**
Pulmonary and extrapulmonary inflammatory myofibroblastic tumours (IMT) show similar immunoprofiles. Immunostains demonstrate that...
the spindle cells express vimentin and smooth muscle actin, and rarely desmin \([107,309,882]\). They fail to express myogenin, myoglobin, CD117 (cKit) and S-100 protein. Focal cytokeratin reactivity is noted in about one third of the cases, perhaps due to alveolar entrapment. Expression of ALK1 and p80 is noted in IMT in about 40% of the cases. \([312,322,383,401,741]\). P53 immunoreactivity is rare and reported in association with recurrence and malignant transformation \([882]\).

**Histogenesis**

Inflammatory myofibroblastic tumour is a proliferation of cells showing myofibroblastic differentiation.

**Somatic genetics**

Inflammatory myofibroblastic tumour is most often euploid, but may occasionally be aneuploid \([170,882]\). Similarly, some cases may show TP53 mutations. IMT show clonal changes in 2/3 of cases involving chromosome 2 at the 2p23 location of the ALK gene \([1771,1842,1895,1896,2223]\). Translocations involving the ALK gene to chromosome 5 create ALK fusion gene products, which are thought to play a role in the development of malignancy \([1701]\). Few inflammatory myofibroblastic tumours have complete cytogenetics reported, and they indicate the presence of ring chromosomes and translocations involving chromosome 1, 2, 4, and 5.

**Prognosis and predictive factors**

In most instances complete excision of pulmonary inflammatory myofibroblastic tumour leads to excellent survival \([654]\). A minority (5%) of inflammatory myofibroblastic tumours may show extrapulmonary invasion, recurrence or metastases, recurrence usually occurring in cases, which were incompletely excised. Histologic features that may be associated with a poor prognosis include focal invasion, vascular invasion, increased cellularity, nuclear pleomorphism with bizarre giant cells, a high mitotic rate (greater than 3/50 hpf), and necrosis \([38,381,384]\).

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**Fig. 1.12** Inflammatory myofibroblastic tumour. **A** Spindle cells growing in interlacing fascicles. **B** Spindle cells with myxoid stroma and mild chronic inflammatory infiltrate. **C** Numerous foamy histiocytes give this lesion a fibroxanthomatous appearance. **D** Prominent lymphocytes and plasma cells infiltrate among the myofibroblastic cells in this lesion. From Travis et al. \(2024\).
Lymphangioleiomyomatosis

Definition
Lymphangioleiomyomatosis (LAM) is a widespread interstitial infiltrate of immature short spindle cells resembling smooth muscle cells, usually associated with cystic change, most commonly occurring in women of reproductive age.

ICD-O code 9174/1

Synonyms
Lymphangiomyomatosis

Clinical features
LAM is very rare with an estimated incidence of 1 per 1,000,000 in the United States, France, and United Kingdom. It most often occurs as a sporadic disease, but also occurs in women with tuberous sclerosis complex (TSC). Among women with TSC, 26-39% show radiographic evidence of LAM [414,610,1391]. Renal angiomyolipomas occur in most TSC patients and in approximately 50% of sporadic LAM patients [97]. LAM is the third most frequent cause of TSC-related death, after renal disease and brain tumours [303]. LAM has been reported in both postmenopausal women and in at least one man [92].

Signs and symptoms
These include progressive dyspnoea on exertion, pneumothorax (often recurrent), cough, haemoptysis and chylous pleural effusions.

Imaging
Chest radiograph may be normal, but as the disease progresses, it typically shows diffuse reticular infiltrates with hyperinflation. Computed tomography shows cystic lesions between 2-20 mm, uniformly distributed in both lungs.

Macroscopy and localization
In advanced cases the lungs show diffuse cystic changes from apex to base. Early lesions may show only a few scattered cysts.

Histopathology
The two major lesions of lymphangioleiomyomatosis are cysts and immature smooth muscle proliferation. The variably sized cystic spaces are lined by plaque-like or nodular aggregates of smooth muscle-like spindle cells. These may be admixed with more rounded epithelioid cells, perhaps representing perivascular epithelioid cells (PECs) or epithelioid smooth muscle cells. Micronodular pneumocyte hyperplasia may also be present in patients with tuberous sclerosis.

Immunohistochemistry
The cells of lymphangioleiomyomatosis show smooth muscle differentiation and express alpha-smooth muscle actin and desmin, as well as vimentin. Unlike normal smooth muscle cells, however, they also show immunoreactivity with a melanocytic marker, HMB-45 [200, 1083]. Not all the cells stain, but when present, together with consistent histological changes, is highly specific and sensitive for LAM. Estrogen and progesteron receptors are present in some cases [153,393].

Differential diagnosis
Benign metastasizing leiomyoma is not usually associated with cysts and the nodules of smooth muscle are generally larger than those seen in LAM. Emphysema lacks the spindle cells. Langerhans’ cell histiocytosis shows the pathognomonic cells, eosinophils and has a characteristic gross and microanatomical distribution.
Histogenesis
The perivascular epithelioid cell (PEC) has been suggested.

Somatic genetics
Germline mutations in both TSC1 and TSC2 are associated with LAM, including missense mutations in the final exon of TSC2 (exon 41) [610,1885]. No genotype-phenotype correlation has been identified. Most women with sporadic LAM do not have germline TSC2 gene mutations [86,1747], but TSC2 mutations have been found in angiomyolipomas, lymph nodes, and microdissected pulmonary LAM cells from sporadic LAM patients [297,961,1747,1839]. These mutations are not present in morphologically normal kidney or lung, or in the peripheral blood, indicating that they arise somatically, and leading to the hypothesis that LAM cells migrate or metastasize to the lung from angiomyolipomas or lymph nodes. LAM can recur after lung transplantation [174,1477,1495]. In one case, a somatic TSC2 gene mutation was used to prove that recurrent LAM cells in the allograft lung arose from the patient’s native LAM [961] consistent with hypothesis that LAM cells migrate in vivo.

Prognosis and predictive factors
The prognosis for women with pulmonary LAM is variable. Progression is common with a median survival of 8 to 10 years from diagnosis [1019,1260,1983]. An elevated TLC and a reduced FEV1/FVC ratio are associated with poor survival [1019]. Kitaichi showed that patients with a predominantly cystic type of LAM had a worse prognosis than those with a predominantly muscular type [1019]. Matusi et al recently showed that the 5- and 10-year survivals for LAM patients were 100% for LAM histology score (LHS)-1, 89.9% and 74.6% for LHS-2 and 59.1% and 47.3% for LHS-3, respectively [1260]. He also found that increasing degrees of hemosiderin deposition were associated with higher LHS scores (p=0.029) and a worse prognosis (p=0.0012) [1260].

Pulmonary vein sarcoma

Definition
A sarcoma arising in a pulmonary vein which almost always shows features of leiomyosarcoma.

ICD-O code 8800/3

Epidemiology
Pulmonary vein sarcomas are rarer than pulmonary artery sarcomas and less than 20 cases have been reported [1512].

Clinical features
The tumours tend to occur in women ranging from 23-67 years (mean 49 years). The most common presenting symptoms are dyspnoea, haemoptysis and chest pain. In most cases, the clinical impression is that of a left atrial or lung tumour.

Macroscopy and localization
The tumours are generally fleshy-tan and tend to occlude the lumen of the involved vessel. They range from 3.0-20.0 cm in greatest dimension. Invasion of either wall of the vein to involve hilar structures of pulmonary parenchyma is common.

Histopathology
The majorities of pulmonary vein sarcomas show smooth muscle differentiation and, therefore, represent leiomyosarcomas. They are moderate to highly cellular spindle cell neoplasms with varying degrees of mitotic activity and necrosis. Epithelioid morphology may be present. Immunohistochemically, the tumours are reactive with antibodies to vimentin, desmin and actin, confirming the presence of smooth muscle differentiation. Aberrant keratin reactivity may be observed in as many as 40% of cases.

Fig. 1.115 Pulmonary vein sarcoma. The wall of the vein is infiltrated by spindle and pleomorphic sarcoma cells.
Pulmonary artery sarcoma

Definition
A sarcoma of the large pulmonary arteries with two types. Intimal sarcomas have an intraluminal polypoid growth pattern and usually show fibroblastic or myofibroblastic differentiation. Mural sarcomas are considered distinct from intimal sarcomas, and are classified separately according to the histologic subtype as in soft tissue sarcomas (leiomyosarcoma).

ICD-O code 8800/3

Synonyms
Intimal sarcoma of the pulmonary artery has been used interchangeably with pulmonary artery sarcoma, since intimal sarcomas comprise the vast majority of pulmonary artery sarcomas. Mural sarcomas are exceedingly rare.

Epidemiology
Pulmonary artery sarcomas are a rare tumour with only a few hundred cases reported. The incidence is unknown and probably underestimated, since many cases are still misdiagnosed as pulmonary embolism preoperatively and may remain unrecognized if not examined histologically. The average age at diagnosis is 49.3 years (range 13-81 years) with a roughly equal sex distribution [419,1079,1488].

Localization
These tumours occur in the pulmonary trunk, most commonly, right pulmonary artery, left pulmonary artery, pulmonary valve, and, least often, the right ventricular outflow tract [419].

Clinical features
The most common presenting symptom is dyspnoea, followed by, in decreasing order, chest / back pain, cough, haemoptysis, weight loss, malaise, syncope, fever, and rarely sudden death [419]. These clinical findings are often indistinguishable from those of chronic thromboembolic disease, but progressive weight loss, anaemia and fever are unusual for benign pulmonary vascular diseases and should raise a suspicion for malignancy [1547]. Common physical signs include systolic ejection murmur, cyanosis, peripheral oedema, jugular venous distension, hepatomegaly, and clubbing [1547].

Imaging
Radiologic findings overlap with those of chronic thromboembolic disease, but the rate of preoperative diagnosis has increased remarkably in the last decade with advances in imaging [419,959,973]. Solid appearing expansion of the proximal pulmonary artery branches is highly suggestive of a sarcoma, especially in the presence of pulmonary nodules, cardiac enlargement and decreased vascularity [419]. The features in computed tomography (CT) and magnetic resonance imaging (MRI) that favor a diagnosis of sarcoma over thrombi include: heterogeneous soft tissue density, smooth vascular tapering without abrupt narrowings and cut-offs [973], and unilateral central pulmonary emboli [419,973]. Vascularization in sarcomas may be seen with bronchial arteriography [419].

Macroscopy and localization
Intimal sarcomas resemble mucoid or gelatinous clots filling vascular lumens. Distal extension may show smooth tapering of the mass. The cut surface may show firm fibrotic areas and bony/gritty or chondromyxoid foci may be present in mural lesions. Haemorrhage and necrosis are common in high-grade tumours. Most cases have bilateral pulmonary artery involvement, although one side is usually dominant.

Tumour spread and staging
Pulmonary artery sarcomas metastasize primarily to the lung and mediastinum (50%). Distant metastases have been reported in 16% cases [419]. There is no recognized staging system.

Histopathology
Intimal sarcomas typically show a proliferation of spindle cells in a myxoid background, alternating with hypocellular collagenized stroma. Recanalized thrombi may be intimately admixed, especially as tumour extends distally. Some intimal and most mural tumours will show foci of more differentiated sarcomas: osteosarcoma, chondrosarcoma or rhabdomyosarcoma [101,182,246,1285,1488,1559,1816].

Immunohistochemistry / Electron microscopy
Most intimal sarcomas show immunohistochemical and ultrastructural evidence of myofibroblastic differentiation [101, 182,246,1285,1488,1559,1816]. The tumour cells, in general, exhibit strong and diffuse immunoreactivity for vimentin [728]. Osteopontin expression can also be expressed [667]. Reactivity for smooth muscle actin is variable. Tumor cells may express desmin or endothelial
markers, such as factor VIII, CD31, and CD34 when they show evidence of smooth muscle or vascular differentiation (728).

**Differential diagnosis and grading**
The diagnosis is fairly straightforward in most cases, though some thrombi may have highly cellular foci. Metastases should always be excluded. There is no specific grading system; NCI and FNCLCC systems for soft tissue sarcoma can be used.

**Histogenesis**
Intimal sarcomas presumably arise from pluripotential mesenchymal cells of the intima (246,1488), but primitive cells of the bulbous cordi in the trunk of pulmonary artery have been also proposed as the origin (1285).

**Somatic genetics**
Comparative genomic hybridization revealed frequent gains or amplification of 12q13-q15 with amplification of SAS/CDK4, MDM2 and GLI. In addition, there was amplification of PDGF receptor A on 4q12. Less consistent alterations have been identified including losses on 3p, 3q, 4q, 9p, 5p, 6p, and 11q.

**Prognosis and predictive factors**
Overall prognosis is very poor regardless of therapy with the mean survival ranging from 14-18 months (246,485,1488). Surgical resection is the single most effective modality for short-term palliation and the role of adjuvant therapy is yet to be determined (55,485).
Pulmonary synovial sarcoma

Definition
Pulmonary synovial sarcoma (SS) is a mesenchymal spindle cell tumour, which variably displays areas of epithelial differentiation. While it can be seen as a metastasis from an extrapulmonary site, it also occurs in the lung in the absence of primary elsewhere.

ICD-O codes
- Synovial sarcoma 9040/3
- Synovial sarcoma, spindle cell 9041/3
- Synovial sarcoma, biphasic 9043/3

Synonyms
- Synovial cell sarcoma
- Malignant synovioma
- Synovioblastic sarcoma

Clinical features
Pulmonary SS usually presents in young to middle age adults and shows no gender predilection [68,546,694,850,957,1777,1992,2234,2236]. Cough, often with haemoptysis is the most common clinical manifestation, followed by chest pain. Low-grade fever and weight loss are rare. These tumours can also present as incidental tumours on chest X-ray. Prognosis is in general poor with almost half of patients dying of disease (mean 23 months) [68,546,694,850,957,1777,1992,2234,2236]. However, prolonged survival without disease, over 5 years, has occurred.

Macroscopy and localization
Pulmonary SS are usually peripheral, well-circumscribed but non-encapsulated, solid tumours. Size ranges between 0.6-17.0 cm (mean 5.6 cm) [546]. Rare cases involving the tracheobronchial tree with formation of an endobronchial mass have been described. Occasionally, the tumour diffusely infiltrates chest wall or mediastinal structures. The cut surface of the tumour can show cystic degenerative changes and necrosis.

Tumour spread and staging
Pulmonary SS mainly spreads and recurs regionally, involving chest wall, periarcadium, diaphragm, paraspinal soft tissue. Direct extension to the abdominal cavity may also occur [68,546,694,850,957,1777,1992,2234,2236]. Metastases to mediastinal lymph nodes are extremely uncommon (5%). Systemic metastases, mainly to liver, bone, brain, and lung, occur in almost a quarter of patients.

Histopathology
Histologic features of pulmonary SS are identical to its soft tissue counterpart [68,546,694,850,957,1777,1992,2234,2236]. Both biphasic and monophasic subtypes have been described. Monophasic SS, the most common pulmonary subtype is comprised solely of the spindle cell component. The spindle-cell component consists of interweaving fascicles of densely packed elongated cells. This subtype often displays a prominent haemangiopericytomatous vascular pattern, and focal areas of dense hyaline fibrosis. Biphasic SS comprises both epithelial and spindle components. Epithelial areas contain cleft-like glandular spaces with scattered tubulo-papillary differentiation. The cells are cuboidal with moderate eosinophilic cytoplasm, round nuclei with granular chromatin and occasional nucleoli. Mucoid secretions are commonly seen. Care should be taken not to confuse the epithelial component with entrapped alveolar epithelium that will be TTF-1 positive and could be mistaken for biphasic synovial sarcoma [2234]. The cells contain scant cytoplasm with oval nuclei. Most pulmonary SS contain focal necrosis. Mitotic activity varies greatly (5-25/10HPF). Calcification and mast cell infiltrates may be seen.

Immunohistochemistry
Most synovial sarcomas show immunoreactivity for cytokeratins (CK) and/or

Fig. 1.118 Synovial sarcoma. A Round to oval and spindle shaped cells with minimal cytoplasm, hyperchromatic nuclei, inconspicuous mitoses and only slight fibrous stroma. B Alternating myxoid and cellular areas with some vessels showing hyalinization.
epithelial membrane antigen (EMA) [410]. The intensity of staining is more prominent in the epithelial rather than the spindle cell component. EMA tends to be expressed more often and more widely than CK. In monophasic lesions, reactivity may be scanty. Cytokeratins 7 and 19 are particularly useful because synovial sarcoma cells express these types of cytokeratins, and these are generally negative in other spindle cell sarcomas [1306,1838]. Vimentin is usually expressed in the spindle cells of synovial sarcoma. Intranuclear and intracytoplasmic immunoreactivity for S-100 protein can be identified in up to 30% of the tumours [585,749]. BCL-2 and CD99 are frequently positive [469,1652,1908]. CD34 is virtually usually negative [2064]. Desmin is absent but focal reactivity for muscle specific actin or smooth muscle actin is noted on occasion in monophasic synovial sarcomas. Lastly, given the differential diagnosis with mesothelioma, it is relevant to note that synovial sarcomas commonly contain foci of calretinin-positive cells [1310].

**Differential diagnosis**

The most important and common differential diagnosis is metastatic SS to the lung, which needs to be excluded with a thorough clinical and radiologic exam. Otherwise the differential diagnosis is wide and includes both more common epithelial and other rare mesenchymal tumours, such as spindle cell carcinoma, malignant mesothelioma, small cell carcinoma, thymoma, pleuropulmonary blastoma, localized fibrous tumour, fibrosarcoma, smooth muscle tumour, and malignant peripheral nerve sheath tumour and Ewing sarcoma. The distinction is usually made on the basis of histologic and immunohistochemical features. In difficult cases, detection of specific cytogenetic/molecular abnormality might be useful.

**Histogenesis**

This remains unknown, though is thought to be a totipotential mesenchymal cell.

**Somatic genetics**

The cytogenetic hallmark of synovial sarcoma is the t (X; 18)(p11; q11) [68,546, 850,957,1992]. This translocation results usually in the fusion of the SYT gene on chromosome 18 to either the SSX1 or SSX2 gene on chromosome X. The translocation has been found in >90% of SS, regardless of histologic type and the fusion transcript, identified either by FISH, RT-PCR, or real time PCR, is considered specific. The translocation or the fusion transcript was present in all evaluated pulmonary SS.
Definition
Pulmonary hamartomas are benign neoplasms composed of varying proportions of mesenchymal tissues, such as cartilage, fat, connective tissue and smooth muscle, typically combined with entrapped respiratory epithelium.

Synonyms
The popular term chondroid hamartoma denotes the usual predominance of cartilaginous matrix. Other terms include benign mesenchymoma, hamartochondroma, chondromatous hamartoma, adenochondroma and fibroadenoma of the lung.

Epidemiology
The population incidence is 0.25% (1065) with a two- to four-fold male predominance and peak incidence in the sixth decade (2066). Hamartomas are rare in children.

Localization
Hamartomas are usually peripheral and less than 4 cm in diameter. About 10% arise endobronchially (2006,2066).

Clinical features
Presentation is typically as an asymptomatic, solitary, well-circumscribed nodule on routine chest x-ray. Hamartomas represent approximately 7-14% of coin lesions. Multiple lesions are rare. Occasionally, the distinctive radiographic appearance of “popcorn calcification” is seen. Endobronchial lesions tend to cause symptoms due to bronchial obstruction (2006,2066).

Macroscopy
Parenchymal tumours are multilobulated, white or gray, firm masses that “shell out” from the surrounding parenchyma. The consistency is cartilaginous, with occasional gritty specks of dystrophic calcification or bone. Endobronchial lesions, which tend to be more lipomatous, are situated within the larger airways as broad-based polyps.

Histopathology
Hamartomas are composed predominantly of lobulated masses of mature cartilage surrounded by other bland mesenchymal elements such as fat, smooth muscle, bone, and fibrovascular tissue. These latter elements rarely predominate. Clefts of respiratory-type epithelium frequently extend as slit-like spaces between the lobules of mesenchymal components. In endobronchial hamartomas, adipose tissue may predominate, and epithelial inclusions tend to be shallow or absent. Cytologic diagnosis of chondroid hamartoma is based on recognition of the mesenchymal components. Immunohistochemistry and ultrastructural studies rarely contribute to the diagnosis.

Differential diagnosis
Hamartomas are separated from monomorphic benign soft tissue tumours by the presence of at least two mesenchymal elements, and from chondrosarcoma by the lack of cytologic atypia. “Cystic mesenchymal hamartoma” refers mainly to neoplasms of children, is readily distinguishable from chondroid hamartoma, and is preferably classified as pleuropulmonary blastoma. Hamartomas must also be distinguished from bronchopulmonary chondromas that tend to be multiple in Carney’s triad (pulmonary chondromas, epithelioid gastric smooth muscle tumours and extra-adrenal paraganglioma). These consist solely of cartilage without cleft-like spaces lined by respiratory epithelium.

Histogenesis
Histogenesis is unknown, although genetic studies indicate a neoplastic rather than hamartomatous origin (2006, 2066).

Somatic genetics
Pulmonary hamartomas have a high frequency of genetic mutations, similar to those seen in other benign mesenchymal neoplasms such as lipomas. Most notable are mutations of high-mobility group (HMG) proteins, a family of non-histone, chromatin-associated proteins, which are important in regulating chromatin architecture and gene expression. Mutations in the regions 6p21 and 12q14-15 are most commonly found (591,824,982,983).

Prognosis and predictive factors
Conservative surgery is appropriate, either by enucleation or wedge resection for parenchymal lesions or by bronchoplastic resection for endobronchial lesions. Recurrence or sarcomatous transformation is exceedingly rare (2066).
Fig. 1.120 Hamartoma.  

A. A bisected, circumscribed hamartoma revealing lobules of firm cartilagenous tissue interspersed by fibrovascular and adipose tissue. Focal cystic change is also seen.  

B. At low power, a hamartoma shows lobules of cytologically bland cartilagenous tissue interspersed by mature adipose tissue. Focal ossification.  

C. Lobules of mature cartilage with deep clefts lined by bronchiolar type epithelium From Travis et al. (2024).  

D. Adjacent to the cartilage are fat vacuoles and a spindle cell mesenchymal stroma. The cleft-like space is lined by bronchiolar-type epithelium From Travis et al. (2024).
Sclerosing haemangioma

Definition
A lung tumour with a distinctive constellation of histologic findings including: solid, papillary, sclerotic, and haemorrhagic patterns. Hyperplastic type II pneumocytes line the surface of the papillary structures. Cholesterol clefts, chronic inflammation, xanthoma cells, haemosiderin, calcification, laminated scroll-like whorls, necrosis, and mature fat may be seen.

ICD-O code 8832/0

Synonyms and historical notation
Pneumocytoma, papillary pneumocytoma (992). It was named sclerosing haemangioma as it was originally believed to be vascular in origin due to prominent angiomatoid features. Current consensus favors a benign or very low-grade neoplasm arising from primitive respiratory epithelium.

Epidemiology
Sclerosing haemangioma predominantly affects middle-aged adults (median = 46, from 11–80 years-old) (1456,1859), with a female predominance (80% of cases) (488). It is rare in western countries. In East Asia (e.g Japan), its frequency is higher and is similar to that of carcinoid tumour.

Localization
Most tumours are solitary and peripheral; 4% of cases are multiple (1153). The tumour may involve visceral pleura (4%), mediastinum (1%), and rarely occurs as endobronchial polyps (1%) (488).

Clinical features
Most patients are asymptomatic (80%). Haemoptysis, cough, and thoracic pain may occur. Chest x-ray shows a solitary circumscribed mass, rarely calcified, and occasionally cystic. CT scans show a well-circumscribed mass with marked contrast enhancement, and foci of sharply marginated low attenuation and calcification (890). By MRI, a haemorrhagic component may help differentiate SH from other coin lesions (627).

Macroscopy
SH presents as a well-circumscribed mass without a preferential lobar distribution. Size ranges from 0.3-8 cm. Sections show a solid, grey to tan-yellow

<table>
<thead>
<tr>
<th>Markers</th>
<th>Round cells (% of cases)</th>
<th>Surface cells (% of cases)</th>
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<tbody>
<tr>
<td>Pan-cytokeratin</td>
<td>-</td>
<td>+</td>
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<tr>
<td>EMA</td>
<td>+ membranous</td>
<td>+ membranous</td>
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<tr>
<td>Low molecular weight keratin (CAM 5.2)</td>
<td>+ focal (17%)</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>+ focal (31%)</td>
<td>+</td>
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<tr>
<td>Cytokeratin 20</td>
<td>-</td>
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<tr>
<td>High molecular weight keratin (CK 5/6; K903)</td>
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</tr>
<tr>
<td>TTF-1</td>
<td>+ nuclear (92%)</td>
<td>+ nuclear (97%)</td>
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<tr>
<td>Pro-Sp A and pro-SpB</td>
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<tr>
<td>Clara cell antigen</td>
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<td>Vimentin</td>
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<td>S-100 protein</td>
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<td>Calretinin</td>
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<td>Estrogen receptors</td>
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<tr>
<td>Progesterone receptors</td>
<td>+ (61%)</td>
<td>-</td>
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<tr>
<td>Chromogranin</td>
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<tr>
<td>Synaptophysin</td>
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<td>Leu-7</td>
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EMA (epithelial membrane antigen); CK 5/6 (cytokeratin 5/6), K903 (keratin 903), TTF-1 (thyroid transcription factor-1), pro-SpA and pro-SpB (surfactant apoproteins A and B), SMA (smooth muscle actin).

Fig. 1.121 Sclerosing haemangioma. A CT scan shows a circumscribed, solid yellow tan mass lying within the posterior segment of the left upper lobe. B Sclerosing haemangioma, presenting as a well-circumscribed solid white tumour at its periphery. C Well-circumscribed unencapsulated nodule with a mixture of papillary, solid and sclerotic patterns.
surface with foci of haemorrhage and occasionally cystic degeneration [1464] or calcification.

**Tumour spread and staging**
These tumours may spread to regional lymph nodes in approximately 1% of cases [488,1009,1334]. Rarely SH may present in the mediastinum without apparent connection to the lung [1728].

**Histopathology**
Two cell types occur: round stromal cells and surface cells, both of which are thought to be neoplastic in origin [970]. Round cells are small with well-defined borders and centrally located round to oval bland nuclei with fine dispersed chromatin, an absence of discernible nucleoli. Mitotic index is low (usually less than 1 per 10 high power fields). Their cytoplasm is eosinophilic but may be foamy or vacuolated with a signet ring appearance. Cuboidal surface cells display the morphology of bronchiolar epithelium and activated type II pneumocytes. They may be multinucleated, or demonstrate clear, vacuolated, foamy cytoplasm or intranuclear inclusions. Focal mild to marked nuclear atypia can be seen in either cell type.

1. Papillary pattern: complex papillae lined by cuboidal surface cells. The stalk of the papillary projections contains the round cells. It can be sclerotic or occasionally myxoid.
2. Sclerotic pattern: dense foci of hyaline collagen at the periphery of the haemorrhagic areas, within papillary stalks, or within the solid areas.
3. Solid pattern: sheets of round cells, with scattered cuboidal surface cells forming small tubules.
4. Haemorrhagic pattern: large blood-filled spaces lined by epithelial cells or foci of haemorrhage and debris containing haemosiderin deposits, foamy macrophages, and cholesterol clefts, rarely surrounded by granulomatous and chronic inflammation. Calcifications sometimes display a psammoma-like configuration. Lamellar structures in the spaces between papillae are also encountered. Rarely, mature fat may be seen. Neuroendocrine cells, isolated or in solid nests (tumourlets) may rarely occur SH combined with typical carcinoid has been described [1153].

**Immunohistochemistry**
Round cells express TTF-1 and EMA, but are pancytokeratin negative. Surface cells express TTF-1, epithelial membrane antigen (EMA), surfactant apoprotein A and pancytokeratin.

**Cytopathology**
Trans-thoracic fine needle aspiration cytology [655] typically shows a moderately cellular, dual cell population. Round cells are small, round or spindle-shaped, with granular cytoplasm, uniform nuclei arranged in cohesive papillary clusters or in flat pavement-type orientation. The nuclei may be atypical, but the absence of nucleoli helps in distinguishing SH from adenocarcinoma. Hyalinized stromal tissue fragments may be seen. Foamy macrophages, haemosiderin, and red cells are seen in the background.

**Differential diagnosis**
The differential diagnosis includes clear cell tumours involving the lung (metastatic renal cell carcinoma, clear cell ‘sugar’ tumours, and clear cell carcinomas of the lung), carcinoids and papillary pulmonary epithelial neoplasms. SH can be usually be distinguished from these by bland cytology, heterogeneous architecture and a characteristic immunostaining pattern.

**Histogenesis**
Since the first description in 1956 [1183], vascular [1183], mesothelial [972], mesenchymal [883], epithelial [1751], and neuroendocrine [2180] origins have been postulated. Immunohistochemical findings suggest that sclerosing haemangioma derives from primitive, undifferentiated respiratory epithelium. Molecular studies have demonstrated...
the same monoclonal pattern in both the round and surface cells, consistent with a true neoplasm rather than a hamartoma (1474). There is no normal counterpart for the neoplastic stromal cell recognized in the human lung.

**Prognosis and predictive factors**
Sclerosing haemangioma behaves in a clinically benign fashion. No recurrence or disease-related deaths have been reported. Reported cases with hilar or mediastinal lymph node involvement do not have a worse prognosis (1464, 2198).

**Fig. 1.123** These epithelioid cells of sclerosing haemangioma are growing in the solid pattern. From Travis et al. (2024).

**Fig. 1.124** Sclerosing haemangioma TTF-1 (thyroid transcription factor-1) is expressed in tumour cells.

**Fig. 1.125** Sclerosing haemangioma. A Sclerotic, solid and papillary patterns are present. B In this haemorrhagic pattern the tumour forms ectatic spaces filled with red blood cells that are surrounded by type II pneumocytes. From Travis et al. (2024).
Clear cell tumour

Definition
Clear cell tumours are benign tumours probably arising from perivascular epithelioid cells (PEC). They comprise cells with abundant clear or eosinophilic cytoplasm that contain abundant glycogen.

ICD-O code
8005/0

Synonyms
Other terms include ‘sugar tumour’ in the lung and PEComa (perivascular epithelioid cell-oma), or myomelanocytomas at other sites.

Epidemiology
This tumour is extremely rare. There is a slight female predominance, with age range of 8-73 years.

Etiology
There is a very rare association with tuberous sclerosis and lymphangioleiomyomatosis (594).

Localization
Most are solitary and peripheral in location.

Clinical features
Clear cell tumours are generally asymptomatic and discovered incidentally (646).

Macrosopy
Tumours are usually about 2 cm in diameter (range 1 mm to 6.5 cm) (59,646). They are well circumscribed and solitary, with red-tan cut surfaces.

Histopathology
Clear cell tumours comprise rounded or oval cells with distinct cell borders and abundant clear or eosinophilic cytoplasm. There is mild variation in nuclear size, nucleoli may be prominent, but mitoses are usually absent. The presence of necrosis is extremely rare and should lead to consideration of malignancy (646), as should significant mitotic activity and an infiltrative growth pattern (1984). Thin-walled sinusoidal vessels are characteristic. Due to the glycogen-rich cytoplasm, there is usually strong diastase-sensitive PAS positivity (1127).

Immunohistochemistry and electron microscopy
Tumours stain most consistently for HMB-45 (59,646,648,652,1127). Electron microscopy shows abundant free and membrane bound glycogen (646,648,1127). Melanosomes have also been identified (646,648,1127).

Differential diagnosis
Clear cell tumours are distinguished from clear cell carcinomas, both primary and metastatic, on the basis of a lack of cytologic atypia, the presence of thin-walled sinusoidal vessels within the tumour, positive staining for S-100 and HMB-45 (melanocytic markers) and negative staining for cytokeratins. Metstatic renal cell carcinomas may contain intracytoplasmic glycogen but show necrosis and stain for epithelial markers. Granular cell tumours stain for S-100 but not for HMB-45 and do not contain abundant glycogen in their cytoplasm. Metastatic melanomas and clear cell sarcomas will have a similar immunophenotype and ultrastructure, but the tumour cells will not show significant atypia and there is usually a history of a previous neoplasm.

Histogenesis
Recent data suggest a pericytic origin and clear cell tumours have been proposed to represent one of the family of PEComas, neoplasms originating from the perivascular epithelioid cells (PEC) (201).

Prognosis and predictive factors
Virtually all tumours have been cured by excision (646,652,1127).

Fig. 1.126 Clear cell tumour. A The abundant cytoplasmic glycogen is stained with periodic acid-Schiff (PAS). B The glycogen is removed in this PAS stain with diastase digestion. C The tumour cells stain positively with immunohistochemistry for HMB-45. From Travis et al. (2024).
Teratoma

Definition
Teratomas are tumours consisting of tissues derived from more than one germ cell line. They may be mature or immature. Criteria for pulmonary origin are exclusion of a gonadal or other extragonadal primary site and origin entirely within the lung.

ICD-O code
Teratoma mature 9080/0
Teratoma immature 9080/3

Epidemiology
The majority of cases occur in the second to fourth decades (range 10 months to 68 years) with a slight female preponderance.

Localization
Teratomas are more common in the upper lobes, principally on the left side (78,1373,1931).

Clinical features
Patients present most often with chest pain, followed by haemoptysis, cough and pyothorax (78,1373,1969). Expectoration of hair (trichoptysis) is the most specific symptom (1373,1971,2056). Radiologically, the lesions are typically cystic masses, often with focal calcification (1373).

Macroscope
Tumours range from 2.8-30 cm in diameter. They are generally cystic and multiloculated, but may rarely be predominantly solid, the latter tending to be immature. Cysts are often in continuity with the bronchi and may have an endobronchial component (1373).

Tumour spread and staging
Pulmonary mature teratomas are benign. Rupture may result in spillage of cyst contents that may cause bronchopleural fistulas and a marked inflammatory and fibrotic reaction.

Histopathology
Mesodermal ectodermal and endodermal elements are seen in varying proportions (78). Most pulmonary teratomas are composed of mature, often cystic somatic tissue, although malignant or immature elements may occur. Of 31 cases reviewed, 65% were benign and 35% were malignant (1373). Mature teratomas of the lung generally take the form of squamous-lined cysts similar to those of the ovary, also known as dermoid cysts. Malignant elements consisted of sarcoma and carcinoma. Immature elements, such as neural tissue, infrequently occur. In mature teratomas, thymic and pancreatic elements are often seen.

Differential diagnosis
Metastatic teratoma requires exclusion via thorough clinical investigation. Of note, teratomas treated by chemotherapy often comprise wholly mature elements in their metastases (268). Carcinosarcomas, pleuropulmonary blastomas and pulmonary blastomas do not recapitulate specific organ structures.

Histogenesis
Pulmonary teratomas are thought to arise from ectopic tissues derived from the third pharyngeal pouch.

Prognosis and predictive factors
Surgery is the treatment of choice with all mature teratomas being cured (1373). Complete surgical resection may be complicated if the tumour has ruptured with bronchopleural fistula and a marked fibroinflammatory reaction. Resection of malignant teratomas has also led to prolonged disease remission, although most cases were unresectable and died within 6 months of diagnosis.

Other germ cell tumours
Germ cell malignancies other than immature teratomas are extremely rare and require exclusion of an extrapulmonary primary. They should also be distinguished from carcinomas of the lung (including pleomorphic and giant cell carcinomas), which may produce alphafetoprotein, chorionic gonadotrophins, or placental lactogen.

Most cases reported as choriocarcinoma of the lung are pleomorphic carcinomas with ectopic beta-HCG production. Instead of a dual population of cytotrophoblasts and syncytiotrophoblasts typical of choriocarcinoma, there is a continuous spectrum of morphology from large to pleomorphic tumour cells.

Fig. 1.127 Mature teratoma. A Mature cartilage, glands and pancreatic tissue. B Pancreatic tissue with acinar and ductal epithelium. From Colby et al. (391) and Travis et al. (2024).
Intrapulmonary thymoma

Definition
Intrapulmonary thymomas are epithelial neoplasms histologically identical to mediastinal thymoma thought to arise from ectopic thymic rests within the lung (1238,1367).

ICD-O code 8580/1

Epidemiology
Sex distribution differs between series, with one series showing a female preponderance (1367) whilst others show greater equality. Ages range from 17-77 years, with a median of about 50 years.

Localization
Tumours may be hilar or peripheral. Pleural tumours are addressed in the pleural chapter.

Clinical features
Symptoms include cough, weight loss, chest pain, fever and dyspnoea. Tumours may occasionally be asymptomatic. Myasthenia gravis has been rarely described (1367).

Macroscopy
Sizes range from 0.5-12cm. Tumours are usually circumscribed encapsulated solitary masses although multiple cases are described. The cut surface is frequently lobulated and may be focally cystic, with variable coloration.

Histopathology
Intrapulmonary thymomas show the same features as those arising in the mediastinum (see thymus chapter).

Immunohistochemistry
Immunohistochemical stains for keratin and epithelial membrane antigen highlight the epithelial cells scattered against the variable lymphoid cell background. Staining CD5 may stain the epithelial elements and the lymphocytes stain for CD1a (632,1609).

Differential diagnosis
Predominantly epithelial thymomas may be mistaken for carcinomas and spindle cell carcinoids, and lymphocyte-rich variants for lymphoma and small cell carcinoma (1367). Conversely, radiographic studies and/or surgical inspection must exclude primary mediastinal thymomas infiltrating the lung. Thymomas usually lack cytologic atypia and have a more lobulated architecture than small and non-small cell carcinomas.

Histogenesis
Probable derivation from thymic epithelial rests.

Prognosis and predictive factors
Surgical resection appears the treatment of choice with disease-free survival in most patients when tumour is confined to the lung. However, invasive tumours will likely require additional treatment. Nodal involvement is also described and nodal dissection should therefore be considered.

Fig. 1.128 Thymoma. A This pleural tumour shows lobules of epithelial cells surrounded by thick bands of fibrous stroma. B The tumour consists of a mixture of thymic epithelial cells with a few lymphocytes. From Travis et al. (2024).
Melanoma

Definition
Melanomas are malignant tumours derived from melanocytes. Criteria for a primary pulmonary origin include an infiltrating tumour arising from junctional change in the bronchial epithelium, a concomitant naevus-like lesion, no history of previous melanoma and no tumour demonstrable at another site at the time of diagnosis.

ICD-O code 8720/3

Epidemiology
Metastatic melanoma to the lungs is common, but primary pulmonary melanoma is extremely rare.

Localization
Most cases are endobronchial but origin in the trachea is also described [515, 928]. Solitary melanomas in peripheral lung are usually metastatic.

Clinical features
There is an equal sex distribution, with a median age of 51 years (range 29-80 years) [928,1522]. Presentation is with obstructive symptoms.

Macroscopy
Most tumours are solitary and polypoid [928,2152], although cases of ‘flat’ melanomas have been described in the trachea [1374]. Most show variable pigmentation.

Histopathology
The tumour is typically lobulated and ulcerative. Architecturally and cytologically, the tumour cells are similar to those of melanoma at other sites. Often, the tumour spreads in Pagetoid fashion within the adjacent bronchial mucosa and rarely, benign naevus-like lesions can also be seen [928,2152]. Immunohistochemistry shows positivity for S-100 protein and HMB-45. Ultrastructural analysis shows melanosomes within the cytoplasm [2152].

Differential diagnosis
Metastatic disease is the most common differential diagnosis and it may be impossible to prove primary pulmonary origin with absolute certainty. Bronchial carcinoids may be pigmented, but will stain for neuroendocrine markers and are typically cytokeratin positive.

Precursor lesions
No precursor lesion is recognized. Nevus-like proliferation of melanocytic cells can be seen in the mucosa adjacent to some primary pulmonary melanomas, but benign naevi are not known to occur in the bronchus and these may be a cytologically bland form of tumour spread, rather than a precursor lesion.

Histogenesis
It is uncertain whether they arise from melanocytic metaplasia or from cells that migrated during embryogenesis.

Prognosis and predictive factors
Once pulmonary origin has been confirmed, treatment is by surgical resection. Prognosis varies between series, but is generally poor [2152]. However, some patients remain free of disease for up to 11 years [928].

Fig. 1.129 Primary malignant melanoma. A Polypoid endobronchial mass with spread along the adjacent bronchial mucosa. B Tumour cells infiltrate the bronchial mucosa and involve the epithelium in a pagetoid fashion. From Colby et al. (391) and Travis et al. (2024).

Fig. 1.130 Cytology of an aspirate of metastatic malignant melanoma. Highly pleomorphic and dissociated malignant cells. Note the presence of nuclear pleomorphism, massive nucleoli, and occasional nuclear pseudoinclusion.
Metastases to the lung

Definition
Tumours in the lung that originate from extra-pulmonary sites or that are discontinuous from a primary tumour elsewhere in the lung.

Synonyms
Secondary tumours in the lung.

Epidemiology
Most common sources of metastatic tumours to lung, in relative order of frequency: breast, colon, stomach, pancreas, kidney, melanoma, prostate, liver, thyroid, adrenal, male genital, female genital.

At autopsy, the lungs are involved with tumour spread from extra-pulmonary solid malignancies in 20-54% of cases (13,426,558,935,1692,2148) and in 15-25% of cases the lungs are the sole site of tumour spread (558). In some 3-7% of cases of diagnosed primary lung tumours, there is another known primary cancer elsewhere (2202).

Pathogenesis
Secondary tumours are the commonest form of lung neoplasm and the lungs receive the most secondary tumours of any organ. This is because the lungs are the only organ to receive the entire blood and lymph flow and they have the densest capillary network in the body, that network also being the first encountered by tumour cells entering the venous blood via the ductus lymphaticus (548, 578,2237). Also there is probably favourable “seed and soil” deposition in the lungs as originally proposed by Paget in 1889 (1531).

Localization
Some generalizations apply to secondary tumours in the lungs. They are usually, peripheral, have more discrete borders, are harder to reach with fiberoptic bronchoscopy forceps and less often shed cells for cytological examination than lung primaries. Pulmonary metastases usually present as multiple, bilateral pulmonary nodules but can also appear as solitary masses (13,319,442,935,1784,1961,2129). Metastatic tumour nodules to the lungs can be present in any intrathoracic location but are most common in the lower lobes (13,126,290,595,781,922,1605).

Clinical features
Signs and symptoms
Most patients with lung metastases do not have pulmonary symptoms. The few with endobronchial spread simulate primary tumours by causing cough, haemoptysis, wheezing, and signs of obstruction such as obstructive pneumonia, atelectasis, dyspnoea and fever (2131). Those with pleural infringement and/or effusion may have chest pain and/or dyspnoea. Those with vascular or lymphangitic spread may have signs of cor pulmonale.

Imaging
Typical metastatic disease to the lungs presents radiographically as multiple well-defined pulmonary nodules. Cavitation may be present and in rare instances, the margins of the nodules may be poorly defined. Calcification is uncommon but may be seen with metastatic osteogenic sarcoma, teratomas and certain adenocarcinomas. On CT, more nodules are routinely detected and their distribution and internal characteristics are better defined. Endobronchial metastases are uncommon but when present cause the same patterns of atelectasis as with primary lung neoplasms. When mediastinal or

Fig. 1.131 A Metastatic carcinoma, intra-arterial spread. Small artery with endoluminal cancer cells and focal thrombus. B Metastatic adenocarcinoma, lymphatic spread. Lymphatic spaces are distended by metastatic adenocarcinoma.
Macroscopy
Metastatic neoplasms presenting with multiple pulmonary nodules are variable in gross appearance according to their site of origin, histopathology and pattern of spread [1605,1961]. They vary in size from small, miliary lesions (e.g. melanoma, ovarian carcinoma, germ cell neoplasms) to large, confluent, "cannonball" masses (e.g. sarcomas, renal cell carcinoma) [781,1605]. Metastatic adenocarcinomas are usually firm, grey-tan with areas of necrosis and haemorrhage [1633]. Mucin-secreting adenocarcinomas of gastrointestinal, pancreatic, breast, ovary and other site origin exhibit a wet, slimy, glistening yellow-tan surface [13,126,935]. Metastatic colonic adenocarcinomas usually exhibit extensive necrosis with/without cavitation [595]. Metastatic squamous cell carcinomas have a grey, dry surface with punctate areas of necrosis [13,126,442]. Renal cell carcinomas usually present as yellow nodule/s [1605]. Metastatic sarcomas and malignant lymphomas usually have a firm, grey, glistening, "fish-flesh" surface. Metastatic angiosarcomas tend to exhibit a dark red, haemorrhagic surface, while melanomas may be black.

Histopathology
Patterns of spread of metastatic neoplasms to the lung are well known [442,911,1590,1605] but are seldom helpful in identifying the site of origin of the metastatic neoplasm. Metastatic tumour emboli (e.g. sarcomas, others) may occlude the main pulmonary artery or present as multiple pulmonary emboli (breast, stomach, others) [90,876]. Metastatic neoplasms may also present as single or multiple endobronchial polypoid lesions (e.g. head and neck, breast, kidney, others), interstitial thickening due to lymphangitic spread (e.g. lung, breast, gastrointestinal, others), cavitory lesions (e.g. squamous cell carcinoma, sarcomas, teratoma, others) pleural nodules or diffuse areas of consolidation that simulate a pneumonia (e.g. pancreas, ovary, others).
Immunohistochemistry

This is a valuable tool for the distinction between primary and metastatic lung neoplasms. For example, approximately 80% of primary lung adenocarcinomas exhibit nuclear TTF-1 immunoreactivity, an epitope that can also be seen in thyroid neoplasms but is absent in other adenocarcinomas [138,352,704,773, 1564]. Thyroid neoplasms exhibit cytoplasmic thyroglobulin immunoreactivity with a high frequency; this is absent in primary lung tumours and it is useful to demonstrate thyroglobulin negativity in TTF-1 positive lung tumours to exclude a metastasis from the thyroid. Primary adenocarcinomas of the lung usually exhibit keratin 7 and variable keratin 20 cytoplasmic immunoreactivity unless the tumour expresses mucin [184,366,368]. In contrast, colonic adenocarcinomas exhibit a cytoplasmic keratin profile of CK 20 positive/CK 7 negative as well as CDX-2 [184,352,366,368,704,766,773, 1307,2082]. Breast neoplasms can exhibit nuclear immunoreactivity for estrogen receptor, a finding that is absent in primary lung lesions [976, 1528,1657,1737]. Renal cell carcinomas usually stain weakly with keratin AE1/AE3, and keratin 7 and exhibit strong cytoplasmic vimentin immunoreactivity. Metastatic carcinomas of the ovary usually express immunoreactivity for CA125, N-cadherin, vimentin, oestrogen receptor, and inhibin and negative CEA immunoreactivity [976,1486,2189].

Differential diagnosis

Some adenocarcinomas have characteristic histopathological features. For example, a cribriform pattern characterizes colonic adenocarcinoma [595]. Necrosis with nuclear debris is also common in metastatic colonic adenocarcinomas. Renal cell carcinomas typically have clear cells arranged in nests surrounded by a rich vascular network [1605]. In squamous cell carcinoma, severe dysplasia or in situ carcinoma favours a primary lung neoplasm [13,935].

Somatic genetics

Cyto genetic s and CGH

In poorly differentiated secondary neoplasms of unknown primary site in which conventional light microscopic, immuno histochemical, and electron microscopic techniques fail to yield a specific diagnosis, cytogenetic analysis promises to increase diagnostic acuity. However, information on nonrandom (recurrent) chromosomal aberrations in solid tumours is currently limited. When data from different cytogenetic studies are combined, a pattern of nonrandom genetic aberrations appears [1890]. As expected, some of these aberrations are common to different types of tumours [270], whereas others are more tumour-specific. For example, recent studies suggest that CGH analysis may be helpful in separating benign mesothelial proliferation, malignant mesothelioma, and metastatic adenocarcinoma [1427]. Continued technical refinement of cytogenetic techniques will lead not only to improved understanding of tumour pathobiology, but also to greater clinical applicability.

Molecular genetic alterations

Many of the same molecular genetic alterations of tumour suppressor genes and oncogenes can be found in both primary pulmonary carcinomas and in metastatic carcinomas. Only those molecular genetic markers that are specific or relatively restricted to metastatic carcinomas are candidates for diagnosis of a metastasis with identification of the primary site. For diagnostic purposes, expression of putative primary site specific molecular markers can be most conveniently accomplished by reverse-tran-