Tumours of the thymus account for less than 1% of all neoplasms and, therefore, do not contribute significantly to the overall human cancer burden. However, their etiology is largely unknown and the biology is complex. Thymomas often manifest clinically by causing autoimmune diseases, in particular myasthenia gravis.

The histological typing of tumours of the thymus remains a challenge for surgical pathologists. The Working Group responsible for this volume largely followed the previous WHO classification published in 1999. Some recently recognized entities have been added, together with updated diagnostic criteria.
### Epithelial tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>ICD-O Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoma&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>8580/1</td>
</tr>
<tr>
<td>Type A (spindle cell; medullary)</td>
<td>8581/1</td>
</tr>
<tr>
<td>Type AB (mixed)</td>
<td>8582/1</td>
</tr>
<tr>
<td>Type B1 (lymphocyte-rich; lymphocytic; predominantly cortical; organoid)</td>
<td>8583/1</td>
</tr>
<tr>
<td>Type B2 (cortical)</td>
<td>8584/1</td>
</tr>
<tr>
<td>Type B3 (epithelial; atypical; squamoid; well-differentiated thymic carcinoma)</td>
<td>8585/1</td>
</tr>
<tr>
<td>Micronodular thymoma</td>
<td>8580/1</td>
</tr>
<tr>
<td>Metaplastic thymoma</td>
<td>8580/1</td>
</tr>
<tr>
<td>Microscopic thymoma</td>
<td>8580/1</td>
</tr>
<tr>
<td>Sclerosing thymoma</td>
<td>8580/1</td>
</tr>
<tr>
<td>Lipofibroadenoma</td>
<td></td>
</tr>
<tr>
<td>Thymic carcinoma (including neuroendocrine epithelial tumours of the thymus)</td>
<td>8586/3</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
</tr>
<tr>
<td>Basaloid carcinoma</td>
<td>8123/3</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>8430/3</td>
</tr>
<tr>
<td>Lymphoepithelioma-like carcinoma</td>
<td>8082/3</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma ( carcinosarcoma)</td>
<td>8033/3</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>8310/3</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>8140/3</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>8260/3</td>
</tr>
<tr>
<td>Carcinoma with t(15;19) translocation</td>
<td></td>
</tr>
<tr>
<td>Well-differentiated neuroendocrine carcinomas (carcinoid tumours)</td>
<td></td>
</tr>
<tr>
<td>Typical carcinoid</td>
<td>8240/3</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>8249/3</td>
</tr>
<tr>
<td>Poorly differentiated neuroendocrine carcinomas</td>
<td></td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>8013/3</td>
</tr>
<tr>
<td>Small cell carcinoma, neuroendocrine type</td>
<td>8041/3</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>8020/3</td>
</tr>
<tr>
<td>Combined thymic epithelial tumours, including neuroendocrine carcinomas</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Germ cell tumours (GCT) of the mediastinum</th>
<th>ICD-O Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCTs of one histological type (pure GCTs)</td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>9061/3</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>9070/3</td>
</tr>
<tr>
<td>Yolk sac tumour</td>
<td>9071/3</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>9100/3</td>
</tr>
<tr>
<td>Teratoma, mature</td>
<td>9080/3</td>
</tr>
<tr>
<td>Teratoma, immature</td>
<td>9080/3</td>
</tr>
</tbody>
</table>

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.
2. For thymus, designated as malignant; change from /1 to /3
### TNM classification of malignant thymic epithelial tumours

<table>
<thead>
<tr>
<th>TNM classification 1,2,3</th>
<th>M – Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T – Primary Tumour</td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour completely encapsulated</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades pericapsular connective tissue</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades into neighbouring structures, such as pericardium, mediastinal pleura, thoracic wall, great vessels and lung</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour with pleural or pericardial dissemination</td>
</tr>
<tr>
<td>N – Regional Lymph Nodes</td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in anterior mediastinal lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in scalene and/or supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

1 (899)
2 A help desk for specific questions about the TNM classification is available at http://www.uicc.org
3 This is not an official UICC TNM Classification.

### TNM classification of thymic germ cell tumours

<table>
<thead>
<tr>
<th>TNM classification 1,2,3</th>
<th>N1 – Metastasis to regional lymph node present</th>
</tr>
</thead>
<tbody>
<tr>
<td>T – Primary Tumour</td>
<td>N2 – Metastasis in other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes</td>
</tr>
<tr>
<td>TX</td>
<td>N3 – Metastasis in scalene and/or supraclavicular lymph nodes</td>
</tr>
<tr>
<td>T0</td>
<td>M – Distant Metastasis</td>
</tr>
<tr>
<td>T1</td>
<td>MX – Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T2</td>
<td>M0 – No distant metastasis</td>
</tr>
<tr>
<td>T3</td>
<td>M1 – Distant metastasis present</td>
</tr>
<tr>
<td>T4</td>
<td>Stage Grouping of the Pediatric Study Group1,3</td>
</tr>
<tr>
<td>N – Regional lymph nodes</td>
<td>Stage I Locoregional tumour, non-metastatic, complete resection</td>
</tr>
<tr>
<td>NX</td>
<td>Stage II Locoregional tumour, non-metastatic, macroscopic complete resection but microscopic residual tumour</td>
</tr>
<tr>
<td>N0</td>
<td>Stage III Locoregional tumour, regional lymph nodes negative or positive; no distant metastasis; biopsy only or gross residual tumour after primary resection</td>
</tr>
<tr>
<td>N1</td>
<td>Stage IV Tumour with distant metastasis</td>
</tr>
</tbody>
</table>

1 (167)
2 A help desk for specific questions about the TNM classification is available at http://www.uicc.org/tnm
3 This is not an official UICC TNM Classification.
Tumours of the thymus: Introduction

Tumours of the thymus comprise neoplasms assumed to arise from or differentiate towards thymic cellular constituents, including thymic epithelial tumours (thymomas, thymic carcinomas, neuroendocrine tumours), germ cell tumours, lymphoid and haematopoietic neoplasms and mesenchymal tumours.

Histogenesis and differentiation
Thymoma. It has long been assumed that thymic epithelial cells originate from both the ectodermal and endodermal germ cell layers. However, a growing body of evidence suggests that the diverse thymic epithelial populations all develop from a common thymic epithelial stem cell of endodermal origin [181, 684]. This concept does not exclude the occurrence of more differentiated “committed stem cells” with medullary, cortical or other phenotypes [1671]. Tumours that we know as thymomas derive from thymic epithelium. In spite of morphological and immunological evidence for tumour differentiation towards a medullary or cortical epithelial phenotype, available data do not allow to unequivocally assign thymic tumours to defined functional and anatomical compartments of the normal thymus [1691].

Neuroendocrine thymic tumours. Both a neural crest and thymic epithelial cell derivation have been considered [316, 471,1139,2116,2137]. The latter hypothesis is supported by combined (mixed) thymoma-neuroendocrine tumours and the occurrence of either thymomas or thymic neuroendocrine tumours in MEN1 syndrome patients [461,1535,1687,2094].

Lymphomas. The thymus is the site of the earliest stages of T-cell and natural killer (NK)-cell development. Precursors of dendritic cells, mature dendritic cells, and small numbers of B cells are also found in the normal thymus. Among thymic haematopoietic neoplasias, there is good evidence that T-lymphoblastic lymphomas arise from lymphoid progenitors, while mediastinal large B-cell lymphomas are of putative thymic B-cell origin. In addition, some histiocytic and myeloid neoplasias are of teratomatous derivation. By contrast, the origins of thymic MALT, NK-cell and Hodgkin lymphomas are less clear. The same holds true for many mesenchymal tumours.

Epidemiology
Tumours of the thymus are among the rarest human neoplasms, comprising <1% of all adult cancers, with an incidence rate of 1–5 / million population / year. Thymomas are the most frequent thymic tumours in adults, followed by mediastinal lymphomas, some of which arise from mediastinal lymph nodes. In children, the mediastinum is the site of 1% of all tumours; most common are non-Hodgkin lymphomas, while thymomas are extremely rare.

Etiology
The etiology of thymic tumours is largely unknown. Some epidemiologic clustering of thymomas and neuroendocrine tumours has been observed among patients with multiple endocrine neoplasia (MEN1) syndrome [461,1687]. Epstein-Barr virus (EBV) infection may play a role in a minority of thymic carci-
nomas, as well as some Hodgkin, rare non-Hodgkin and NK/T-cell lymphomas.

Clinical features
Patients may exhibit symptoms due to local complications (pain, superior vena cava syndrome, respiratory insufficiency or tachycardia because of pleural or pericardial implants and effusions), as well as systemic symptoms (fever or weight loss).

In addition, thymomas can cause a large variety of autoimmune diseases (Table 3.01) which are often typical for a specific tumour type and may precede or follow thymoma resection [987]. Type A, AB and B thymomas exhibit an unrivaled frequency and spectrum of autoimmune phenomena, comprising neuromuscular, haematopoietic, dermatologic, rheumatic/vasculitic, hepatic and renal diseases. Myasthenia gravis is by far the most frequent and preferentially associated with type AB and B2, B3 thymomas, while hypogammaglobulinaemia (Good syndrome) is more typical for type A thymoma. Pure red cell aplasia is also a rare complication of type A thymomas, though recent data find a less specific association with this thymoma subtype [1086]. Thymic carcinomas are not associated with myasthenia gravis or hypogammaglobulinaemia, but occasionally with other autoimmune diseases. Cytopenias and/or hypogammaglobulinaemia can result in serious bacterial and opportunistic infections. Lymphocytosis and thrombocytosis can occur. Whether the increased incidence of second cancers in thymoma patients is related to genetic or environmental etiologies or thymoma-induced immunodeficiency is unknown [1395,1537].

Histopathological classification
Thymomas
Histological classification schemes for thymomas traditionally have been descriptive (predominantly spindle, predominantly lymphocytic, predominantly epithelial, mixed lymphoepithelial) {158, 1086,1134,1172,1732}, or were based on the combined consideration of morphologic (spindle, polygonal, mixed tumour cells) and lymphocyte content {1086, 1808}. Except for the spindle cell type, these classifications largely lacked prognostic significance independent of stage {1172,1253,1808}.

The histogenetic or functional classification included terms (medullary, cortical) that reflected the normal differentiation of the major functional and anatomic com-
entiation, resembling carcinomas outside the thymus. This category includes neuroendocrine epithelial tumours. *Germ cell, lymphoid, haematopoietic and mesenchymal tumours*.

The classification of these tumours follows the WHO Classification of gonadal germ cell tumours (526), tumours of haematopoietic and lymphoid tissues (919) and tumours of soft tissues and bone (590).

### Useful morphological terms

**Encapsulated.**

A thymoma completely surrounded by a fibrous capsule of varying thickness which is not infiltrated by tumour growth. Thymic tumours that infiltrate into, but not through, the capsule still belong in this category.

**Minimally invasive.**

A thymoma surrounded by a capsule which is focally infiltrated by tumour growth with invasion of the mediastinal fat. The capsular invasion needs to be complete in order for the tumour to be placed in this category. Minimally invasive thymomas are usually identifiable as such only after microscopic examination in so far as they generally appear to the surgeon indistinguishable from encapsulated thymomas at the time of excision.

**Widely invasive.**

A thymoma spreading by direct extension into adjacent structures such as pericardium, large vessels or lung. This type of thymoma usually appears invasive to the surgeon at the time of excision, which may be incomplete as a result.

**Implants.**

A thymoma in which tumour nodules separate from the main mass are found on the pericardial or pleural surface. These implants tend to be small and multiple and their microscopic appearance is usually, but not always, similar to that of the parent tumour.

**Lymph node metastases.**

A thymoma that involves one or more lymph nodes anatomically separate from the main mass. This excludes direct extension into the node by the tumour. The nodes most commonly involved by metastatic thymoma are mediastinal and supraclavicular. It is a rare event even in long-standing cases, but may exceptionally be the first clinical manifestation of the tumour.

**With distant metastases.**

A thymoma with metastases to distant site(s), most commonly lung, liver, and skeletal system. This excludes metastases to lymph nodes and local extension into adjacent organs.

### Grading of malignancy

Thymic epithelial tumours consist of several histological subtypes, i.e., thymoma types A, AB, B1, B2 and B3, and thymic carcinomas, in increasing order of malignancy (1691). Thymoma type A and AB generally behave like a benign tumour, type B1 as a low-grade malignant tumour (10-year survival rates of over 90%), type B2 has a greater degree of malignancy, and type B3 in the advanced stage shows a poor prognosis, just like thymic carcinoma and malignant tumours of other organs (1511). Among the various subtypes of thymic carcinoma, squamous cell carcinoma, basaloid and mucosoepidermoid carcinoma have a better prognosis than other histological subtypes. The malignancy grade of thymic neuroendocrine tumours (carcinoids) is intermediate between thymoma and thymic carcinoma. The rare small cell and large cell carcinomas tend to be highly malignant.

### TNM Classification and stage grouping

The TNM Classification and stage-grouping has been applied to malignant tumours of many organs (2045), but there is currently no authorized TNM system for thymic epithelial and neuroendocrine tumours. In the TNM Supplement 2nd edition (899), a tentative classification of malignant thymomas appeared for testing. It is mainly based on the Masaoka system and its revised versions (1255,2036,2184). While the tentative classification applies only to malignant thymic epithelial tumours (899), it has in this chapter been extended to include neuroendocrine tumours.

### Invasion

Crucial points in defining the T-categories are invasion through the capsule and invasion into neighbouring structures. Although invasive growth outside the thymus detected by the surgeon at
the time of thoracotomy has been repeatedly reported to have significant impact on the prognosis [693,1043], the prognostic significance of minor degrees of invasion detected by histological examination remains controversial. Many reports on thymoma have shown little or no difference in survival between Masaoka stage I and stage II thymomas [693,1043,1130,1511,1579,1645]. Furthermore, some thymomas and most thymic carcinomas are devoid of a capsule entirely or in part, which makes the definition of “encapsulation” meaningless. Therefore, the current and proposed categories “T1 (completely encapsulated)” and “T2 (with invasion of pericapsular connective tissue)” may not be biologically meaningful and may be impossible for pathologists to use. Criteria for minimal invasion need to be better defined.

**Tumour size**

On the other hand, tumour size has been used as an important parameter to define T-categories; critical dimensions of 11 cm and 15 cm have been reported [183,1172]. Especially in Blumberg’s report, tumour size was one of the significant parameters for survival by multivariate analysis [183]. Critical size may be quite different among thymoma and thymic carcinoma, including neuroendocrine tumours. This consideration of tumour size might also be necessary in a revised definition of the T-category.

**Surgical resectability**

The present T denominator includes tumours with different characteristics: one extreme is an easily resectable tumour with minimal invasion into the pericardium and a good prognosis and another extreme is a non-resectable tumour with invasive growth into multiple neighbouring organs. A further division of T3 tumours into potentially resectable and curable ones and non-resectable ones with a poor prognosis is desirable, especially for planning treatment.

**Lymph node metastasis**

This is rare in thymoma, and the basis for the definition of stage IVB (Masaoka) for thymomas with lymph node metastasis [1255]. In the tentative TNM classification, N1 (metastasis to anterior mediastinal lymph nodes) is defined as stage III. However, the prognostic equivalence between T3 and N1 has not yet been assessed. The appropriateness of the nodal grouping N1 to N3 needs to be investigated further. Depending on the tumour location in the anterior mediastinum, the lymphatic pathway by which tumour cells spread might be different. Consequently, the sentinel lymph node might be located elsewhere other than the anterior mediastinum.

**Stage-Grouping**

The most important issue in stage-grouping is the definition of stages I and II. The survival curves of patients with thymomas of stages I and II are superimposed at around 100% at 5 and 10 years after surgery [693,1511]. In other reports, a minimal difference has repeatedly been reported [1043,1130,1579,1645]. If the definition of the T-category remains unchanged, the present stages I and II could be merged into a new stage I; however, no data are available on thymic carcinoma with respect to stages I and II. Stage III in the present tentative system, which is a heterogeneous group, is recommended to be divided into a potentially resectable group with a favourable prognosis and an unresectable group with a poor prognosis, respectively.

**Table 3.03**

Malignant potential in terms of mortality, combining WHO histologic type and tumour stage, according to Shimosato et al. [1808]. Stage IV thymomas should be considered as tumours of high malignant potential, although metastatic type A or AB thymomas with long-term survival have been reported.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Tumour Stage</th>
<th>Malignant potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A, AB, (B1) thymoma</td>
<td>I and II</td>
<td>None (very low)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Low</td>
</tr>
<tr>
<td>Type B2, B3 thymoma</td>
<td>I</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>II and III</td>
<td>Moderate</td>
</tr>
<tr>
<td>Thymic carcinoma:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-grade squamous cell, basaloid</td>
<td>Stage I and</td>
<td>Moderate</td>
</tr>
<tr>
<td>or mucoepidermoid carcinoma,</td>
<td>II</td>
<td>High</td>
</tr>
<tr>
<td>carcinoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other histological types</td>
<td>Any stage</td>
<td>High</td>
</tr>
</tbody>
</table>

<sup>1</sup>These tumours amount to 40-50% of all thymomas [341,1511,1631].
Tumours of the thymus - Thymomas

Definitions
Thymomas (type A, AB, B thymomas) are neoplasms arising from or exhibiting differentiation towards thymic epithelial cells, regardless of the presence and relative numbers of non-neoplastic lymphocytes [1691]. Their malignant potential is either absent or low to moderate. Thymic carcinomas are malignant epithelial tumours because of overt cytological atypia, almost invariable invasive-ness and lack of “organotypic” (thymus-like) features. Combined thymoma, combined thymoma/thymic carcinoma. These terms are used for a combination of thymoma subtypes and of thymomas with thymic carcinomas, including thymic neuroendocrine carcinomas, within one tumour mass. Thymoma (type X) with anaplasia is the suggested diagnostic term for a very uncommon group of tumours with borderline morphological features between thymoma and thymic carcinoma.

Epidemiology
Thymomas and thymic carcinomas are uncommon tumours with an annual incidence of approximately 1-5 per million population. There are only very limited epidemiologic data, but cautious interpretation of data from the Danish National Board of Health suggests that the incidence has not changed significantly over the last three decades. Thymomas and thymic carcinomas occur at almost all ages (range 7-89 years) with a peak incidence between 55-65 years. They are exceedingly rare in children and adolescents [1577,1876]. There is no pronounced sex predilection [318,341,1016,1630]. Patients exhibit an increased incidence of second cancers irrespective of the histology of the thymic epithelial tumour [1537].

Etiology
The etiology of thymomas is still largely unknown. They have been repeatedly observed in patients with MEN1 syndrome [461,1535,1644,1648,2094]. Epstein-Barr virus appears to play an etiologic role in subsets of lymphoepithelial-like, poorly differentiated squamous and undifferentiated thymic carcinomas both in Asian [343,1174,1265,2174] and Western countries [785,894,1234,1876]. There is no increased risk of developing thymomas in patients receiving radio-chemotherapy for mediastinal Hodgkin lymphoma [1455] or breast cancer [1498].

Principles of thymoma classification
1. There are two major types of thymoma depending on whether the neoplastic epithelial cells and their nuclei have a spindle or oval shape, and are uniformly bland (Type A thymoma) or whether the cells have a predominantly round or polygonal appearance (Type B) [1691].
2. Type B thymomas are further subdivided on the basis of the extent of the lymphocytic infiltrate and the degree of atypia of the neoplastic epithelial cells into three subtypes B1 (richest in lymphocytes), B2, and B3 (richest in epithelial cells).
3. Thymomas combining type A with B1-like or (rarely) B2-like features are designated type AB.
4. Thymic carcinomas are termed according to their differentiation (squamous cell, mucoepidermoid, etc.). In the 1999 WHO classification [1690], the term WHO type C thymoma was the “headline designation” to stress their thymic epithelial origin. In the current classification, this term was eliminated since all non-organotypic malignant epithelial neoplasms other than germ cell tumours are designated thymic carcinomas.
5. Combined thymomas are specified by the WHO histology and approximate percentage contributed by each component of the combined thymoma.
6. Traditionally, the term “malignant thymoma” has been used for (i) thymomas with advanced stage, i.e. local invasiveness, pleural or pericardial implants or metastasis, irrespective of tumour histology or (ii) thymic epithelial tumours with marked atypia (thymic carcinomas), irrespective of tumour stage [1170,1691,1841,1924]. The use of the term “malig-

Table 3.04
Differential diagnosis of thymomas types A, AB, B and thymic carcinomas

<table>
<thead>
<tr>
<th>Feature</th>
<th>Thymomas</th>
<th>Thymic carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organotypic (thymus-like) histological features</td>
<td>Almost always present (lobular pattern, perivascular spaces, immature, TdT+ / CD1a+ / CD99+ T-cells)</td>
<td>None or abortive</td>
</tr>
<tr>
<td>CD5, CD70 and CD117 expression in epithelial cells</td>
<td>No</td>
<td>Frequent (~60%)</td>
</tr>
<tr>
<td>Invasion</td>
<td>Variable</td>
<td>Almost always</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Variable: 10–80%</td>
<td>No</td>
</tr>
<tr>
<td>Other autoimmune diseases</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Clinical behaviour</td>
<td>Often curable by surgery; metastases are rare. Usually long survival due to indolent clinical course</td>
<td>Often unresectable (318); metastases are frequent Often short survival due to progressive disease</td>
</tr>
</tbody>
</table>
nant thymoma” as a synonym for a locally invasive thymoma irrespective of the WHO histological type is discouraged, since it may not properly reflect the excellent prognosis of type A and AB thymomas of advanced stage [318,341, 1510,1511,1630].

Prevalence of thymoma subtypes
The predominant histological subtypes in most published series are type B2 and AB thymomas (each 20-35% of all cases), while type B1 and type A thymomas count among the rare types (5-10% in most studies) [856,1510,1967]. The percentage of thymic carcinomas has been reported to be about 10–25% [318,341,541,1404,1510].

In children, type A, B1 and B2 thymomas have been observed, in addition to undifferentiated and EBV-positive lymphoepithelioma-like thymic carcinomas [274, 1577,1876]. The morphologically heterogeneous and rare carcinomas with t(15;19) translocation typically occur in children and young adults [1081,1148,2072].

Genetic features
Recurrent genetic alterations have so far been reported for type A and B3 thymomas as well as for thymic squamous cell carcinomas [896,1567,2238,2242]. Type A thymomas only show few genetic alterations, with deletions of chromosome 6p reported as a recurrent genetic alteration [437,2065,2238]. Type A areas in type AB thymomas are genetically distinct from type A thymoma [699,896]. Type B3 thymomas frequently show gains of chromosome 1q and losses of chromosomes 6 and 13q. Type B2 thymomas are genetically related to type B3 thymomas [896]. Thymic squamous cell carcinomas frequently show gains of chromosomes 1q, 17q and 18 and losses of chromosomes 3p, 6, 16q, and 17p [2238]. The shared genetic abnormalities underline the close relationship between type B3 thymomas and thymic squamous cell carcinomas.

Prognosis and predictive factors
The most relevant prognostic factors in thymoma are tumour stage [341,1511,1630,1808], WHO histologic type [341, 1511] and completeness of resection [318,1419]. Type A and AB thymomas in stages I and II virtually always follow a favourable clinical course [341,476,1511], and even at higher stages may not be fatal due to a very slowly progressive course [1808]. They are considered benign tumours [784,1404] or neoplasms of low malignant potential. Type B1 thymomas have a very low malignant potential; rare local recurrences or late metastases may occur [318]. Type B2 and B3 thymomas and thymic carcinomas, are clear-cut malignant tumours. B2 and B3 thymomas and well differentiated squamous, basaloïd and mucoepidermoid carcinomas follow a more favourable course than poorly differentiated squamous cell carcinomas and other thymic carcinomas [1924]. The prognosis of combined thymomas may be determined by the most malignant component [1093,1912]. Paraneoplastic pure red cell aplasia, other cytopenias, or hypogammaglobulinaemia (Good syndrome) have an adverse effect [987] whereas paraneoplastic myasthenia gravis had no or a positive factor on survival [318,341].

Table 3.05
Genetic alterations reported for the different WHO histological thymoma subtypes.

<table>
<thead>
<tr>
<th>WHO Type</th>
<th>Chromosomal Gains</th>
<th>Chromosomal Losses</th>
<th>Source</th>
</tr>
</thead>
<tbody>
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<td>-6p</td>
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</tr>
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<td>-5q21-22, -6q, -12p, -16q</td>
<td>(699,896,897)</td>
</tr>
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<td>-6, -13q</td>
<td>(896,897,2238,2242)</td>
</tr>
<tr>
<td>Thymic squamous cell carcinoma</td>
<td>+1q, +17q, +18</td>
<td>-3p, -6, -13q, -16q, -17p</td>
<td>(896,897,1848,2238)</td>
</tr>
</tbody>
</table>

Fig. 3.04 Kaplan-Meier survival statistics of patients with thymic epithelial tumours. A Survival of patients with thymomas or thymic carcinomas according to stage. Masaoka tumour stage is the most important and statistically most significant independent prognostic parameter for survival in almost all clinico-pathological studies. From G. Chen et al. [341]. B Survival of patients with thymomas or thymic carcinomas according to histological type. WHO-based histology was a statistically significant prognostic parameter for survival in most clinico-pathological studies. In some studies, B3 thymomas and thymic carcinomas had a significantly worse prognosis than B2 thymomas (L. Quintanilla-Martinez et al. [1631]; M. Okumura et al. [1511]), but not in others (G. Chen et al. [341]). C WHO-based histological subtype is an independent prognostic marker in patients with thymomas and thymic carcinomas infiltrating beyond the tumour capsule into the mediastinal fat (Masaoka stage II). A no/low-risk group of tumours (type A, AB, B1 thymomas) is distinguished from a moderate/high-risk group (B2 and B3 thymomas and thymic carcinomas). From G. Chen et al. [341].
Type A thymoma

Definition
Type A thymoma is an organotypic thymic epithelial neoplasm composed of bland spindle/oval epithelial tumour cells with few or no lymphocytes. The tumour cells can form a variety of histologic structures.

ICD-O code 8581/1

Synonyms
Spindle cell thymoma, medullary thymoma

Epidemiology
Type A thymoma is a relatively uncommon type of thymoma and accounts for 4-19% of all thymomas [541,1510,1511,1808]. The age at manifestation ranges from 32 to 83 years, with a mean age of 61 years [1538,1540,1630], which is higher than the mean age of 50 years of all thymoma patients [341,1095]. No consistent gender predilection has been reported [318,1511,1540,1630].

Clinical features
Approximately 24% of type A thymomas are found in patients with myasthenia gravis [318,341,1511,1538,1540,1630]. Others are found because of local symptoms or incidentally discovered on imaging examination. Association with pure red cell aplasia may occur, but in contrast to earlier reports, pure red cell aplasia may also occur in other thymoma types [1096].

Macroscopy
Grossly, type A thymoma is usually well circumscribed and encapsulated. The cut surface is tan white and shows vague lobulation with less distinct dissecting white fibrous bands than is seen in other types. Cystic change or calcification of the capsule may be seen. Average tumour size is 10.5 cm.

Histopathology
Histologically, the tumour has few or no lymphocytes and shows neither distinct lobules nor dissecting fibrous bands as seen in other types of thymoma. The tumour cells are spindle and/or oval-shaped with bland nuclei, dispersed chromatin and inconspicuous nucleoli; they are arranged in solid sheets without any particular pattern or in a storiform pattern [1403]. Type A thymoma...
Type A thymoma cells can form cysts of various size, glandular structures, glomeruloid bodies, rosettes with or without a central lumen, Masson’s haemangioma-like papillary projections in cystic spaces, or meningioma-like whorls [1086, 1095, 1403, 1538, 1691, 1808]. Extremely elongated fibroblast-like spindle cells may be seen focally. Vessels in the background may impart a haemangiopericytoma-like appearance [1538]. Perivascular spaces are less commonly seen than in other types of thymoma [318]. Although type A thymoma is a lymphocyte-poor tumour, spindle cell micronodules in a lymphoid stroma may be present at places [1981]. Most tumour cells are individually surrounded by reticulin fibers [1086, 1691]. Cells in mitosis are seldom found, but lobular infarcts can occur. Rarely, thymic carcinoma can arise in type A thymoma. Areas of necrosis may be a clue to this phenomenon; examination of these areas reveals hyperchromatic anaplastic nuclei and/or mitotic figures indicating the presence of carcinoma [1093].

**Immunophenotype**

The tumour cells are strongly positive for AE1-defined acidic cytokeratins (CKs), and negative for AE3-defined basic CKs. Other CKs of different molecular weights show variable expression except that CK20 is negative [1086]. In general, the cystic and glandular structures express stronger CK [1808]. CD20-positive tumour cells may be detected focally [354, 1403, 1538]. There is no expression of CD5 [1538], and BCL-2, CD57 and EMA are variable and usually only focally expressed [227, 1631, 1808, 1872, 1981]. Most tumour cells are surrounded by basement membrane-like deposits as demonstrated by anti-laminin and anti-type IV collagen antibodies. TP53 protein and Ki-67 show only low or no expression [1539, 1872, 1980, 1981]. Two antigens, metallothionein and PE-35, found in normal thymic medullary cells are also expressed in type A thymoma cells [798, 1087]. The few lymphocytes, if present, are T cells positive for CD3 and CD5. CD1a+ and CD99+ immature T cells may be present but comprise a minority of the T cells. CD20+ B cells are usually absent except in focal micronodular areas with a lymphoid stroma, if these are present.

**Histogenesis**

Type A thymoma has been postulated to derive from the normal thymic medullary epithelial cells [1403, 1404]. Evidence in support of this postulate include their similar immunohistochemical expressions of CD20, cytokeratins, metallothionein, and PE-35 as well as the relative paucity of immature T cells [354, 798, 1086, 1087, 1095, 1452, 1538, 1631].

![Fig. 3.07 Type A thymoma. A Type A thymoma cells can form cysts of various size. B Type A thymoma cells with haemangiopericytoma-like appearance. C Rosettes without a lumen. D Anaplastic malignant cells arising in type A thymoma.](image-url)
Somatic genetics

Type A thymoma has been found to have t(15;22)(p11;q11) or a partial loss of the short arm of chromosome 6. Consistent loss of heterozygosity has been found only in the region 6p23.3-25.3, which is common to type A and B3 thymomas and squamous cell thymic carcinomas. Unlike type B3 thymomas and squamous cell thymic carcinoma, no aberrations in the APC, RB1, and TP53 gene loci or in regions 3p22-24.2 and 8q11.21-23 are found in type A thymoma, which could be the genetic basis for its generally benign clinical course.

Prognosis and predictive factors

The overall survival of patients with type A thymoma has been reported to reach 100% at 5 years and 10 years, even though approximately 20% of them have stage II or stage III tumours. Generally, type A thymoma is regarded as a benign tumour without having a risk of recurrence if the tumour can be completely removed surgically. However, exceptional case reports of local recurrence or distant metastasis have been documented. Rarely, type A thymoma can undergo malignant transformation into thymic carcinoma. The association with myasthenia gravis has been reported to have either a better or no effect on prognosis.
Type AB thymoma

**Definition**
Type AB thymoma is an organotypical thymic epithelial neoplasm composed of a mixture of a lymphocyte-poor type A thymoma component and a more lymphocyte-rich type B-like component. The tumour cells in the type B-like component are composed predominantly of small polygonal epithelial cells with small round, oval or spindle pale nuclei showing dispersed chromatin and inconspicuous nucleoli, and are smaller and paler than those of B1 or B2 thymomas. Lymphocytes are more numerous than in the type A component, but may be less numerous than in B1 thymomas. There is a great variation in the proportion of the two components, and while usually both components are present in most sections, either type A or type B areas can be scanty.

**ICD-O code** 8582/1

**Synonym**
Mixed thymoma

**Epidemiology**
Type AB thymoma is either the most or the second most common type of thymoma and accounts for 15-43% of all thymomas (341,541,1095,1510,1511,1538,1540,1631,1808). The patients’ ages range from 29-82 years with a slightly younger mean age of 55 years than type A thymoma (1538,1540,1630). A slight male predominance has been noted in most reports (1511,1538,1540,1630).

**Clinical features**
The clinical presentation is similar to that of type A thymoma. Approximately 14% of type AB thymomas are associated with myasthenia gravis (341,541,1510,1511,1538,1540,1630,1808). Paraneoplastic pure red cell aplasia has also been reported (1096). Other tumours manifest by local symptoms or can be asymptomatic and are found incidentally upon imaging examination.

**Macroscopy**
Grossly, type AB thymoma is usually encapsulated and the cut surface shows multiple tan coloured nodules of various size separated by white fibrous bands. Average tumour size is 7.7 cm.

**Tumour spread and staging**
The majority of type AB thymoma (71.7%) occur in the anterior mediastinum as Masaoka stage I followed by stage II (21.6%) and stage III (5.6%) (341,437,1404,1510,1511,1539,1540,1691). Rare cases of stage IV type AB thymoma (1.1%) have been reported (1325,1404,1510,1539,1691).

**Histopathology**
Histologically, type AB thymoma shows a nodular growth pattern with diffuse areas and is composed of a variable mixture of a lymphocyte-poor type A thymoma component and a more lymphocyte-rich type B component. All histological features of type A thymoma can be seen in the type A component. However, the type B areas are distinctive and different from either B1, B2, or B3 thymoma. The tumour cells in the type B component are composed predominantly of small polygonal epithelial cells with small round, oval or spindle pale nuclei showing dispersed chromatin and inconspicuous nucleoli (1086,1403,1691,1808). The type A component in the latter areas may form bundles of extremely elongated fibroblast-like spindle cells. Type AB thymomas associated with myasthenia gravis have been reported (1096). Other tumours manifest by local symptoms or can be asymptomatic and are found incidentally upon imaging examination.

**Fig. 3.11** A Macroscopic appearance of a type AB thymoma showing multiple nodules separated by fibrous bands. **B** Type AB thymoma composed of lymphocyte-associated type B nodules and diffuse lymphocyte-poor type A areas.

**Fig. 3.12** Type AB thymoma. **A** Medullary differentiation in type B component. **B** The lymphocytes in the focus of medullary differentiation are distinctively CD5+ T cells.
cles are absent. There is a great variation in the proportion of both components and in particular, type A areas can be extremely scanty to almost absent [1086,1403,1691]. Unlike type A thymoma areas, type B areas show reticulin fibers around tumour nodules rather than around individual tumour cells.

**Immunophenotype**
The patterns of cytokeratin (CK) expression of type AB thymoma are essentially similar to those of type A thymoma, except that the epithelial cells in type B areas are usually CK14+ [1086]. CD20+ tumour cells can be seen in both type A and type B areas, and the associated lymphocytes are T cells positive for CD3 and CD5, including varying proportions of CD1a+ CD99+ immature T cells. The lymphocytes in the foci of medullary differentiation are distinctively CD5+ T cells. B cells are usually absent. The fibroblast-like elongated type A cells are strongly positive for vimentin and EMA and may show weak CK staining. There is no expression of CD5. BCL-2 and CD57 are variably and usually weakly expressed [227,1631,1808,1872,1981]. TP53 protein and Ki-67 are extremely low or absent [1539,1872,1980,1981]. In contrast to type A thymoma areas, the type B areas show less production of laminin and type IV collagen.

**Histogenesis**
The cellular origin of the type A component, like in type A thymoma, has been postulated to derive from or differentiate towards thymic medullary epithelial cells [798,1087,1403,1404]. The type B component ultrastructurally resembles epithelial cells at the corticomedullary junction [1017], but is similar to thymic subcapsular epithelial cells in expression of CK14 [1086]; thus its normal counterpart is uncertain.

**Somatic genetics**
Deletion of chromosome 6 with or without formation of ring chromosome 6 has been found in type AB thymoma [437,1043,1076,2065]. In addition, complex multiple chromosomal aberrations have been described in individual cases [699]. Loss of heterozygosity at 5q21-22 (APC), as seen in type B thymoma, has been detected in a minority of type AB thymoma [897].

**Prognosis and predictive factors**
The overall survival rate of patients with type AB thymoma is 80-100% at 5 years and 10 years [1403,1511]. Although type AB thymomas may present as stage II or stage III tumours, they can be usually cured by radical surgery [1095,1403,1404]. Therefore, they are generally regarded as clinically benign tumours [1403,1404]. Recurrence and metastasis are exceptionally rare [1043,1403,1538]. An association with myasthenia gravis has been reported to have either a better or no effect on prognosis [318,1511,1630].
Type B1 thymoma

Definition
Type B1 thymoma is a tumour of thymic epithelial cells with a histological appearance practically indistinguishable from the normal thymus, composed predominantly of areas resembling cortex with epithelial cells scattered in a prominent population of immature lymphocytes, and areas of mediullary differentiation, with or without Hassall's corpuscles, similar to normal thymic medulla.

ICD-O code
8583/1

Synonyms
Lymphocyte-rich thymoma; lymphocytic thymoma; organoid thymoma; predominantly cortical thymoma

Epidemiology
B1 thymoma is a relatively rare tumour of the adult age (mean of 41-47 years) with no significant difference in the distribution of genders. B1 thymoma corresponds to 6% to 17% of all thymomas.

Localization
B1 thymoma arises in the anterosuperior mediastinum, but rare localizations are described in the neck, pleura or lung.

Clinical features
B1 thymoma is often diagnosed because of associated immunological diseases such as myasthenia gravis, hypogammaglobulinemia and pure red cell aplasia. It can be detected by X-ray, CT or MRI imaging as an enlarged mediastinal area or mass.

Macroscopy
B1 thymoma is usually a well-defined or encapsulated greyish mass. Thick fibrous capsule and septa can be present, as well as cystic spaces or small haemorrhagic and necrotic areas.

Tumour spread and staging
B1 thymoma is considered to have a low-grade malignant potential being completely encapsulated (stage I) in about 53-58% of the cases or invading only the mediastinal fat (stage II) in another 24-27% of the cases. Less frequently it can invade the pleura, pericardium, great vessels or adjacent organs; metastases are exceedingly rare.

Histopathology
Type B1 thymoma has also been called predominantly cortical, organoid or lymphocyte-rich thymoma because it contains predominantly expanded areas closely resembling the normal functional thymic cortex. The neoplastic epithelial cells are scant, small, with very little atypia, and are surrounded by non-neoplastic T lymphocytes.

Differential diagnosis
Type B1 thymoma is distinguishable from the normal non-involuted thymus mainly based on architectural differences, including the large excess of cortical areas compared to small areas resembling the thymic medulla.

Fig. 3.15 Type B1 thymoma. A CD1a staining highlights immature T-cells in the cortex-like areas. B CD20 staining highlights B-cells in the medullary areas.
Immunophenotype
The neoplastic epithelial cells express a cytokeratin pattern similar to normal cortical epithelial cells (CD19 diffuse, CK7, CK14, CK18 focal positivity, CK20, CD5, CD20 and CD70 negative) (354, 851, 854, 1086) and have a low fraction of growth (1290). Admixed cortical T lymphocytes are CD1a+, CD4+, CD8+, CD5+, CD99+ and TdT+, with high proliferation rate, whereas lymphocytes in medullary islands are mostly mature T cells: CD3+, CD5+, CD1a−, CD99−, TdT− (355).

Histogenesis
The postulated cell of origin is a thymic epithelial cell capable of differentiating towards both cortical and medullary type.

Prognosis and predictive factors
B1 thymoma is slightly more aggressive than A and AB thymomas, but less malignant than B2, B3 thymomas and thymic carcinomas. In B1 thymoma, complete surgical resection is possible in 91-94% of the cases (318,1511), with less than 10% of recurrences (318,1511). Actuarial 10-year survival rates are more than 90% due to the frequent stage I or II presentation (318,341,1511). Staging is the most important prognostic indicator, whereas age, gender and myasthenia gravis are not significant prognostic parameters (318,341,1511,1631).

Fig. 3.16 Type B1 thymoma. A Medullary island (MI) showing Hassall corpuscles. The abnormal localization of MI adjacent to septa or the tumour capsule is very typical. B High-power of cortex-like areas in B1 thymoma showing a vast majority of lymphoid cells compared to few inconspicuous epithelial cells characterized by vesicular, clear nuclei and distinct but small nucleoli. C Small medullary island (light), that is devoid of Hassall corpuscles is surrounded by a predominant, cortex-like component rich in immature T-cells (dark). This pattern has been the rationale for labelling B1 thymoma as “organoid thymoma”. D Cytokeratin 19 staining labels a network of epithelial cells which is more delicate than in B2 thymoma (compare with fig. 3.18D)
Type B2 thymoma

**Definition**
Type B2 thymoma is an organotypical thymic epithelial neoplasm composed of large, polygonal tumour cells that are arranged in a loose network and exhibit large vesicular nuclei with prominent large nucleoli, closely resembling the predominant epithelial cells of the normal thymic cortex. A background population of immature T cells is always present and usually outnumbers the neoplastic epithelial cells.

**ICD-O code** 8584/1

**Synonyms**
Cortical thymoma; lymphocytic thymoma (obsolete); mixed lymphocytic and epithelial thymoma (obsolete)

**Epidemiology**
Type B2 thymoma accounts for 18-42% of all thymomas (318,341,776,1016,1540,1630,1631,1967). Differences in the prevalences of type B2 thymomas among different institutions reflect the strong correlation with myasthenia gravis (MG) rather than real demographic differences. Patients´ ages range from 13-79 years, with a mean of 47-50 years (318,1016,1631). There is no consistent gender predominance (341,1016,1511,1630).

**Localization**
B2 thymomas are almost always located in the anterior mediastinum. Ectopic cases are on record, including cases with extensive pleural involvement ("pleural thymoma"). Similarly to all types of thymoma, they may arise ectopically in the head and neck region, pleura or lung (632,1238,1500).

**Clinical features**
The most frequent manifestations are symptoms of MG (30-82% of cases) (318,341,1016,1511,1630). Local symptoms (chest pain, dyspnoea, cough) occur in about 20% of cases. Rare complications are superior vena cava syndrome (1651), pure red cell aplasia (1088,1651), hypogammaglobulinaemia (Good syndrome) (987) and other autoimmune phenomena.

**Macroscopy**
Grossly, type B2 thymomas are encapsulated or vaguely circumscribed and show a mean diameter of 6.3 cm (318,1630). They can invade mediastinal fat or adjacent organs. The cut surface is soft or firm and exhibits tan-coloured nodules separated by white fibrous septae. There may be cystic changes, haemorrhage, and fibrosis.

**Tumour spread and staging**
The majority of type B2 thymomas occur in the anterior mediastinum as Masaoka stage I (10-48%), stage II (13-53%) or stage III (19-49%) tumours. Metastatic stage IV B2 thymomas are less common (mean 8.9%) (318,341,1511,1630), and distant metastases (stage IVB) are rare (up to 3%) (1511).

**Histopathology**
There are usually large, coarse lobules of tumour with delicate septa, somewhat resembling the lobular architecture of the normal thymic cortex. Neoplastic cells are large and polygonal, and their large nuclei display an open chromatin pattern with prominent central nucleoli, similar to the appearance of normal cortical thymic epithelial cells. The neoplastic epithelial cells form a delicate loose network, forming palisades around perivascular spaces and along septa; large, confluent sheets of tumour cells are not a usual feature, but may occur. If such foci are present, they should be examined closely to make sure that the tumour cells are of B2 and not B3 type. Small epidermoid foci resembling abortive Hassall’s corpuscles (1016) may occur in up to 25% of cases, but medullary islands are missing or inconspicuous, and typical Hassall’s corpuscles are exceptional find-

**Fig. 3.17** Type B2 thymoma. A Lobular growth pattern and invasion into mediastinal fat (Masaoka stage II) B Medium power of B2 thymoma resembling B1 in terms of the very high number of lymphoid cells. However, the nuclei and nucleoli are larger and more conspicuous here than in B1 thymoma. C Medium power showing a relatively high number of large tumour cells among a slightly more numerous lymphoid component. Note inconspicuous cytoplasm but prominent large nuclei of tumour cells with prominent medullary-sized nucleoli. D High magnification of the former illustration.
Tumours of the thymus - Thymomas

Tumour cells are usually outnumbered by non-neoplastic lymphocytes. Areas of B3 thymoma occur in association with B2 thymoma in 17-29% of the cases (341,541). These are recognized as lymphocyte-poor areas in which the tumour cells are often smaller, with more nuclear irregularity, less conspicuous nucleoli, and distinct cell borders. If any component is of B3 type, it should be classified as combined B2/B3 thymoma.

Lymphoid follicles in perivascular spaces or septa are more frequent in MG-associated cases. Regressive changes, either spontaneous or induced by immunosuppressive treatment, include necrosis and lymphocyte depletion followed by collapse of the epithelial network and infiltrates of histiocytes and lipidized macrophages. A decreased tumour cell size is often apparent in condensed or sponge-like postnecrotic areas.

**Immunophenotype**

Immunophenotypically, neoplastic cells are cytokeratin (CK) 19+ (100%), CK5/6+ (90%), CK7+ (80%), CK20-, EMA-; antibodies AE1/3, Cam5.2 and Leu7 (anti-CD57) are almost always reactive (367,1016,1086,1631). CD5, CD20, CD70 are not expressed by epithelial cells of B2 thymoma (354, 851,854). Intraepithelial lymphocytes are predominantly immature T-cells: CD1a+, CD4+, CD8+, CD5+, CD99+, TdT+ with a high Ki67 index of 70-90%. Lymphocytes in rare medullary islands are mostly mature T-cells: CD3+, CD5+, CD1a-, CD99-, TdT-, and significantly less proliferative (327,355,1016,1631).

**Differential diagnosis**

B1 thymoma is also lymphocyte-rich but epithelial cells are inconspicuous, smaller, and less numerous than in B2 thymomas. In addition, the nuclei and nucleoli are smaller and the medullary islands are more prominent than in B2 thymomas. B3 thymoma, in contrast to B2 thymoma, is relatively lymphocyte-poor. Neoplastic epithelial cells form confluent sheets and solid areas with a small but distinctive population of intraepithelial immature T-cells. The neoplastic cells are usually slightly smaller than those of B2 thymoma, with irregular nuclear membranes, smaller nucleoli, nuclear grooves, and less vesicular chromatin. T-lymphoblastic lymphoma (T-LBL) may exhibit the same immunophenotype and proliferative activity of lymphoid cells as those of type B1 and B2 thymomas. However, the

---

**Fig. 3.18** Type B2 thymoma. **A** Lymphoid follicle with prominent subcapsular germinal centre, associated with myasthenia gravis. **B** Type B2 thymoma after massive corticosteroid treatment: paucity of lymphoid cells, shrinkage of tumour cell nuclei and prominent infiltration of macrophages. **C** Perivascular space with prominent palisading of elongated large tumour cells. High number of lymphoid cells in the perivascular space (center) and in an intraepithelial position (periphery of image). **D** Cytokeratin 19 immunoreactivity of neoplastic epithelial cells highlights the lobular growth pattern of B2 thymoma.
Type B2 thymoma

epithelial network is destroyed in T-LBL, and lymphoblasts usually infiltrate beyond the epithelial compartment into thymic septa and mediastinal fat. Very high CDK6-expression is a distinguishing feature of T-LBL [355].

Histogenesis

The postulated cell of origin is a thymic epithelial cell capable of differentiating towards cortical-type epithelial cells.

Somatic genetics

Recurrent genetic aberrations have not been reported. More than 80% of B2 thymomas are aneuploid [743]. In a single case with marked anaplasia and giant cell formation, a t(1;8)(p13;p11) translocation has been reported [1722].

Prognostic and predictive factors

Type B2 thymoma is a tumour of moderate malignancy, with higher malignant potential than B1 thymoma, but appears to be slightly less aggressive than type B3 thymoma [1016,1511,1630]. It is often invasive, thus non-resectable at presentation in 5-15% of cases. Recurrences, even after complete resection, are reported in 5-9%, and metastases in up to 11% [341,1511,1630]. Recurrences typically occur after 1-7 years, but are compatible with long-term survival (>10 years) [1510]. The most relevant prognostic factors are tumour stage and resectability, while gender, age, and MG have no adverse effect on survival [318,341,1645]. Reported 10 year survival rates range between 50-100% [341,1511,1540,1630].

Fig. 3.19 Type B2 thymoma. A Relatively high number of tumour cells with medium-sized nucleoli among a majority of small lymphocytes. B Differential diagnosis B2 thymoma versus lymphoblastic lymphoma (T-LBL): CD1a expression in a rare initial T-LBL that is in a pre-infiltrative phase without infiltration of thymic septum (top of image). C CD1a-positive immature T-cells between B2 thymoma tumour cells with large clear nuclei and conspicuous nucleoli. D High Ki67 index. Note the non-infiltrated septum at top of image.

Fig. 3.20 Thymoma with anaplasia. A Anaplastic giant epithelial cells in a B2 thymoma with few intraepithelial lymphocytes. B Anaplastic giant cells are cytokeratin 19+ but not histiocytes. Note unusual down-regulation of cytokeratin 19 expression in many other neoplastic epithelial cells. C Anaplastic thymoma harbouring a significant population of CD1a+ immature T-cells like other thymomas but in contrast to thymic carcinomas. D Ki-67 immunohistochemistry showing proliferations of anaplastic giant cells.

Fig. 3.21 Anaplastic thymoma (B2 thymoma with anaplasia). Metaphase with t(1;8)(p13;p11) translocation. G-banded karyotype showing 46, XY, t(1;8)(p13;p11).
Type B3 thymoma

Definition
Type B3 thymoma is an organotypic thymic epithelial tumour predominantly composed of medium-sized round or polygonal cells with slight atypia. The epithelial cells are mixed with a minor component of intraepithelial lymphocytes, resulting in a sheet-like growth of epithelial cells.

ICD-O code
8585/1

Synonyms
Well-differentiated thymic carcinoma (ICD-O code 8585/3); epithelial thymoma; squamoid thymoma

Epidemiology
Type B3 thymoma accounts for 7-25% of all thymomas [318,341,1016,1540,1630]. Patients’ age ranges from 14-78 years, with a mean age of 45-50 years [318,1016,1511]. There is no consistent sex predominance [341,1016,1511,1630].

Clinical features
The most frequent manifestations are symptoms of myasthenia gravis (30-77% of cases) [318,341,1016,1511,1630]. Local symptoms like chest pain, dyspnoea or cough are common, while superior vena cava syndrome [1651], pure red cell aplasia [1088,1651], hypogammaglobulinaemia (Good syndrome) [987] or other autoimmune phenomena are rare.

Macroscopy
Grossly, type B3 thymomas are usually not encapsulated but show a vaguely infiltrative border with extension into mediastinal fat or adjacent organs. Diameters range from 2-13 cm (mean: 7.6 cm) [318,1016,1630]. The cut surface is typically firm and exhibits grey to white nodules separated by white fibrous septa. Soft yellow or red foci, cyst formation or hard calcified regions indicate regressive changes that are particularly frequent among large and, paradoxically, small (<3 cm), encapsulated or sclerotic type B3 thymomas [1085].

Tumour spread and staging
The majority of type B3 thymomas occurs in the anterior mediastinum as Masaoka stage II (15-38%) or stage III tumours (38-66%), while stage I cases are rare (mean: 4.2%) [318,341,1016,1511,1540]. Stage IV type B3 thymomas, comprising cases with either pleural spread (stage IVA) or distant metastases (stage IVB), occur in 6-26% (mean: 15%) [318,341,1016,1511,1630]. Distant metastases have been reported in up to 7% of cases [1511] and preferentially involved the same organs as in type B2 thymomas: lung, liver, bone and soft tissues.

Histopathology
Histologically, tumour cells form lobules that are separated by thick fibrous and hyalinized septa. A major diagnostic criterion is the paucity of intraepithelial lymphocytes, resulting in the formation of tumour cell sheets with a vaguely solid or epidermoid appearance. Intercellular bridges are, however, not a feature of B3 thymoma. In the majority of cases, tumour cells are polygonal, medium-sized, and the round or elongated nuclei are often folded or grooved and characteristically smaller with less prominent nucleoli than in B2 thymomas. Palisades around perivascular spaces and along septa are often conspicuous. While medullary islands are usually absent, small foci of keratinization mimicking Hassall corpuscles may be present.

Variants
In a minority of cases, slightly more atypical, enlarged and hyperchromatic nuclei occur focally. Other rare variants show either polygonal cells with nuclei and nucleoli more similar to those in B2 thymomas (large cell variant) or partial clear cell changes with focal loss of interepithelial lymphocytes. Focal or extensive spindle cell formation may also occur.

Fig. 3.22 Type B3 thymoma. CT scan showing a well circumscribed tumour in the anterior mediastinum

Fig. 3.23 Type B3 thymoma with invasion of pleura and pericardium.

Fig. 3.24 Macroscopy of B3 thymoma (left) and remnant thymus (right). The cut surface of the tumour is white, lobulated and shows infiltration into the surrounding mediastinal fat. Focal regressive changes just left from the tumour centre.
None of these variants has been shown to affect the biological behaviour of type B3 thymomas. Combined thymomas exhibiting B2 and B3 areas are common (17-29%) \cite{341,541}, while tumours combining features of type B3 thymoma and thymic carcino-
moma are rare (3\%) \cite{341}.
As in B2 thymomas, lymphoid follicles inside septa or perivascular spaces may occur particularly in myasthenia gravis-
associated cases. Steroid treatment may produce a sponge-like appearance and accumulation of foam cells in intraepithe-
lial microcysts \cite{1016}. Anaplasia can occur in type B3 thymomas: a small
group of tumours show a high degree of atypia with the maintenance of organ-
otypical features that is characteristic of thymomas. “B3 Thymoma with anaplasia” is the suggested diagnostic ter-
minalogy.

**Immunophenotype**
The epithelial cells are positive for cytoker-
eratin (CK) 19, CK5/6, CK7, CK10, CK 8, as well as for AE1/3 and Leu7 (anti-
CD57), while CK20 is not expressed
\cite{367,1016,1086,1631}. In contrast to
type B2 thymomas, focal EMA positivity
is a characteristic feature. CD5, CD20, CD70 \cite{354,851,854} and TTF1 are not
expressed in epithelial cells. Most intraepithelial lymphocytes are
immature T-cells: CD1a+, CD4+, CD8+, CD5+, CD99+ and TdT+.

**Differential diagnosis**
B2 thymoma, in contrast to B3 thymoma,
is lymphocyte-rich. Neoplastic epithelial
cells are scattered among lymphocytes
and do not form confluent sheets or
extensive solid areas. B2 thymomas do
not express epithelial membrane antigen
(EMA). 
Low-grade squamous cell carcinoma of
the thymus shows more pronounced epi-
dermoid differentiation, usually with read,
ily detectable intercellular bridges. 
Significant numbers of immature intraep-
ithelial lymphocytes are absent.
Type A thymoma may resemble the spin-
dle cell variant of B3 thymoma. In type A
thymoma, there is usually a significant reticulin network around individual
tumour cells, the degree of atypia is
lower, and perivascular spaces with
epithelial palisades are absent.

**Histogenesis**
The postulated cell of origin is a thymic
epithelial cell capable of differentiating
wards a less differentiated cortical-type
epithelial cell than in B2 thymoma.

**Somatic genetics**
In a series of 16 B3 thymomas investigat-
ed by comparative genomic hybridiza-
tion (CGH), all tumours showed genetic
imbalances. Recurrent genetic gains
were observed on chromosome 1q in
69\%, recurrent losses on chromosome 6
in 38\% of cases, and on chromosome
13q in 31\% \cite{2238}. In microsatellite
analysis, two major pathways in the
tumorigenesis of B3 thymoma were
described, one characterized by losses
of 6q (6q23.3-q25.3), the other by losses
of chromosome 3p (3p22-p24.2; 3p14.2,
FHIT locus), 5q (5q21, APC locus), 13q
(13q14, RB1 locus) and 17p (17p13,
TP53 locus) \cite{896,2242}. Virtually 100\% of
B3 thymomas are aneuploid by DNA
cytometry \cite{743}.

**Prognosis and predictive factors**
B3 thymoma is a tumour of intermediate
malignancy. It is almost always invasive,
shows frequent local recurrences (15-17% of cases) \( \{1016,1630\} \), is often unresectable at presentation (17-47%) \( \{318,1511,1630\} \) and metastasizes in up to 20% of cases \( \{341,1511\} \). Recurrences typically occur after 1-6 years, but late recurrences (after 14 years) have been reported \( \{1016\} \). Some authors \( \{1016,1511,1630\} \) but not others \( \{341,1540\} \) found B3 thymomas slightly more aggressive than B2 thymomas in terms of survival. The most relevant prognostic factors are tumour stage and resectability, while gender, age, and MG status have no adverse effect on survival \( \{318,341,1645\} \). Reported 10 year survival rates range between 50-70% \( \{341,1511,1540,1630\} \).
Micronodular thymoma with lymphoid stroma

Definition
Micronodular thymoma (MNT) is an organotypic thymic epithelial tumour characterized by multiple, discrete epithelial nodules separated by an abundant lymphocytic stroma that usually contains prominent germinal centres. The epithelial component is composed of bland, oval to spindle-shaped cells with few intraepithelial lymphocytes. The epithelial component is similar to type A thymomas.

ICD-O code 8580/1

Synonym
Micronodular thymoma with lymphoid B-cell hyperplasia

Epidemiology
MNT is a rare entity accounting for only about 1-5% of all thymomas. The age at diagnosis ranged between 45–95 years [1914]. While the mean age in a published series was 58 years [1914], in a recent unpublished series of 33 cases it was 70 years. There was no sex predilection.

Localization
All published cases occurred in the anterior mediastinum. We have observed a single ectopic MNT in the lateral cervical region [1294].

Clinical features
Clinical features usually are related to the size and local extention of the tumour. With very few exceptions (<5%) [1538], MNT is not associated with paraneoplastic myasthenia gravis. Other autoimmune phenomena that are common in other thymoma types have not been reported.

Macroscopy
Size of MNT varies between 3-15 cm in diameter. Cystic tumour areas of variable size are common macroscopic findings.

Tumour spread and staging
MNT is encapsulated (>90%) or minimally invasive [1914]. Local excision has been unproblematic and curative [1914]. In our own series, two advanced tumours with infiltration of the pericardium and pleura, respectively, were encountered. No tumour-associated deaths have been reported.

Histopathology
Microscopically, MNT is characterized by multiple, discrete or focally confluent epithelial nodules separated by an abundant lymphocytic stroma that may contain follicles with prominent germinal centres surrounded by mantle and enlarged marginal zones. There is a variable number of mature plasma cells. The epithelial nodules are composed of slender or plump spindle cells with bland looking oval nuclei and inconspicuous nucleoli. Rosette formation of epithelial cells may be seen. Nodules contain few interspersed lymphocytes. There are no Hassall corpuscles or perivascular spaces. Mitotic activity is absent or minimal. Micro- and macrocystic areas, particularly in subcapsular localization, are common.

Immunohistochemistry
The epithelial component in MNT stains positive for cytokeratins 5/6 and 19. CAM5.2 and CD57 are positive in about 60% each. CD20 is generally not expressed in the epithelium of MNT [1538], in contrast to the epithelial component in about half of conventional type A and AB thymomas. Cysts in MNT stain positive for CK 5/6, 7, 8, 19, EMA, and CAM5.2. The majority of the lymphocytes in MNT are CD20+ B-cells, but mature CD3+CD5+ T cells can outnumber B cells focally. Moreover, immature, Ki67+, CD1a+, CD10+, TdT+ and CD99+ thymocytes are almost always present.
restricted to a narrow band surrounding the epithelial cell nodules, while intraepithelial lymphocytes are scarce. B-cells frequently form follicles with or without germinal centres with a well developed network of follicular dendritic cells and a population of CD57+ T-cells. Germinal centre B-cells are CD10+ and bcl-2-. Mantle zones consist of IgD+ B-cells, while marginal zones are IgD- and CD23-. Plasma cells are usually polyclonal. In a recent series of 18 MNTs, expansion of monoclonal B cell populations was observed in 33% of cases, with half of them showing features of low grade lymphoma (MALT type and follicular lymphoma) (P. Ströbel et al., submitted).

**Differential diagnosis**

MNT should be differentiated from conventional type AB thymomas, which in rare cases may also contain single lymphoid follicles. In contrast to type AB and other organotypic thymomas, the lymphocytic-rich areas in MNT do not contain epithelium. Of note, MNT may rarely (10%) occur together with an otherwise typical type A and AB thymoma (1538,1630). Single combinations with B2 thymoma have been observed (452).

**Histogenesis**

A medullary epithelial cell origin has been postulated (452).

**Prognosis and predictive factors**

There have been no reports on recurrences, metastasis or tumour-related deaths.
Metaplastic thymoma

Definition
Metaplastic thymoma is a circumscribed tumour of the thymus in which anastomosing islands of epithelial cells are intermingled with bland-looking spindle cells.

ICD-O code 8580/1

Synonyms
Metaplastic thymoma has been reported in the literature under the designations “thymoma with pseudosarcomatous stroma”, “low grade metaplastic carcinoma” and “biphasic thymoma, mixed polygonal and spindle cell type” (1808,1919,2210).

Epidemiology
This rare tumour occurs in adult patients, with a median age of 53 years and mean age of 50.9 years. There is male predominance (M:F ratio 3:1) (1485,1919,2210,2211).

Localization
The tumour has not been described outside the thymus.

Clinical features
Most patients are asymptomatic, being incidentally found to have an anterior mediastinal mass, while some present with cough. None of the patients have myasthenia gravis or other paraneoplastic syndromes.

Macroscopy
The tumour is well circumscribed to encapsulated, but can exhibit invasive buds. The cut surfaces show homogeneous, rubbery, grey-white tumour. The reported maximum dimensions of the tumours range from 6-16 cm.

Tumour spread and staging
The Masaoka stage distribution at presentation is as follows: 75% stage I, 17% stage II, 8% stage III (1485,1919,2210,2211). Occasional tumours can show infiltration of adjacent tissues (2210) and may recur (2211).

Histopathology
The tumour is well circumscribed, sometimes with a narrow rim of residual thymic tissue incorporated in its peripheral portion. Occasional cases can show invasion of the surrounding tissues. In contrast to conventional thymomas, it does not show a lobulated growth pattern. Typically, the tumour exhibits a biphasic architecture comprising epithelial islands intertwining with bundles of delicate spindle cells. The two components are present in highly variable proportions from area to area of a single tumour and from case to case. The epithelial component takes the form of anastomosing islands to broad trabeculae, and often exhibits a squamoid quality or whorled configuration. The constituent cells are polygonal, ovoid or plump spindle, with oval vesicular nuclei, small distinct nucleoli and a moderate

Fig. 3.32 Metaplastic thymoma. A The tumour is well circumscribed. A thin rim of residual thymic tissue is incorporated into the peripheral portion. B Anastomosing rounded islands of epithelial cells are disposed among spindle cells. C Broad trabeculae of epithelium are separated by narrow zones of spindle cells. D A storiform growth pattern is seen.
amount of lightly eosinophilic cytoplasm. Some cells can exhibit large empty-looking nuclei, large hyperchromatic nuclei or nuclear pseudoinclusions. Despite the nuclear atypia, mitotic figures are rare. Twig-like hyaline or sclerotic material may be abundant around and within the epithelial islands. The spindle cells show a short fascicular or storiform growth pattern. They are often separated by small amounts of loose tissue or delicate collagen fibrils. They are always bland-looking and often mitotically inactive, with fine nuclear chromatin and slender bipolar cell processes. They may show sharp delineation or gradual merging with the epithelial islands. In the rare recurrences, the spindle cells can show nuclear atypia and mitotic activity, associated with acquisition of additional genetic aberrations [2211]. Lymphocytes are usually sparse, but some cases can exhibit a light infiltrate of small lymphocytes and plasma cells. There can be scattered foci of stromal calcification. While both the epithelial and spindle cell components are readily recognizable in most cases, some cases show marked predominance of one component to the exclusion of the other in some or most areas. A diagnosis of such cases can be difficult without extensive sampling to identify the typical biphasic pattern.

Immunophenotype
Epithelial cells show strong staining for cytokeratin and variable staining for epithelial membrane antigen, and they do not show cell membrane staining for CD5. The spindle cells show focal weak or negative staining for cytokeratin and epithelial membrane antigen, positive staining for vimentin, and inconsistent staining for actin. CD20 is negative. Proliferative fraction (Ki67 index) is low (<5%). The T lymphocytes within the tumour proper usually exhibit a mature immunophenotype (TdT negative). Ultrastructurally, the spindle cells may or may not show epithelial characteristics such as tonofilaments and cell junctions [1485,1919].

Differential diagnosis
It is most important not to mistake metaplastic thymoma for the vastly more aggressive sarcomatoid carcinoma (carcinosarcoma). The latter often shows prominent coagulative necrosis, significant atypia in the spindle cells and readily identified mitotic figures.

Histogenesis
Biphasic metaplastic thymoma is a tumour of thymic epithelial cells. The spindle cell component probably arises as a metaplastic phenomenon, rather than a stromal reaction in view of its marked predominance and presence of genetic aberrations in a recurrent case. Tumour circumscription, relatively bland cytology and usually good prognosis suggest that the tumour is benign. However, lack of association with myasthenia gravis, tumour lobulation and perivascular spaces suggest some relation to thymic carcinoma. Molecular studies, however, favour interpretation of this tumour as a thymoma.

Somatic genetics
Comparative genomic hybridization and microsatellite studies on a limited number of cases have shown no or few genetic alterations, suggesting a closer relationship with type A or type AB thymoma than with thymic carcinoma or type B3 thymoma. Tumour recurrence is apparently associated with acquisition of multiple genetic aberrations.

Prognosis and predictive factors
Among 11 patients with follow-up information, 10 have remained well after surgical excision at 1.5-20 years (median 5 years) [1485,1919,2210,2211]. One patient developed local recurrence at 14 months, and died at 6 years [2211].
Rare thymomas

**Microscopic thymoma**

ICD-O code 8580/1

Microscopic thymoma is the term applied to usually multifocal epithelial proliferations (<1 mm in diameter) that preferentially occur in myasthenia gravis-associated thymuses (15% of cases) without a macroscopically evident tumour (1580). Respective epithelial nodules occur at lower frequency in 4% of non-myasthenic control thymuses (1626). Microscopic thymoma may arise in cortical or medullary thymic compartments (1580). Histologically, it shows marked heterogeneity and can be composed of bland-looking or more pleomorphic, polygonal or plump spindle cells, usually without intraepithelial immature T-cells. Though microscopic thymoma may occur adjacent to conventional thymoma, its role as a precursor lesion of “macroscopic thymoma” is unresolved (1580).

**Sclerosing thymoma**

ICD-O code 8580/1

This is an exceedingly rare tumour (<1%) exhibiting the features of a conventional thymoma in terms of epithelial cell morphology and lymphocyte content, but with exuberant collagen-rich stroma. While some cases were small (<3 cm) and probably resulted from tumour regression (1085), we observed a well circumscribed B2-like thymoma with a diameter of 18 cm exhibiting a collagenous, partially hyalinized stroma harbouring scant and bland looking fibroblasts. There was neither necrosis nor haemorrhage, suggesting that the stroma resulted from a fibrogenic stimulus delivered by thymoma epithelium. The 18-year-old male, non-myasthenic patient remained free of complications after complete resection.

**Lipofibroadenoma**

Lipofibroadenoma of the thymus is a recently described neoplasm that occurred adjacent to a conventional type B1 thymoma in a patient with pure red cell aplasia (1096). The tumour resembles fibroadenoma of the breast, taking the paucity of lymphocytes and the extended narrow strands of epithelial cells into account. With respect to the predominance of stroma over the epithelial component (including rare Hassall corpuscles), the tumour shares morphological features with thymolipoma. As with thymolipoma, it is unknown whether the epithelial, the fibrolipomatous or both components are neoplastic or whether the “lesion” is a hamartoma.

![Fig. 3.36 Microscopic thymoma. Small nodule of oval and spindle epithelial cells in an atrophic thymus. There are almost no intraepithelial lymphocytes.](image)

![Fig. 3.37 Sclerosing thymoma. A Higher magnification shows a residual B3 thymoma in the center of a sclerosing thymoma. B Cytokeratin 19 immunoreactivity of epithelial tumour cells resembling a B1 thymoma.](image)
Definition
Thymic squamous cell carcinoma is a type of thymic tumour with features of squamous cell carcinoma as seen in other organs, with or without clear-cut evidence of keratinization in routinely stained sections (1094,1691,1806,1808,1841,1924,2032,2143). In contrast to thymomas of the A and/or B categories, thymic carcinomas lack immature T-lymphocytes (632,1748).

ICD-O code 8070/3

Synonym
Epidermoid keratinizing and nonkeratinizing carcinoma.

Epidemiology
Thymic carcinomas are rare. The incidence of thymic carcinomas occurring in combination with a thymoma has been reportedly 10-20%. Squamous cell carcinoma is the most frequent subtype of thymic carcinoma, and the frequency is higher in Asia (90%) (1510,1808) than in the West (30%) (318,1094,1841,1924,2032,2143). Most cases occur at middle age, and the male to female ratio varies from 1 to 2.3 (1808).

Localization
Thymic squamous cell carcinoma exclusively presents as an anterior mediastinal tumour, and frequently invades the adjacent lung tissue.

Clinical features
The most frequent symptom is chest pain. Other symptoms are cough, fatigue, fever, anorexia, weight loss, and superior vena cava syndrome. There have been no reports on myasthenia gravis (MG) or pure red cell aplasia, but paraneoplastic polymyositis can occur. A few MG-associated thymomas have been reported to progress to thymic squamous cell carcinoma (1808). Thymic squamous cell carcinoma can be detected by imaging techniques. Cystic changes and calcium deposits are rare. A relatively larger size and the lack of septal or nodular structures within the tumour support the diagnosis of carcinoma rather than invasive thymoma (501,946).

Macroscopy
Squamous cell carcinomas usually lack encapsulation or internal fibrous septation that are common in thymomas. They are firm to hard with frequent foci of necrosis and haemorrhage.

Tumour spread and staging
Thymic squamous cell carcinomas frequently invade the lungs, pericardium, and major vessels. The most frequent sites of metastases are the lymph nodes (mediastinal, cervical, and axillary), followed by the bone, lung, liver and brain (1808).

Histopathology
There are two hallmarks for the diagnosis of thymic squamous cell carcinoma: the clear-cut cytological atypia in the large epithelial cells that are arranged in nests and cords, and the broad zone of fibrohyaline-stroma separating the tumour cell nests (1094,1806,1808,1841,1924,2143).

Most cases of thymic squamous cell carcinomas belong to Masaoka stage III and IV at the time of surgery.

Fig. 3.38  A Squamous cell carcinoma occurring in multilocular thymic cysts. Papillary growth of the tumour in a large and haemorrhagic cyst.  B Well differentiated squamous cell carcinoma, showing papillary growth in the cystic space and invasion of the underlying stroma.

Fig. 3.39 Immunohistochemistry of squamous cell carcinoma of the thymus.  A Diffuse immunostaining to CD70.  B CD5 is also expressed in nearly all neoplastic cells. Note the immunolabelling of lymphocytes in the stroma.  C Neuroendocrine differentiation in thymic squamous cell carcinoma. CD56-positive cells scattered in neoplastic cells.
Squamous cell carcinoma

A lobular growth pattern and some remnant perivascular spaces may be recognized. Lymphocytes, when present, are mature and usually admixed with plasma cells.

Squamous cell carcinoma is composed of large polyhedral cells arranged in nests and cords, and shows evidence of keratinization and/or intercellular bridges. The nuclei are vesicular or hyperchromatic, and nucleoli are usually readily apparent. Cytoplasm is eosinophilic. The number of mitotic figures is variable. Foci of spontaneous necrosis are frequently seen, as is the invasion of intratumoural blood vessels.

**Immunohistochemistry**

The epithelial cells of most thymic squamous cell carcinomas are immunoreactive to CD5, CD70 and CD117. Thymomas are negative to CD5 except for some cases of type B3. Squamous cell carcinomas of other organs are negative to CD5 and CD70, and thus both markers are quite useful to confirm the thymic origin of squamous cell carcinomas in the anterior mediastinum. However, tumour cells in nasopharyngeal carcinoma and Hodgkin lymphoma may be CD70+

Neuroendocrine markers (chromogranin, synaptophysin, GTP binding protein Go-alpha subunit, or CD56/NCAM) alone or in combination are positive in two-thirds of thymic squamous cell carcinomas in focal or dispersed distribution. Some of these neuroendocrine cells show positivity for alpha-subunit of human chorionic gonadotropin or ACTH.

**Differential diagnosis**

It is sometimes difficult to exclude the possibility of lung carcinoma showing a prominent extra-pulmonary growth. Palisading or radial arrangement of the cells at the borders of nests as often seen in squamous cell carcinoma of the lung and oesophagus, is not commonly observed. In addition, immunohistochemical evidence (CD5, CD70 and CD117 positivity) may support the thymic origin of the neoplastic squamous cells. Infiltration of immature T-cells (CD1a+, TdT+, CD99+) as seen in thymoma is not observed in thymic carcinomas. Well-differentiated squamous cell carcinoma may rarely occur in a thymic cyst. This type of carcinoma needs to be differentiated from the pseudopapillary growth found in the multilocular thymic cyst, and should be classified in a different category.

**Precursor lesions**

Some cases of thymic squamous cell carcinoma are thought to arise from pre-existing thymomas based on the observation of combined thymic epithelial tumours that harbour squamous cell carcinoma and conventional (usually B3) thymoma components. The two components may be widely separated, or observed in admixture or in a gradual transition within the same tumour mass.

**Histogenesis**

Thymic squamous cell carcinomas may be derived from thymic epithelial stem cells.

**Somatic genetics**

Trisomy 8 and der(16)(1;16) have been reported in a single case of thymic squamous cell carcinoma. Loss of
chromosome 16q, 6, 3p, and 17p and gain of 1q, 17q and 18 are frequently observed by comparative genomic hybridization [2238]. Deletion of chromosome 6 [896] and gain of 1q are common alterations in type B3 thymomas, whereas alterations at 3p, 16q, 17p, 17q and 18 are characteristic of squamous cell carcinoma. TP53-overexpression has been observed in most of thymic carcinomas, but the frequency of TP53-overexpression in thymomas varies considerably [339,835,1980,2118]. TP53 gene mutation can be detected in 30% of thymic carcinomas [339]. Inactivation of p16 (CDKN2A) and methylation of promoter region of p16 are relatively more frequent in thymic carcinomas than in thymomas [835]. Bcl-2 expression is observed in nearly all thymic carcinomas, while it is absent in most thymomas except for type A [1979].

Prognosis and predictive factors
The prognosis of squamous cell carcinoma is largely dependent on tumour stage and grade [1808]. They have a better prognosis than other types of thymic carcinomas with the exception of basaloid carcinoma.

Fig. 3.42 A Thymic squamous cell carcinoma, nonkeratinizing type. In contrast to B3 thymoma, this tumour shows moderate atypia and lacks intraepithelial immature T-cells. The prominent perivascular spaces hint to the thymic origin of this tumour. B Squamous cell carcinoma. Apparent evidence of keratinization, a squamous pearl, within the tumour nest.
Basaloid carcinoma

Definition
Basaloid carcinoma is a thymic carcinoma composed of compact lobules of tumour cells with peripheral palisading and a basophilic staining pattern due to a high nuclear-cytoplasmatic ratio. Basaloid carcinoma shows a remarkable tendency to originate in multilocular thymic cysts.

ICD-O code  8123/3

Synonym
Basaloid squamous cell carcinoma of the thymus [1663].

Epidemiology
A very rare variant of thymic carcinoma with only 10 cases reported in the literature so far [861,886,980,1266,1841,1924,1974]. In a large series of thymic carcinomas, only 5% were basaloid carcinomas [1924]. Most cases occur in the 5th decade of life (reported age range 41 to 65), male and female patients are equally affected.

Clinical features
The symptoms are non-specific. Patients may show symptoms related to a mediastinal mass, e.g. chest pain or dyspnoea. In asymptomatic patients, the tumour may be detected by routine X-ray or during unrelated thoracotomy. No paraneoplastic autoimmune phenomena such as myasthenia gravis are observed.

Etiology
More than half of the reported cases of basaloid carcinoma were associated with a multilocular thymic cyst [886,980,1841,1974]. Basaloid carcinoma of the thymus may thus incidentally arise within a preexisting multilocular thymic cyst or may induce cystic changes in the non-neoplastic thymus as a reactive response [886].

Morphology
The tumour size ranges between 5 and 20 cm. Basaloid carcinomas are mostly well-circumscribed, grey to tan masses surrounded by a thin fibrous capsule with focal haemorrhage and cyst formation. In about 60% of reported cases basaloid carcinomas were found as a mural nodule in a multilocular thymic cyst and/or showed cystic changes in the tumour. Microscopically, basaloid carcinoma is composed of rather monotonous, small to medium-sized, columnar, round to oval, or vaguely spindled tumour cells with high nucleo-cytoplasmic ratios, hyperchromatic round to oval nuclei with inconspicuous nucleoli, scant amount of amphophilic cytoplasm, and indistinct cytoplasmic borders. The cells are haphazardly arranged in trabeculae, anastomosing cords, islands and nests, and typically show prominent palisading at the periphery with the tumour cells being elongated and radially arranged similar to patterns seen in basal cell carcinoma of the skin. Perivascular spaces can be prominent. Mitoses are frequent. Occasionally, focal keratinization in the centre of the cell nests with concentric whorls of bland, metaplastic-appearing squamous epithelium in continuity with the basaloid cells are noted [886,1924]. In some cases, globular eosinophilic deposits of basement membrane-like material is observed [1663]. There may be tumour areas with numerous poorly formed gland-like, cystic spaces lined by basaloid tumour cells and containing PAS-positive/mucicarmin negative stromal mucin [1663,1924]. The multilocular thymic cyst frequently associated with basaloid carcinoma is lined by benign appearing squamous epithelium which may imperceptibly blend with the basaloid tumour cells.

Immunohistochemistry
On immunohistochemistry, basaloid carcinomas express keratin and EMA. As other thymic carcinomas, they can express CD5 [511]. Basaloid carcinomas are negative for S-100, neuroendocrine markers (NSE, chromogranin and synaptophysin) [886,980].

Differential diagnosis
A mediastinal metastasis of a basaloid carcinoma of other primary location, particularly of the upper and lower respiratory tract needs to be excluded. Neuroendocrine carcinomas may histologically mimic basaloid carcinoma.

Genetics
CGH analysis of a single case of basaloid carcinoma of the thymus showed multiple gains and losses of chromosomal material, among them gain of chromosome 1q and losses of chromosomes 6 and 13. These abnormalities strongly overlap with those previously found in thymic squamous cell carcinomas [2238].

Prognosis
Initially regarded as low-grade malignancy [1924], metastasis to lung and liver have been reported in 30% of cases [1266,1841,1924].
**Definition**

Mucoepidermoid carcinoma of the thymus is a rare morphologic variant of primary thymic carcinoma characterized by the presence of squamous cells, mucus-producing cells and cells of intermediate type. Mucoepidermoid carcinoma of the thymus closely resembles mucoepidermoid carcinomas of other organs.

**ICD-O code** 8430/3

**Epidemiology**

This rare tumour comprises approximately 2% of published thymic carcinoma cases [785,1841,1924]. It tends to occur in aged individuals.

**Clinical features**

Mucoepidermoid carcinomas are not associated with myasthenia gravis and may be asymptomatic [1924].

**Morphology**

On macroscopy, the cut surface of mucoepidermoid carcinomas is nodular with fibrous bands and a mucinous appearance [1663,1841]. On histology, the mucous tumour cells are polygonal, columnar or more goblet-like and form solid masses or line cysts [1663,1841]. Mucin-producing cells are strongly PAS-positive [1841]. Areas with squamous differentiation can be solid or form part of a cyst linings. The squamous epithelial cells show minimal to moderate atypia with rare mitoses. The intermediate cells are polygonal or spindle shaped with a moderate amount of eosinophilic cytoplasm and round to oval nucleolus with finely dispersed chromatin.

**Postulated cell of origin**

Pluripotent epithelial stem cells of endodermal origin have been postulated in the pathogenesis of mucoepidermoid carcinoma of the thymus by some authors [1841].

**Prognosis and predictive factors**

Only single case reports on the clinical course have been published. Snover et al. [1841] described one case of mucoepidermoid carcinoma of the thymus with a “low grade morphology” that was completely resectable and the patient was alive after 28 months. However, a number of cases of “thymic adenosquamous carcinoma” with focal mucin production but a high grade morphology [1663] and unfavourable prognosis have been described [625,1094,1264,1381,1946,1965,2009,2032,2098]. At the moment, it is not clear whether these cases represent poorly differentiated mucoepidermoid carcinomas or form a separate tumour entity.
Lymphoepithelioma-like carcinoma

**Definition**
Lymphoepithelioma-like carcinoma (LELC) of the thymus is a primary thymic carcinoma characterized by a syncytial growth of undifferentiated carcinoma cells accompanied by a lymphoplasmacytic infiltration similar to undifferentiated carcinoma of the nasopharynx. Thymic LELC may or may not be associated with Epstein-Barr virus (EBV). However, undifferentiated carcinoma in a dense fibrous stroma without a significant lymphoid infiltration but positive for EBV is tentatively included in this category.

**ICD-O code**
8082/3

**Synonym**
Lymphoepithelial carcinoma

**Epidemiology**
Thymic LELC is a rare tumour. It occurs twice more commonly in male than female patients. The patient's age ranges from 4-76 years with a median of 41 years and a bimodal peak age incidence at 14 years and 48 years (328,343, 785,873,885,899,1472,1876,1924, 2143,2174).

**Localization**
Thymic LELC occurs in the anterior mediastinum and usually extends into contiguous structures. Lymph node, lung, liver, and bone are frequent sites for metastasis (785,2143).

**Clinical features**
The patients usually complain of dull chest pain, cough, or dyspnoea and constitutional symptoms, but some patients are asymptomatic and incidentally found to have an anterior mediastinal mass upon imaging examination (785,2143). Superior vena cava syndrome is seen in patients with more advanced disease (785,873,889,2143). There is no association with myasthenia gravis or other paraneoplastic syndromes, but hypertrophic pulmonary osteoarthropathy has been reported in children (491,873,889,1472).

**Macroscopy**
Grossly, the tumour is solid and yellow white with areas of necrosis. It is usually incompletely encapsulated.

**Histopathology**
Histologically, the tumour is composed of nests or anastomosing cords of carcinoma cells in a lymphoplasmacytic stroma. Germinal centres, eosinophils, and granulomas may be seen. The tumour cells have large vesicular nuclei with open chromatin and one or more distinct eosinophilic nucleoli and show indistinct cytoplasmic membranes. The nuclei are unevenly crowded and may appear to be overlapping. Lymphocytes are not only present in the stroma, but are also intimately admixed with the carcinoma cells. Mitotic activity is variable but is often pronounced. Foci of tumour necrosis are usually observed. The histopathologic appearances of LELC may overlap with those of poorly differentiated squamous cell carcinoma with a lymphoplasmacytic stroma. Currently, with lack of molecular data on LELC and squamous cell carcinoma of the thymus to determine their relationship, if any, the diagnosis of thymic LELC should be restricted to tumours showing the typical histologic appearances similar to that of nasopharyngeal undifferentiated carcinoma (but allowing for presence of focal primitive squamous cell differentiation in the form of eosinophilic mildly keratinizing cytoplasm). Furthermore, since the so-called "undifferentiated carcinoma" has not...
been clearly defined for the thymus \cite{1691}, cases that do not show all classical appearances of LELC should not be included under this category.

**Immunohistochemistry**
The tumour cells are strongly positive for AE1-defined acidic cytokeratins (CKs), and negative for AE3-defined basic CKs. CK7 and CK20 are also negative. CD5 may be expressed focally or not at all \cite{511}. The carcinoma cells also commonly express BCL-2 \cite{338}. The majority of lymphoid cells are CD3+, CD5+, CD1a-, CD99-, and TdT- mature T cells \cite{327}. Smaller numbers of CD20+ B cells are present in the stroma and among the carcinoma cells. Plasma cells that are present are polyclonal.

**Histogenesis**
Thymic LELC presumably arises from thymic epithelial cells.

**Somatic genetics**
Overall, approximately 47% of cases of thymic LELC show association with EBV as demonstrated by EBER in situ hybridization or DNA analysis \cite{328,343,491,873,1472,1876,2174}. EBV is almost always positive in thymic LELC occurring in children and young adults, while EBV positivity rate is lower in adults over the age of 30 years. In two childhood cases studied, the latent membrane protein-1 gene of EBV did not have a 30-base pair deletion as seen in other EBV associated neoplasms \cite{873,1089}. The association with EBV is not related to geographic or ethnic factors \cite{885}. Based on the EBV status, LELCs can be designated as either EBV+ LELC or EBV- LELC pending clinicopathologic and further molecular genetic investigation for their differences. The rare lethal carcinoma with t(15;19) translocation \cite{985,1876} occurring in the mediastinum and respiratory tract of young people may share histologic features of LELC, but it is not associated with EBV \cite{616,985}. This unique neoplasm is believed to be a different entity, although no chromosomal genetic information is currently available for thymic LELC.

**Prognosis**
Thymic LELC is a highly malignant neoplasm with a poor prognosis. The estimated average survival is 16 months in 88% of patients \cite{885}. The presence or absence of EBV does not seem to have prognostic significance.
Sarcomatoid carcinoma

Definition
Sarcomatoid carcinoma is a thymic carcinoma in which part or all of the tumour resembles soft tissue sarcoma morphologically.

ICD-O code 8033/3

Synonyms
Carcinosarcoma, spindle cell thymic carcinoma

Epidemiology
Sarcomatoid carcinoma is uncommon and accounts for only up to 7% of all thymic carcinomas [1924]. It is a tumour of late adulthood, predominantly fourth to eighth decades.

Localization
The tumour is located predominantly in the anterior mediastinum, with frequent invasion of the adjacent structures.

Clinical features
The patients present with cough, dyspnoea, dysphagia, chest pain, weight loss, or superior vena cava syndrome [1478,1897,2143]. Imaging studies reveal the presence of a large anterior mediastinal mass.

Macroscopy
Grossly, the tumour is unencapsulated, often with infiltrative borders. The cut surfaces show whitish or greyish fleshy tumour with variable extent of necrosis and haemorrhage. Microcysts may be present.

Tumour spread and staging
The tumour is locally invasive, with frequent invasion of the adjacent pleura, lung and pericardium, and encroachment on the major blood vessels in the mediastinum. Metastases to mediastinal lymph nodes and parenchymal organs (especially the lungs) are common.

Histopathology
Sarcomatoid carcinoma is an infiltrative tumour often with large areas of coagulative necrosis. It shows intimate intermingling of carcinomatous and sarcomatoid components, but the carcinomatous component can be subtle or demonstrable only by immunohistochemistry or electron microscopy in some cases. The carcinomatous component usually comprises cohesive clusters and sheets of poorly differentiated epithelial cells with significant nuclear pleomorphism, and some cases may show obvious squamous differentiation. The sarcomatoid component frequently comprises fascicles and storiform arrays of discohesive spindle tumour cells with pleomorphic nuclei, coarse chromatin, distinct nucleoli and frequent mitotic figures. Heterologous elements may be observed, most commonly rhabdomyosarcomatous and occasionally osteosarcomatous; the term ‘carcinosarcoma’ is sometimes applied for such cases [534,1478,1509,1841,1897]. In the rhabdomyosarcomatous areas, spindle cells with cross striations and large cells with abundant eosinophilic fibrillary cytoplasm are found. In the osteosarcomatous component, osteoid production by tumour cells is seen. Immunohistochemically, the carcinomatous component expresses epithelial markers such as cytokeratin and epithelial-specific antigen.

Fig. 3.48 Sarcomatoid carcinoma of the thymus. A Usually spindle cells predominate, and there are areas of geographic necrosis. B A biphasic pattern is obvious in this case. The carcinomatous component takes the form of a squamous cell carcinoma, and it gradually merges into a spindle cell (sarcomatoid) component.
Tumours of the thymus  -  Thymic carcinomas

In the sarcomatoid areas, cytokeratin-positive tumour cells range from abundant to scanty or even absent [534,1093,1478,1509,1841,1897,1916]. Variable expression of myoid markers (e.g. desmin, actin, myogenin, myoD1, myoglobin) is seen in the rhabdomyosarcomatous component [534,1478,1509,1841,1897]. The cases studied for CD5 have been negative for this marker [1093,1916]. Only rare tumours have been examined ultrastructurally, but desmosome-like junctions have been described in the spindle cell area of one case [534].

**Immunohistochemistry**

In a tumour where only sarcomatoid component is identified despite extensive sampling, distinction from a sarcoma depends on the demonstration of epithelial differentiation in at least some tumour cells by immunohistochemistry (e.g. cytokeratin, epithelial membrane antigen) or electron microscopy. Sarcomatoid carcinoma predominated by rhabdomyosarcomatous component may have been confused with mediastinal rhabdomyosarcoma in the literature. The latter sarcoma more commonly affects children and young adults. Although rhabdomyosarcoma can express cytokeratin, the positive tumour cells coexpress myoid markers, whereas at least some tumour cells in sarcomatoid carcinoma express cytokeratin only [534,1509].

The entity reported as “spindle cell thymic carcinoma” comprises lobules and compact sheets of atypical spindle cells, and is probably an unusual form of sarcomatoid carcinoma. There is frequent transition with thymoma with spindle cell (type A) morphology. The spindle cells show epithelial characteristics and no evidence of true mesenchymal differentiation on immunohistochemical evaluation [1509,1916].

**Differential diagnosis**

Sarcomatoid carcinoma has to be distinguished from biphasic metaplastic thymoma, which differs in showing good circumscription of the tumour and bland-looking spindle cells, even though the interspersed squamoid epithelial islands may sometimes show nuclear pleomorphism [1919,2210]. Spindle cell carcinoid can be distinguished from sarcomatoid carcinoma by the presence of delicate fibrovascular septa, granular cytoplasm, generally less striking nuclear pleomorphism, and usually presence of a conventional carcinoid component in some foci; the diagnosis can be further confirmed by positive immunostaining for neuroendocrine markers. The biphasic pattern of sarcomatoid carcinoma may raise the differential diag-

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**Fig. 3.49 Sarcomatoid carcinoma of the thymus.**

A An elongated rhabdomyoblast with cross striations is seen among polygonal carcinoma cells with pleomorphic nuclei. B Skeletal muscle differentiation characterized by rounded rhabdomyoblasts with vacuolated cytoplasm are interspersed among the spindle sarcomatoid cells. C Osteoid formation. D So-called spindle cell thymic carcinoma. The tumour comprises sheets and islands of compact atypical spindle cells.
noses of synovial sarcoma and mesothelioma. Synovial sarcoma differs in showing more monotonous and uniform spindle cells and glandular differentiation in the epithelial component. The diagnosis can be further confirmed by the identification of t(X;18)(p11.2;q11.2) or SYT-SSX1 or SYT-SSX2 gene fusion. Mesothelioma differs in being pleural or pericardial-based, showing papillary-glandular formation in the epithelial component, expressing mesothelial-associated markers (e.g. calretinin), and showing mesothelial differentiation ultrastructurally (e.g. bushy microvilli).

**Precursor lesions**
Some cases show an identifiable component of thymoma, most commonly with spindle cell (type A) morphology, suggesting transformation from an underlying thymoma (1093,1897,1916).

**Histogenesis**
The sarcomatoid component may arise from metaplasia of the carcinomatous component, wherein the tumour cells often gradually lose epithelial characteristics and simultaneously acquire mesenchymal or mesenchymal-like features. Alternatively, the tumour is derived from primitive cells with multidirectional differentiation.

**Somatic genetics**
Only one case has been studied by cytogenetics, with identification of a complex chromosomal abnormality including der(16)(t1;16)(q12;q12.1) (534). Interestingly, this chromosomal translocation has also been previously reported in a case of thymic squamous cell carcinoma (1847), suggesting a pathogenetic relationship with thymic squamous cell carcinoma in at least some cases.

**Prognosis and predictive factors**
Sarcomatoid carcinoma is an aggressive tumour, with most patients dying of disease within three years of diagnosis despite aggressive multi-modality therapy.

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**Fig. 3.50** Sarcomatoid carcinoma of the thymus. **A** In this example, pale-staining nodules are disposed among spindle cells. **B** The pale-staining nodules represent areas with subtle epithelial differentiation. This field shows some resemblance to metaplastic thymoma. **C** The sarcomatoid component comprises closely packed spindle cells with moderate nuclear atypia and frequent mitotic figures. **D** Immunostaining for EMA highlights nodular structures.

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**Fig. 3.51** G-banded metaphase spread shows a complex karyotype, including der(16)(t1;16)(q12;q12.1).
Clear cell carcinoma

Definition
Clear cell carcinoma is a thymic carcinoma predominantly or exclusively composed of cells with optically clear cytoplasm. Thymomas with clear cell features are not included in this group.

ICD-O code 8310/3

Synonym
Carcinoma of the thymus with clear-cell features [797]

Epidemiology
This is a very rare variant of thymic carcinoma, with only 13 “pure” cases reported to date [797,1094,1877,1924,2032,2166]. Clear cell carcinomas constitute only 3% of all thymic carcinomas [1924]. Clear cell carcinoma has also been reported as a high-grade component in a combined thymoma/thymic carcinoma that, in addition, showed areas of spindle cell (WHO Type A) thymoma, squamous cell carcinoma and undifferentiated carcinoma [1093]. The age range of the reported cases is 33 to 84 years, and the tumour tends to prevail in men (male : female ratio 1.6) [797, 1663].

Clinical features
Patients may show symptoms related to a mediastinal mass, e.g. chest pain or dyspnoea. Some patients are asymptomatic, with the tumour being detected by routine X-ray or during unrelated thoracotomy. There are no associated paraneoplastic autoimmune phenomena gravis.

Macroscopy
Macroscopically, the reported tumour size ranges between 4 and 12 cm (average 9 cm). The tumours may appear encapsulated and non-infiltrative, or may extensively infiltrate the surrounding tissues. The cut-surface shows solid or cystic tumour with or without haemorrhage and focal necrosis.

Histopathology
Microscopically, clear cell carcinomas of the thymus often show rather bland cellular features which contrast their clinical aggressiveness. Tumour cells are rather monotonous and polyhedral, and usually display slight cellular pleomorphism with round to oval, vesicular nuclei, moderate nuclear atypia, finely dispersed chromatin, and small discernible nucleoli. They have abundant lucent, mostly clear granular cytoplasm, sometimes faintly eosinophilic, cytoplasm which mostly, but not always is due to accumulation of glycogen. Clear cell carcinomas commonly show a lobulated architecture with nests, lobules or sheets of tumour cells being surrounded by a dense fibrous stroma, and lack the sinusoidal vasculature characteristic of metastatic clear cell carcinoma of the kidney. Rarely, few scattered intratumoral lymphocytes, minute foci of squamous differentiation or focal necrosis are observed. The tumour commonly exhibits an infiltrative growth, with tumour extending into the surrounding mediastinal fat and remnant thymus, even in cases which macroscopically appear well-delineated.

Special studies
Tumour cells usually show cytoplasmic diastase-labile PAS positivity, but PAS negative cases have also been reported [1877]. Clear cell carcinomas are keratin positive (cytokeratin 7 expression may be absent), EMA is expressed in 20% of cases studied [797]. As in other types of thymic carcinomas, a subgroup of clear cell carcinomas may express CD5 [511,1093]. They are negative for PLAP, vimentin, CEA and S-100 [797], and do not contain a population of immature (CD1a- or CD99-positive) T-lymphocytes.

Differential diagnosis
When making the diagnosis of thymic clear cell carcinoma, metastatic clear cell epithelial malignancies, particularly renal, pulmonary and thyroid clear cell carcinoma have to be excluded. Other differential diagnoses include mediastinal diffuse large B-cell lymphoma, mediastinal seminoma, mediastinal parathyroid neoplasms, metastatic clear cell sarcoma or melanoma, glycogen-rich alveolar rhabdomyosarcoma, and clear cell paraganglioma. Furthermore, thymoma with clear cell features must be differentiated from clear cell carcinoma and from combined thymoma/thymic clear cell carcinoma [1093]. Clear cell features are common only in WHO Type B3 thymomas and they are almost always focal [797,2032]. Most tumours show a predominance of conventional B3 areas that exhibit gradual transitions to foci of bland-looking clear cells. While the conventional B3 areas harbour at least few CD1a+ and CD99+ immature T-cells, they may be absent in the clear cell areas. Significant PAS-positivity, necrosis, increased proliferative activity, desmoplastic stroma or TP53 overexpression are typically absent in clear cell foci of WHO Type B3 thymomas. By contrast, the clear cell carcinoma (with squamous features) arising in a WHO Type A thymoma (combined thymoma/thymic carcinoma) was PAS+, showed extensive necrosis, cyst formation and a desmoplastic stromal reaction [1093].

Prognosis
Clear cell carcinomas are highly malignant, aggressive mediastinal neoplasms with frequent local recurrences and metastases. Most reported patients died of the disease. Deaths are related to metastatic disease or local infiltration of organs in recurrence [797].
Papillary adenocarcinoma

**Definition**
Papillary adenocarcinoma is a rare type of primary thymic carcinoma, characterized by a prominent papillary pattern of growth. Although reports of this tumour are rare, it may be the source of some metastatic papillary carcinomas with psammoma bodies in the cervical lymph nodes of patients without tumours in the thyroid gland.

**ICD-O code** 8260/3

**Synonym** Papillary carcinoma

**Epidemiology**
Papillary adenocarcinoma of the thymus is a rare neoplasm, and only five cases have been reported (1263). It affects elderly individuals in their sixth to seventh decades of life. Males and females appear to be equally affected.

**Clinical features**
Papillary adenocarcinoma generally presents as an enlarging anterior mediastinal mass. The tumour may appear cystic. Paraneoplastic symptoms such as myasthenia gravis or pure red cell aplasia have not been described.

**Macroscopy**
The tumours are more or less encapsulated, and usually large (measuring 5-10 cm). The cut surface is irregularly lobulated, white and firm. Prominent cyst formation containing serohaemorrhagic fluid may be seen. Adhesion or direct invasion to the adjacent lung, pleura or pericardium is observed in most cases. Pleural implants may be found.

**Histopathology**
The tumour shows a tubulopapillary proliferation of uniform cuboidal to columnar cells, mainly lying in a monolayer, but occasionally showing a glomeruloid arrangement. The tumour cells have eosinophilic or clear cytoplasm. Their nuclei are round to ovoid, with coarsely condensed chromatin, and a few small but prominent nucleoli. Psammoma bodies may be present. Areas of coagulation necrosis, sometimes massive, are scattered throughout the tumour. Invasion into the adhesive extrathymic tissues accompanied by a dense collagenous stroma may be seen. A small number of tumour cells show positive staining for mucin. The mitotic count may vary from 1 to 7/10 HPF among cases. Permeation of tumour cells into lymphatics such as the subpleural or intrapulmonary perivascular lymphatics may be extensive. In the majority of cases, type A thymoma is found as a component within the tumour mass; one case showed high-grade histology and a predominantly solid and sheet-like growth accompanied by well-developed papillary structures, high-grade atypia and high mitotic rate. In contrast to the other four cases, there was no evidence of a type A thymoma component.

**Immunophenotype**
Papillary adenocarcinoma shows variable degrees of staining for LeuM1 and BerEP4. CEA and CD5 may also be positive, but CD20, thyroglobulin, pulmonary surfactant apoprotein and calretinin are negative. In addition, CD99-positive lymphocytes are absent, but may be found in the coexisting thymoma portion.

**Differential diagnosis**
Differential diagnosis of this rare type of thymic carcinoma includes mediastinal thyroid neoplasm (i.e. papillary carcinoma), malignant mesothelioma, germ cell tumour, metastatic adenocarcinoma, and adenocarcinoma of foregut cyst origin (1915).

**Histogenesis**
It has been suggested that papillary adenocarcinoma originates from type A thymoma as an expression of malignant transformation (1263). This is based not only on the morphological similarities between the tubuloglandular or papillotubular structures sometimes seen in type A thymomas and those of the carcinoma, but also the occasional coexistence of a type A thymoma component within the tumour.

**Prognosis and predictive factors**
Since the number of reported cases is limited, specific information on the histopathologic prognostic factors of papillary carcinoma of the thymus is not available.

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**Fig. 3.53** Papillary adenocarcinoma of the thymus. Highly papillary configuration resembling papillary carcinoma of the thyroid (1690).
Non-papillary adenocarcinomas

There have been rare reports about non-papillary adenocarcinomas in the thymus. Among them are: an adenocarcinoma with glandular differentiation arising in a thymic cyst (98), as is also typical for papillary carcinoma (541); an adenoid cystic carcinoma equivalent to the analogous salivary gland carcinoma (1841); and a mucinous (colloid) carcinoma of the thymus (360). The latter case arose in a 15 year old boy and was CD5-negative by immunohistochemistry.

An exceptional tumour in the thymus exhibiting features of a hepatoid carcinoma was observed in a 78 year-old female without an extrathymic neoplasm. The tumour had a diameter of 10 cm, was not encapsulated and virtually devoid of fibrous or inflammatory stroma. Respiratory distress was the only clinical symptom. The tumour recurred locally two years after surgery and responded to radiotherapy. Considering the female sex and protracted clinical course, lack of a yolk sac component and absence of alpha-fetoprotein in the tumour and the patient’s serum, a diagnosis of hepatoid carcinoma of thymus appears more likely than a “monophasic” variant of hepatoid yolk sac tumour of the mediastinum (606,1349,1355).

Fig. 3.54 Thymic adenoid cystic carcinoma. This salivary gland-type thymic carcinoma shows a glandular and cribriform pattern.

Fig. 3.55 Thymic hepatoid carcinoma. A Tumour nodules composed of large polygonal tumour cells resembling activated hepatocytes. No hepatic sinuses, no portal structures and absence of a tumour stroma. B Large polygonal cells with abundant eosinophilic cytoplasm. PAS+ globules (immunoreactive for alpha-1-antitrypsin, not shown) occurred inside the cytoplasm and in between epithelial cells.
Carcinoma with t(15;19) translocation

Definition
Carcinoma with translocation t(15;19)(q13;p13.1) is a rare, aggressive and lethal carcinoma of unknown histogenesis arising in the mediastinum and other midline organs of young people.

Synonyms
Aggressive t(15;19)-positive carcinoma, midline lethal carcinoma

Epidemiology
Six cases of t(15;19)-positive carcinoma have been reported [439,616,985,1081,1148,2072]. All occurred in children or young adults (age range: 5-34 years), particularly females (F : M ratio = 5:1).

Etiology
The etiology of t(15;19)-positive carcinoma is unknown. Epstein-Barr virus does not play a role [985,2072].

Localization
Translocation t(15;19)-positive carcinoma has been reported to arise in supradiaphragmatic midline organs. Three of 6 cases arose adjacent to the thymus in the mediastinum [985,1081,1148]. Other primary locations were epiglottis [2072], sinonasal region [616], lung [439], and bladder (unpublished findings (C.A.F., J.A.F.)).

Clinical features
Aggressive local invasiveness is characteristic. Intracranial extension occurred in a sinonasal case. Pleural effusions and superior vena cava syndrome are common in thoracic cases. Metastases are common and may involve lymph nodes, lung, bone, skin and subcutaneous soft tissue [2072].

Histopathology
The presence of undifferentiated, intermediate sized, vigorously mitotic cells is characteristic. Commonly seen are sheets of undifferentiated cells forming syncytia with inter-epithelial lymphocytes, a pattern indistinguishable from lymphoepithelioma [616]. Focal squamous differentiation is common [616, 1081,1148], but not always seen, whereas glandular differentiation (mucoepidermoid carcinoma) [1148]) has only been reported once. Electron microscopy revealed squamous differentiation (rare desmosomes [1081,1148,2072], tonofilaments [1148,2072]) in three cases. Care must be taken not to confuse the discohesive, undifferentiated round cells of t(15;19)-positive carcinoma with large cell lymphoma or germ cell tumour [616, 985,1081].

Immunophenotype
The tumours consistently react, at least focally, with pan-cytokeratin markers [616,2072]. Inconsistent and usually focal positivity occurs for vimentin, EMA, and carcino-embryonic antigen (CEA) [985,2072], CD30, CD45, PLAP, HMB45, S100, and neuroendocrine markers are negative.

Differential diagnosis
This lesion must be distinguished from large cell lymphoma, germ cell tumour, and t(15;19)-negative carcinomas, par-
particularly lymphoepithelioma-like, poorly
differentiated squamous cell, mucoepidermoid, and undifferentiated carcinoma.

**Histogenesis**
Despite various considerations (616,985, 1081,1148,2072), derivation of this tumour is unknown.

**Somatic genetics**
The specific t(15;19)(q13;p13.1) translocation, which generates the 6.4-kb
BRD4-NUT fusion oncogenes, is often
the only demonstrable cytogenetic aber-
ration. The translocation fuses the 5´10
exons of the ubiquitously expressed
BRD4 bromodomain gene on chromo-
some 19 with nearly the entire transcript
of the 15q13 gene NUT (nuclear protein
in testis), that is normally exclusively
expressed in testis {617}. Cytogenetics,
fluorescence in situ hybridization (FISH),
Southern blotting and RT-PCR studies
can identify the translocation {616,617}.
Additional chromosomal aberrations are
rare {2027}.

**Prognosis and predictive factors**
All cases reported so far followed an
extremely aggressive clinical course
(average survival 18 weeks; range 8-38
weeks) {616}.

![Fig. 3.57 Aggressive carcinoma with t(15;19) translocation. Karyotype from a teenage girl with the t(15;19)
carcinoma. A reciprocal translocation involving chromosomes 15q13 and 19p13.1 has occurred. The der (19)
contains the functional fusion oncogene.]

![Fig. 3.58 Aggressive carcinoma with t(15;19) translocation. A Schematic of the BRD4 and NUT genes dis-
rupted in the t(15;19)(q13;p13.1) chromosomal translocation. Exons are represented by horizontal bars, and
introns by connecting lines. All characterized breakpoints (N=2), represented by vertical arrows, occur in
intron 10 of BRD4 (gray), and intron 1 of NUT (green), splitting BRD4 roughly in half, and fusing to it nearly
the entire NUT transcript. Both bromodomains (pink) of BRD4 are preserved in the fusion oncogene. The
oncogenic mechanism is believed, at least in part, to result from unscheduled expression of NUT (normally
expressed only in testis) driven by the promoter of BRD4, which is ubiquitously expressed. B Fluorescent
in situ hybridization (FISH) depicting the t(15;19)(q13;p13.1) in a paraffin section. The red-green probe dou-
blet, which normally flanks the NUT gene on chromosome 15, is split apart by the translocation.

186 Tumours of the thymus  -  Thymic carcinomas
**Undifferentiated carcinoma of the thymus**

**Definition**
A thymic carcinoma growing in a solid, undifferentiated fashion but without sarcomatoid (spindle cell, pleomorphic, metaplastic) features [1924].

**ICD-O code** 8020/3

The diagnosis of this rare type of thymic carcinoma is one of exclusion. Defining its epithelial nature usually requires immunohistochemistry. In children and young adults, carcinoma with t(15;19) translocation should be excluded by cytogenetics or RT-PCR [617, 1081]. The most important differential diagnosis in adults is large cell carcinoma in the lung extending or metastasizing to the mediastinum. Small cell carcinoma without (immunohistochemically) recognizable differentiation is traditionally classified among the neuroendocrine carcinomas of the thymus.

![Undifferentiated thymic carcinoma. A A solid growth pattern composed of large polygonal to round tumour cells, large nuclei and a slightly basophilic cytoplasm. No keratinization, no intercellular bridges, no glandular differentiation, no sarcomatoid features and no EBER expression by in situ hybridization. The prominent population of bland looking myoid cells with round inconspicuous nuclei and eosinophilic cytoplasm unequivocally identifies this carcinoma as a tumour of thymic differentiation. Myoid cells show no significant proliferative activity (in contrast to rhabdomyosarcoma cells). B Desmin staining demonstrates intratumorous myoid cells.](image-url)
Thymic neuroendocrine tumours

Definitions
Thymic epithelial tumours that are predominantly or exclusively composed of neuroendocrine cells are classified as neuroendocrine carcinomas (NECs) of the thymus \cite{1691}. They have to be distinguished 1) from otherwise typical thymic carcinomas, which may contain scattered or groups of neuroendocrine cells \cite{853,1091,1139}, and 2) from non-epithelial neurogenic tumours, particularly paragangliomas.

Neuroendocrine differentiation can be demonstrated by immunohistochemistry (positivity for chromogranin, synaptophysin, neuron-specific enolase, CD56) and/or by ultrastructural identification of neurosecretory granules. Neoplasms combining features of NEC and either thymoma or thymic carcinoma are included in the category of “combined thymic epithelial tumours”.

Since the seminal work of Rosai and Higa, thymic neuroendocrine tumours that are “related to carcinoid tumours” have been distinguished from thymomas \cite{1686,1688,2144}. The epithelial neuroendocrine tumours of the thymus comprise typical and atypical carcinoids, as well as large and small cell carcinomas.

Well differentiated neuroendocrine carcinomas
In line with the nomenclature of neuroendocrine tumours occurring in other sites of the body, it is proposed that thymic carcinoids be termed well differentiated neuroendocrine carcinomas of the thymus \cite{349,1691}. The rationale for considering all these tumours as carcinomas \cite{1691} is the observation that even “innocent” looking and encapsulated carcinoids bear a significant risk for recurrence, metastasis and tumour-associated death \cite{628,1845,2140}. The carcinoids are further subdivided into typical and atypical carcinoids.

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

Typical and atypical carcinoids
Following the introduction of the term “atypical carcinoid” by Arrigoni et al. in 1972 for a subgroup of moderately aggressive neuroendocrine neoplasms of the lung \cite{75}, it became clear that the vast majority of carcinoids in the thymus correspond to atypical carcinoids when the same criteria are applied as in the lung \cite{450,628,723,1361,1688,1808,2136,2062}. As a group, atypical carcinoids more often show a diffuse growth pattern, advanced stage disease, and a higher degree of cytologic atypia \cite{723,1362,1691,1808,2062}.

Since virtually all thymic carcinoids are atypical carcinoids (see epidemiology), most studies report thymic carcinoids to have a worse prognosis compared with bronchial carcinoids \cite{628,1361,1808,2136}. However, varying criteria have been used for definition of atypical carcinoids of the thymus in these series \cite{628,1361,1845,2062}. In fact, the only clinicopathological study applying WHO-defined criteria to classify atypical thymic carcinoids \cite{723} challenged the view that thymic atypical carcinoids are clinically more aggressive than morphologically identical carcinoids of the lung. A better prognosis of atypical thymic carcinoids as compared to pulmonary carcinoids was even suggested by a recent study \cite{1049} (5-year and 10-year survival rates of 84% and 75% respectively, compared with 87% and 87% for pulmonary typical carcinoids and 56% and 35% for pulmonary atypical carcinoids \cite{2028}).

Fig. 3.60 Typical carcinoid. A Solid and trabecular growth pattern. Note absence of necrosis and mitoses. B On high magnification, rosettes, and bland cytology can be seen, but no mitoses.
Neuroendocrine carcinomas

Poorly differentiated neuroendocrine carcinomas

Small cell carcinoma, neuroendocrine type. A high-grade thymic 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 or spindle-shaped, and nuclear molding is prominent. The mitotic count is high. The morphologic features are indistinguishable from those of small cell carcinoma arising in the lung.

Variant: Combined small cell carcinoma: A small cell carcinoma that also contains a component of non-small cell carcinoma such as squamous cell carcinoma or adenocarcinoma.

Large cell neuroendocrine carcinoma: A high-grade thymic tumour composed of large cells with neuroendocrine morphology such as palisading, trabeculae, nesting or rosette-like features; necrosis that is usually extensive; a high mitotic rate; and either neurosecretory granules by electron microscopy or positive neuroendocrine immunohistochemical markers.

ICD-O codes

- Large cell neuroendocrine carcinoma 8013/3
- Small cell carcinoma, neuroendocrine type 8041/3

Table 3.06
Classification of thymic neuroendocrine tumours (Neuroendocrine carcinomas, NECs) [1691].

<table>
<thead>
<tr>
<th>Neuroendocrine Carcinomas (NECs)</th>
<th>Well-differentiated NEC</th>
<th>Poorly differentiated NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Carcinoid</td>
<td>Atypical Carcinoid</td>
<td>LCNEC*</td>
</tr>
<tr>
<td>No necrosis; &lt;2 mitoses per 2 mm² (10HPF)</td>
<td>Necrosis present and/or 2-10 mitoses per 2 mm² (10 HPF)</td>
<td>Non-small cell NEC with &gt;10 mitoses per 2 mm² (10 HPF)</td>
</tr>
<tr>
<td>Atypical Carcinoid</td>
<td></td>
<td>Small cell cytology</td>
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<tr>
<td>LCNEC*</td>
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<td></td>
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<tr>
<td>Morphological Variants</td>
<td>Variants</td>
<td></td>
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<tr>
<td>Spindle cell type</td>
<td>SCNEC combined with</td>
<td></td>
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<tr>
<td>Pigmented type</td>
<td>Non-NECs</td>
<td></td>
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<tr>
<td>With amyloid (extrathyroidal medullary carcinoma)</td>
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<tr>
<td>Oncocytic/oxyphilic type</td>
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<td></td>
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<tr>
<td>Mucinous</td>
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<tr>
<td>Angiomatoid type</td>
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<tr>
<td>Combinations of the above variants</td>
<td></td>
<td></td>
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<tr>
<td>Thymic NECs with shared features of (atypical) carcinoid and LCNEC/SCC Carcinoid with sarcomatous change (&quot;metaplastic NEC&quot;)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1LCNEC, large cell neuroendocrine carcinoma;
2SCC, small cell carcinoma; HPF, high power field

Definitions

Four major categories of thymic neuroendocrine neoplasms are recognized:

Typical (classic) carcinoid. A carcinoid tumour comprised of polygonal cells with granular cytoplasm arranged in ribbons, festoons, solid nests and rosette-like glands. Tumours have less than 2 mitoses per 2 mm² (10 HPF) and necrosis is absent.

Atypical carcinoid. A carcinoid tumour with architectural features of the classic type but exhibiting a greater degree of mitotic activity and/or foci of necrosis (including comedonecrosis).

Basis of the classification

Considering the paucity of data on clinicopathological correlations in thymic NECs [723,1361,1845] as compared to the statistically better analyzed pulmonary NECs [128,218,2023,2026], the first edition of the WHO classification of tumours of the thymus [1691] suggested thymic neuroendocrine tumours to be classified using the same criteria applied for NECs of the lung [218]. Although this approach was not based on sufficient statistical data, it was meant to provide a morphological basis from which prospective and retrospective clinical studies

Fig. 3.61 Atypical carcinoid. Macroscopy of a well circumscribed tumour.

Fig. 3.62 Atypical carcinoid. Despite circumscription, there is lymphatic invasion outside the main tumour mass.
are launched to generate statistical data. This approach is maintained in the present edition of the WHO classification.

**Epidemiology**

Thymic NECs are rare, constituting 2-5% of thymic epithelial tumours (723,1361, 1808,2062). In contrast to the lung [218, 1128,2023], the great majority of cases are represented by atypical carcinoid. MEN-1-associated thymic NECs have all been carcinoids and occurred almost only in male adults (31-66 years; mean 44 years) [1987,1989]. Epidemiological data on typical carcinoids are lacking. Atypical carcinoids are mainly tumours of adults (18–82 years; mean 48-55 years in both males and females) [723,1361,1845,2062], but have also been rarely observed in children (8-16 years of age) [666,1185].

There is a male preponderance (M:F = 1:2-7) [528,723,1361,1845]. By contrast, small cell carcinomas show no gender predilection and the patients on average are slightly younger [1094, 2032,2143]. The case of thymic large cell neuroendocrine carcinoma reported by Chetty occurred in a 68 year-old male patient [349].

**Etiology**

About 25% of patients with thymic carcinoids have a positive family history of MEN-1 [1989]. Conversely, among MEN-1 patients, thymic carcinoids were found in 8% of cases [681]. Since thymic NECs cluster with only a minority of MEN-1 families, exhibit diverse mutations and are not associated with loss of heterozygosity (LOH) at the 11q13 (MEN-1) locus, it appears that genetic alterations in addition to MEN-1 abnormalities (possibly involving a tumour suppressor gene(s) on chromosome 1p) are required for thymic carcinoids to develop [1988, 1989]. The role of a MEN-2 genetic background for the development of thymic carcinoids is less clear [1239].

**Localization**

Thymic neuroendocrine carcinomas occur in the anterior mediastinum. A single case occurring in an ectopic thymus adjacent to the thyroid has also been published [900].

**Clinical features**

Most poorly differentiated neuroendocrine carcinomas and about 50% of well differentiated neuroendocrine carcinomas exhibit local symptoms (chest pain, cough, dyspnoea, or superior vena cava syndrome) [723,1361,1845].

Carcinoid syndrome is exceedingly rare (<1%) [1845]. On the other hand, 17-30% of adult and >50% of childhood carcinoids of the thymus are associated with Cushing syndrome due to ACTH production [456,1845,1918]. In fact, 10% of all cases of “ectopic ACTH syndrome” are due to thymic carcinoids [162,2095]. Cutaneous hyperpigmentation due to tumour-derived alpha-MSH frequently accompanies and, rarely, precedes Cushing syndrome [666]. Cushing syndrome is exceptionally rare in thymic SCC [812].

Acromegaly (due to tumour-derived GHRH) [924], and inappropriate production of antidiuretic hormone or atrial natriuretic peptide [1507] are uncommon. Hypercalcaemia/hypophosphataemia in thymic carcinoid patients may result either from tumour production of PTHrP [2214] or from primary hyperparathyroidism in the context of the MEN-1 syndrome [1989].

MEN-1-associated thymic NECs are typically insidious tumours (carcinoids) that manifest by local symptoms, metastases, disturbances of calcium/phosphate metabolism or, rarely, with acromegaly [196], while Cushing syndrome has not been reported [1988,1989]. Paraneoplastic autoimmune disorders, such as the Lambert-Eaton myasthenic syndrome, are very rare.

**Macroscopy**

Thymic carcinoids and poorly differentiated thymic NECs are virtually identical macroscopically. The majority are unencapsulated and can appear either circumscribed or grossly invasive. The size ranges from 2–20 cm (mean 8 -10 cm) [450,1361]. Cases associated with Cushing syndrome tend to be smaller (3-5 cm) due to earlier detection. They are grey-white and firm on cut section, can have a gritty consistency, and usually lack the characteristic lobulated growth pattern of thymomas. Oncocytic/oxyphilic variants may show a tan or brown cut surface. Foci of haemorrhage and necrosis are apparent in 70% of cases [2137]. Calcifications are frequent in thymic NECs (30%) compared with extrathymic NECs [924].

**Tumour spread and staging**

Locally restricted atypical carcinoids (capsulated pT1 or infiltrating the mediastinal fat or thymus pT2) make up 40-50% of cases, but half of them exhibit local metastasis (pN1) [723,2062]. Invasion into adjacent organs (40-50%, pT3) or pleural or pericardial cavity (10%, pT4) is common [723,2062].
Metastases are present in 30-50% of cases [723,1845]. Lymph node metastases can involve mediastinal, cervical and supraclavicular lymph nodes [924] or they can be systemic [723]. Haematogenous metastasis to bone, liver, skin, brain, kidney, heart, adrenals and soft tissues have been reported [723,1013,1845,2143]. Pericardial and pleural cavities can be sites of late NEC recurrences (up to 9 years after resection) [2035]. Only very few cases of stage II SCC have been reported [1808,1841], one with distant metastases [1841]. The vast majority of SCC are in stage III or IV [812,1094,1841,2143], and about half of them show lymph node or haematogenous metastases [1094,2032].

Histopathology of well differentiated neuroendocrine carcinomas

Typical carcinoids
By definition, these are devoid of necrotic areas and exhibit a low mitotic rate (<2 mitoses per 2 mm² or 10 HPF using certain microscopes). The “classic” carcinoid can show a variety of “organoid” features: ribbons (trabeculae), festoons, solid nests, rosettes, glandular structures, and nuclear palisades, accompanied by a richly vascularized stroma. The trabecular and rosette patterns are the commonest, being found in over 50% of cases. The tumour cells are uniform and polygonal, with relatively small nuclei, finely granular chromatin, and eosinophilic granular cytoplasm. Lymphovascular invasion is common.

Atypical carcinoids
These show (1) areas of necrosis and a maximum of 10 mitoses per 2 mm² (10 HPF) of non-necrotic tumour area or (2) absence of necrosis but a proliferation rate of 2-10 mitoses/2 mm² or 10HPF. All architectural features of typical carcinoids can occur. Even small “punctate” area of necrosis (comedonecrosis) in an otherwise typical carcinoid justifies a diagnosis of “atypical carcinoid”. Compared to typical carcinoids, atypical carcinoids more frequently show some degree of nuclear pleomorphism including rare “anaplastic” cells [723], a focal diffuse growth pattern (so-called “lymphoma-like”) [723,1361,1845,2062] or extensive desmoplastic stroma with Indian filing of tumour cells [2136]. Calcifications are also more characteristic of atypical carcinoids (up to 30% of cases) [924].

Variants of thymic carcinoids
The morphologic variants should be assessed as being “typical” or “atypical” using the criteria listed above. Among the reported cases, almost all are classifiable as atypical carcinoids.

Spindle cell carcinoid
This is the commonest thymic carcinoid variant, being predominantly or totally composed of spindle cells often arranged in fascicles. Occasionally, spin-
Tumours of the thymus - Neuroendocrine tumours

dle cell carcinoid can be admixed with a classic carcinoid [1169,1691,2141].

**Pigmented carcinoid**
This variant of thymic carcinoid is characterized by presence of intracytoplasmic melanin (neuromelanin) in a variable number of tumour cells. Melanosomes can be detected by electron microscopy. There can be admixed melanophages containing phagocytosed melanin granules with a coarser appearance. Pigmented tumour cells can exhibit an otherwise classic or spindle cell morphology. This variant has also been reported to be associated with Cushing syndrome [857,1028,1114].

**Carcinoid with amyloid**
This variant is accompanied by amyloid deposition in the stroma that can be identified by Congo stain [2141]. The tumour cells are usually spindle shaped and immunoreactive for calcitonin, so that the tumour is indistinguishable from medullary carcinoma of the thyroid (“extrathyroidal medullary carcinoma”). The histogenesis of this tumour is unclear. A derivation from extra-thyroidal C-cells or a thymic epithelial origin has been postulated [1691].

**Oncocytic/oxyphilic carcinoid**
This is a rare variant that is composed of polygonal, large tumour cells with oxyphilic cytoplasm due to accumulation of mitochondria [1362,2183]. Oncocytic carcinoid is rarely associated with MEN-1 or Cushing syndrome [1362,2183].

**Mucinous carcinoid**
This is a very rare variant that exhibits an alcian blue-positive mucinous stroma [1501,1911]. The tumours are often large (>8 cm) and can resemble metastatic mucinous carcinoma, such as from the gastrointestinal tract or breast. The stromal mucin is believed to result from regressive changes rather than production by the tumour cells. There can be a focal component of classic carcinoid. The few reported cases have not been associated with Cushing syndrome.

**Angiomatoid carcinoid**
This rare variant resembles haemangioma macroscopically and microscopically due to the presence of large blood-filled cystic spaces. However, closer scrutiny shows that the spaces are lined by polygonal tumour cells but not endothelial cells [1360].

**Carcinoid with sarcomatous change**
Carcinoids in combination with sarcomatous tumour areas have been described rarely, and have pursued a highly aggressive clinical course [1090, 1557]. The sarcomatous component shows fibrosarcomatous, myoid, osseous or chondroid differentiation. The cases have been interpreted as examples of dedifferentiation or divergent development from a common precursor rather than collision of two clonally unrelated tumours.

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Fig. 3.65  **A** Atypical carcinoid. Rosette formation.  **B** Atypical carcinoid. Small islands of tumour cells in oedematous stroma.  **C** Pigmented carcinoid. Melanin is present in the cytoplasm of some tumour cells.  **D** Carcinoid with amyloid. Tumour cells are accompanied by deposits of extracellular amyloid.
Neuroendocrine carcinomas

Carcinoids as components in other combined tumours
Carcinoids can be admixed with thymic small cell carcinoma (see below), and with thymoma or thymic carcinoma, particularly squamous cell carcinoma, adenosquamous carcinoma or undifferentiated carcinoma (1094, 1783, 1913). Three examples of carcinoid (including one goblet cell carcinoid (1124)) have been reported as components of mature cystic teratomas of the thymus (1124, 1707, 1787). Two of the three patients (age: 43–63 years) were females. The reported outcome was favourable after complete surgical removal, but follow-up time was short.

Poorly differentiated neuroendocrine thymic carcinomas

Large cell neuroendocrine carcinoma (LCNEC)
LCNECs of the thymus are non-small cell NECs with a mitotic rate of > 10 per 10 HPF (1691). Necrosis is almost always present and often extensive. The higher mitotic rate is the essential differentiating feature of this tumour from atypical carcinoid. In addition, large tumour cell size, including frankly anaplastic giant cells, are more common than in atypical carcinoids (349, 723, 1361). Neuroendocrine-type architectural features, such as nesting, cribriform, trabecular, and rosetting, may occur but are often less well developed compared with atypical carcinoids (1691).

Immunophenotype
NECs are virtually all immunoreactive for broad spectrum cytokeratins (AE1/3, CAM5.2), often showing a dot-like staining. In contrast to Merkel cell carcinoma, cytokeratin 20 is not expressed in small cell carcinomas of neuroendocrine type (SCNECs) (326).

Postulated cell of origin
Not definitively known. The relatively common occurrence of mixed NECs, squamous cell carcinomas of the thymus and the rare occurrence of neuroendocrine carcinoma associated with thymom argue in favour for a common thymic epithelial precursor as the progenitor of thymic NECs (2137).

Somatic genetics and genetic susceptibility
Classical cytogenetic or comparative genomic hybridization data on sporadic thymic NECs have not been published. In a small series of MEN-1-associated...
NECs, 2 of 7 cases show losses in the 1p region, while LOH at the MEN-1 locus at 11q13 is consistently absent [1989]. Therefore, a tumour suppressor gene on 1p, in addition to MEN-1 mutations, has been considered a candidate playing a role in the oncogenesis of thymic NECs. In one study of atypical carcinoids, DNA cytometry revealed aneuploidy in only 1 of 12 cases [723]. This aneuploid case was extensively metastatic (as were 3 euploid cases).

**Differential diagnosis**

NECs of the thymus are difficult to distinguish from the much more frequent mediastinal metastasis of pulmonary NECs [2137]. Immunohistochemical detection of TTF-1 expression might be helpful in distinguishing carcinoids and LCNEC of the lung from their thymic counterparts, since most thymic carcinoids [1513] and LCNECs are TTF-1 negative, while pulmonary NECs are TTF-1 positive in 50–75% of cases [272, 600,975], although the TTF-1 expression status in pulmonary carcinoids has been questioned recently [1894]. Of note, TTF-1 negativity of a carcinoid in the mediastinum does not exclude metastasis from a gastrointestinal or pancreatic primary, since carcinoids in these locations are generally TTF-1 negative [272]. Whether TTF-1 is a useful marker to distinguish thymic SCNEC from the metastasis of small cell carcinoma of lung cancer is unclear [27,351,975]. Otherwise typical thymic carcinomas with endocrine cells have to be distinguished from thymic NECs. The latter typically express neuroendocrine markers in a diffuse manner in >50% of tumour cells, while reactivity is restricted to scattered cells in thymic carcinomas [853,1139].

Spindle cell carcinoids can resemble other spindle cell tumours of the thymus, including type A thymoma and synovial sarcoma, which are also cytokeratin-positive but lack finely granular chromatin pattern and neuroendocrine features. Nerve sheath tumours can be positive for NCAM/CD56, but lack cytokeratin and more specific neuroendocrine markers like chromogranin or synaptophysin. Paragangliomas can closely mimic carcinoids by virtue of the similar architecture, high vascularity, strong expression of neuroendocrine markers, possible pigmentation, and possible association with Cushing syndrome [857,1028,1092,1114,1350,1548]. In addition, carcinoids can occasionally show S100 positive sustentacular cells around nests of tumour cells [109,450]. The distinguishing features of carcinoids include: trabecular growth pattern, if present, and expression of cytokeratins. In morphologically equivocal cytokeratin-positive neuroendocrine tumours, ultrastructural analysis may be helpful [2140].

**Prognosis and predictive factors**

Tumour stage has been found in most studies to be an important prognostic factor [528,628,723,1845,2144]. Atypical carcinoids are clearly aggressive, with 5-year and 10-year survival rates of 50-82% and 30%, respectively [628,723,1845,2141]. Among atypical carcinoids, a lower mitotic rate (<3/10 HPF), minimal atypia, and lack of necrosis [1361,1362] are associated with a more favourable prognosis. Sarcomatoid differentiation may denote highly malignant clinical behaviour [1090]. It appears that the prognosis of LCNEC is worse than that of atypical carcinoid. Thymic SCNEC are more aggressive than atypical carcinoids (median survival: 25–36 months) [1094,1841,2032,2143], although they are said to have a slightly better prognosis than their pulmonary counterparts [1808]. The poorly differentiated thymic NECs (small and large cell types) and NECs with combined features of carcinoid plus SCC are similarly highly aggressive, with patients dying of disease within 1 to 4 years [1361,1363]. Early and late recurrences (local or systemic) are common (1–10 years) [528,1902,2035] and appear to be associated with a bad prognosis [628,723,1362,1845]. Local progression or local recurrence is observed in the majority of patients that finally die [349,450,1094,1841,2032,2136]. Since the thymic NECs exhibit a poor response to chemo- and radiotherapy, radical resection of the primary tumour (together with local lymph nodes) must be a major therapeutic goal [450,628,723].

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Fig. 3.68 Large cell neuroendocrine carcinoma (LCNEC). A Brisk mitotic activity distinguishes this LCNEC from atypical carcinoid, while the degree of necrosis and cytologic atypia is not different. B Note cytological details on this high power magnification.
Fig. 3.69 Small cell carcinoma of the thymus. A Poorly differentiated neuroendocrine carcinoma: small cell carcinoma showing focal crush artifacts (low power). B Photomicrograph of primary small-cell neuroendocrine carcinoma of the thymus. C Cytological details: cellular crowding, elongated nuclei with salt and pepper chromatin structure, without recognizable nucleoli, scant cytoplasm, and high mitotic activity (high power). D Dense core granules are numerous in the cytoplasm of the tumour cells.
Tumours of the thymus

**Definition**

Combined thymic epithelial tumours are neoplasms with at least two distinct areas each corresponding to one of the histological thymoma and thymic carcinoma types, including neuroendocrine carcinomas. The approximate percentage of each component should be specified in the diagnosis. Type AB thymoma is a separate entity by definition and does not fall under this category.

**ICD-O code:** Code the most aggressive component.

**Synonyms**

Composite thymomas; Composite thymoma-thymic carcinoma; Mixed neuroendocrine carcinoma-thymoma.

**Epidemiology**

Combined thymic epithelial tumours showing either A or AB thymoma areas combined with one of the type B thymoma subtypes or thymic carcinoma components are exceptionally rare (<1%). Likewise, combined neuroendocrine thymic carcinoma-thymoma, and combined neuroendocrine/non-neuroendocrine thymic carcinomas are exceedingly seldom (<1%), while combined B3 thymoma-thymic squamous cell carcinomas are a bit more common (~1%). By contrast, various combinations of the type B thymoma subtypes B1, B2 and B3 account for 10-15% of all cases in large series [341,541]. Combined B2/B3 thymoma is by far the most common combined thymoma (8-12%), in accordance with the close morphologic and genetic relationship between B2 and B3 thymomas [897]. Combined thymomas are not different from the respective individual thymomas in terms of age and sex association. Combined neuroendocrine thymic carcinoma-thymoma are tumours of adults, with most cases reported at age 50-60. There is a male predominance.

**Etiology**

The etiology of these tumours remains enigmatic. Unpublished genetic studies suggest that combined thymic epithelial tumours can arise by dedifferentiation of thymoma/thymic carcinoma or by biphasic differentiation of a multipotential thymic epithelial precursor. The concept of tumour collision awaits genetic evidence [1841].

**Localization**

Almost all cases were observed in the anterior mediastinum.

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**Clinical features**

There are no differences in the clinical manifestations of combined thymomas as compared to the individual components. Myasthenia gravis (MG) is by far the most common paraneoplastic manifestation (60-72%). One patient in our series of 107 combined thymic epithelial tumours presented with sarcoidosis, another patient with amyotrophic lateral sclerosis in addition to MG. In combined neuroendocrine thymic carcinoma-thymoma, myasthenia gravis, pure red cell aplasia [358,1336] and the carcinoid syndrome [1557] may occur.

**Macroscopy**

The size of combined tumours does not differ from that of the respective non-combined individual components.

**Tumour spread and staging**

All reported cases occurred in the anterior or mediastinum as Masaoka stage I (6%), stage II (45%), stage III (29%), or stage IV (19%) tumours with intrathoracic metastases to pleura, lung and lymph nodes.

**Histopathology**

Among thymomas and thymic carcinomas, over 80% of combined tumours have clearly distinguishable, circumscribed areas showing typical B2 and B3 differentiation. Other common combinations are those of B1 and B2 (10%) or of B3 and non-neuroendocrine thymic carcinoma (5-7%). The carcinoma component in most cases is a squamous cell carcinoma. Lymphoepithelioma-like, sarcomatoid/anaplastic or undifferentiated carcinomas are uncommon. Rare cases of combined AB and B2 thymoma [341,1912], and spindle cell (type A) thymomas in combination with thymic squamous cell [1912], papillary [541,1263], sarcomatoid or undifferentiated carcinoma have been observed, implying emergence of thymic carcinoma from a benign thymoma subtype. Among neuroendocrine carcinomas (NECs), tumours composed of a (usually

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**Table 3.07**

Combined neuroendocrine carcinoma–thymoma/thymic carcinomas reported in the literature.

<table>
<thead>
<tr>
<th>Type of thymoma: descriptive terms</th>
<th>Corresponding WHO Classification</th>
<th>Corresponding neuroendocrine tumour</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spindle cell thymoma</td>
<td>AB (?)</td>
<td>Thymic carcinoid</td>
<td>(358)</td>
</tr>
<tr>
<td>Lymphocyte-rich thymoma</td>
<td>B2</td>
<td>Thymic carcinoid</td>
<td>(1336)</td>
</tr>
<tr>
<td>Epithelial cell predominant thymoma</td>
<td>B3</td>
<td>Thymic carcinoid</td>
<td>(1808)</td>
</tr>
<tr>
<td>Undifferentiated thymic carcinoma</td>
<td>C</td>
<td>Thymic carcinoid</td>
<td>(1783)</td>
</tr>
<tr>
<td>Sarcomatoid thymic carcinoma</td>
<td>C</td>
<td>Thymic carcinoid</td>
<td>(1557)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>C</td>
<td>Small cell carcinoma</td>
<td>(1841)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>C</td>
<td>Small cell carcinoma</td>
<td>(1094)</td>
</tr>
</tbody>
</table>
Combined thymic epithelial tumours

Atypical) carcinoid component and a poorly differentiated NEC (small cell carcinoma or large cell neuroendocrine carcinoma) component have been reported {1362,1363,2142}. To be designated combined neuroendocrine carcinoma–thymoma/thymic carcinoma, both tumour components should make up such a proportion of the tumour that both components can be readily recognized on H&E staining. By immunohistochemical or ultrastructural studies, scattered epithelial cells or small epithelial cell clusters with neuroendocrine features can be detected in rare conventional thymomas and many thymic carcinomas {39,853,1091,1139}. The term mixed neuroendocrine carcinoma–thymoma should not be used for these cases.

Somatic genetics

Genetic data have not been published. CGH studies on single cases of combined B2 and B3 thymomas or B3 and thymic carcinoma components suggest that the genetic alterations in these tumours are identical to those of their non-combined counterparts {896,2238, 2242} and that the individual components are clonally related. In one case of combined B3 thymoma and large cell neuroendocrine carcinoma, shared genetic alterations were observed, suggesting a common clonal origin of both tumour components.

Prognosis and predictive factors

Available data on combined thymomas suggest that the most aggressive component determines the clinical outcome {341,1912}. In one case of combined WHO Type B3 thymoma and thymic large cell neuroendocrine carcinoma, the patient died of widespread metastasis of the neuroendocrine carcinoma component.

Fig. 3.70 Combined thymic epithelial tumours. A Combined B2 + B3 thymoma. Lymphocyte-rich B2 component (left) adjacent to lymphocyte-poor B3 component (right). B Combined carcinoid and small cell carcinoma. Combined neuroendocrine carcinoma: carcinoid (right) and small cell carcinoma (left). C Combined neuroendocrine carcinoma/thymoma. Type B3 thymoma (right) adjacent to poorly differentiated (spindle cell) neuroendocrine carcinoma of the thymus (left). D Combined small cell and keratinizing squamous cell carcinoma. Sharp segregation between foci of small cell carcinoma and the round clusters of keratinizing squamous cell carcinoma.
The mediastinum is among the compartments of the body most frequently affected by germ cell tumours (GCT), second only to the gonads and ahead of other extragonadal GCT (EGGCT) that affect the retroperitoneum, sacrococcygeal region and central nervous system. Like their gonadal counterparts, mediastinal GCT can contain more than one histologic type of GCT and have been categorized for therapeutic purposes into pure seminomas, malignant non-seminomatous germ cell tumours (NSGCT, including embryonal carcinoma, yolk sac tumour, choriocarcinoma, and mixed GCTs), and teratomas. Mixed GCTs account for 34% of all mediastinal GCT and are, therefore, relatively less frequent than gonadal mixed GCTs.

As with the testicular germ cell tumours, there is a separate group of mediastinal germ cell tumours that present in infancy and early childhood that are comprised solely of teratomatous and yolk sac tumour components. The preference of germ cell tumours (GCT) for the mediastinum has been explained by the distribution of fetal germ cell precursors (primordial germ cells) that migrate from the yolk sac to paired midline structures called germinal ridges which during very early development extend virtually throughout the axial dimension of the body during fetal development [1204]. If arrested during migration, some germ cell precursors may survive and serve as cells of origin for subsequent GCT development. Although mediastinal NSGCTs exhibit a worse prognosis than their gonadal counterparts [199] and can show virtually unique biological features (like clonally related haematologic neoplasms [315,1461,2246]), recent genetic and epigenetic data support the concept that most gonadal and mediastinal GCTs share a common primordial germ cell ancestry [257,316,1764,1766]. However, since thymic epithelial stem cells and their plasticity have only partially been characterized [181], a somatic stem cell derivation of at least some mediastinal GCTs has not been excluded to date [860,2116].

**Basis of the classification**

The terminology recommended for mediastinal GCT is the same as for germ cell tumours of the gonads [526]. The close embryologic relationship and generally similar morphological, genetic, clinical and biological features of GCTs support this concept. However, GCTs associated with haematologic malignancies are virtually unique to mediastinal GCTs, while monodermal teratomas, which are well known in the gonads, have not been observed in the mediastinum.

**Epidemiology**

Mediastinal germ cell tumours are rare neoplasms, representing less than 1% of all malignancies and 3-4% of all germ cell tumours in both adults and children [1033,1764]. Mediastinal GCT account for up to 16% of mediastinal neoplasms in adults and for 19-25% of mediastinal tumours in children [1356,1954]. Although annual incidence rates for testicular GCT are strikingly different between Caucasians (~10/100,000) and Africans and Asians (1-2/100,000) similar incidence rates for mediastinal GCTs of about 0.1-0.2 per 100,000 can be calculated from Japanese [1955] and European nation-wide data [674]. Mediastinal GCTs occur at all ages (0-79 years), though there is a bimodal age distribution, with a distinct peak in infancy [1356]. Children and adolescents (<18 years) account for 16-25% of all cases [1356,1954]. These can be divided into post-pubertal mediastinal germ cell tumours (which simply represent the lower end of the age distribution of adult GCT) and prepubertal mediastinal GCT [1764]. This bimodal age distribution corresponds to differences in genetic aberrations, sex predilection, and clinical outcome.

Post-pubertal mediastinal GCT account for 1-3% of all GCTs [721]. The mean age of affected adults is 33 years for seminoma patients and 28 years for patients with an NSGCT [199,721,790]. The distribution of the histologic types varies from study to study. In some studies, mature teratoma is the most common single entity, while seminoma represents the largest histologic subentity among malignant mediastinal GCTs [1954]. In other studies, seminoma is the leading entity overall [721,1033]. In adults, mature teratomas [1356] and malignant mediastinal germ cell tumours for all practical purposes are restricted to males [1691], though rare exceptions occur [411], including germinomas in females [229,1805,1954,2116].

In children (including adolescents), mediastinal GCT account for 4% of all paediatric GCTs [1764]. Among extragonadal germ cell tumours mediastinal cases are third only to sacrococcygeal and central nervous system GCTs [721,1763]. In prepubertal children (<8 years), teratoma and yolk sac tumours are most prevalent, and other malignant histologic subtypes are virtually nonexistent [1764,1955]. The majority of these lesions present in infancy and early childhood. In prepubertal patients, teratomas have no sex predilection, whereas yolk sac tumours demonstrate a female predominance in young children with a 4:1 F: M ratio [1763].

**Etiology**

The etiology of mediastinal germ cell tumours is unknown. The only established risk factor for mediastinal non-seminomatous GCT development is Klinefelter (KF) syndrome (reported risk 50 to several hundred-fold) [793,795]. The underlying pathogenetic mechanisms are, however, not understood. In KF patients, NSGCT develop from early adolescence to the age of 30. The increased frequency of GCTs is linked to the 47, XXY genotype, while men with mosaic KF syndrome (46, XXY) have no significantly increased risk [480,793]. Of note, testicular GCTs are not increased in patients with Klinefelter syndrome (793), suggesting a unique oncogenic pathway for mediastinal non-seminomatous germ
Table 3.08
Clinical categorization of mediastinal germ cell tumours helps to guide the decision about neoadjuvant chemotherapy before radical resection and complete histological work-up. Clinical categories are derived from the synopsis of (i) the pathological diagnosis that is usually based on fine needle biopsies, (ii) serum tumour marker levels (AFP, beta-hCG) and (iii) imaging studies.

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>Therapeutic implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Chemotherapy and/or irradiation</td>
</tr>
<tr>
<td>Malignant &quot;non-seminomatous GCTs&quot;</td>
<td>Chemotherapy, followed by resection of tumour remnants (irrespective of the histology)</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>Resection</td>
</tr>
<tr>
<td>Yolk sac tumours</td>
<td>Children: resection</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Adults: depending on tumour stage</td>
</tr>
<tr>
<td>Mixed germ cell tumours</td>
<td></td>
</tr>
<tr>
<td>Mature teratoma&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Immature teratoma&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

1 If patients with “pure” seminomas or “pure” teratomas as defined by fine needle biopsy exhibit elevated, age-adjusted tumour marker levels (696), tumours are included in the “non-seminomatous” category. Sampling error is the most likely explanation for the discrepancy between histopathological diagnosis and clinical category.
2 Elevated beta-hCG levels <100 IU/L (in adults) and <25 IU/L (in children) are compatible with a fine needle biopsy-based diagnosis of “pure” seminoma (197,696,1764).

Germ cell tumours (NGST) development in KF patients. Apart from the well established association between haematologic malignancies and mediastinal NSGCTs, the frequency of other neoplasms is not increased (788) in patients with mediastinal GCT, arguing against a role of common cancer susceptibility genes in the development of mediastinal GCTs.

Site of involvement
The large majority of primary mediastinal GCTs arise within or adjacent to the thymus, but teratomas and yolk sac tumours (123) have also been described in the posterior mediastinum (1955), in an intrapericardial location (172,1129,1293), and sometimes even within the pericardium (1764).

Clinical features
Signs and symptoms
Mature teratomas are incidental findings in 50% of children and 66% of adults, while only 38% and 10% of patients with seminoma and malignant NSGCT, respectively, are asymptomatic (1954). Presenting symptoms of GCTs are related to the local mass lesion and comprise chest pain (52%), respiratory distress (48%), cough (24%), hoarseness (14%) and the superior vena cava syndrome (14%) (1954).

Respiratory compromise is more common in neonates and children than in adults, usually due to the extreme size of the neonatal vena cava syndrome is more frequent in adults than children. Hydrops fetalis is a typical complication of pericardial teratoma (1129,1834).

Fever and formation of multilocular thymic cysts result from local inflammatory reactions that frequently accompany GCTs and are most prominent in seminomas.

Precocious puberty due to increased beta-hCG levels can accompany mediastinal NSGCTs or mixed GCT (1769). Children with Klinefelter syndrome and mediastinal NSGCTs have a particularly high frequency of precocious puberty (795,1106).

Metastasis. Clinical symptoms related to metastatic spread may dominate. Most often symptoms are related to metastasis to the bone, liver, brain (518), retroperitoneum and heart (40).

Paraneoplastic autoimmune diseases, particularly myastenia gravis, are virtually non-existent.

Haematologic proliferations associated with mediastinal GCT. An almost unique complication of mediastinal NSGCTs as compared to other extragonadal or testicular (1243) GCTs is the development of acute leukaemias (199,1132), malignant or benign (2246) histiocytosis (83,129,474,1112,1461), myelodysplastic syndromes (MDS) or myeloproliferative diseases and haemophagocytic syndromes (83,1450,2055). These haematologic proliferations occur in 2-6% of NSGCTs (199,789), are clonally related to the GCTs (315,1113,1461) and develop independently of chemotherapy (474,1461).

Secondary MDS and AML that are related to etoposide chemotherapy in patients with mediastinal GCTs (100,1047) must be distinguished from clonally-related haematologic malignancies. Secondary MDS and AML occurred in ~1.0% of cases in a large series (1047). Chemotherapy-related AMLs usually manifest later (25–60 months after chemotherapy) than GCT-related AMLs (median time to onset 6 months, range 0–122) (789,1461).

Metachronous testicular cancers in mediastinal GCTs. The risk for the development of metachronous testicular cancer (MTC) is low in mediastinal GCTs (10-year cumulative risk ~6%) (199,787). MTCs are seminomas in ~70% of cases, although the underlying extragonadal GCT usually is a NSGCT (787). Intratubular germ cell neoplasia of the testis is a rare accompanying finding in mediastinal GCTs (757).

Imaging
Pure seminomas, with few exceptions (1810), form uncalcified, homogeneous masses indistinguishable from lymphoma (1888). By contrast, NSGCTs are usually heterogeneous masses, exhibiting central attenuation and a frond-like periphery (1888). Since multilocular thymic cyst formation is a stereotypic response of the thymus to inflammatory stimuli, multilocular cystic lesions are not only typical for mature teratomas but accompany many other mediastinal GCT (particularly seminoma), thymomas, thymic carcinomas, Hodgkin or non-Hodgkin lymphomas or metastasis to the mediastinum.

A diagnosis of primary mediastinal GCT requires absence of a testicular or ovarian tumour on physical examination, high resolution ultrasonography, or MRI scan (198). A bilateral testicular biopsy is not...
mandatory for diagnosis of mediastinal GCTs.

**Tumour markers**

In patients with mature teratomas, tumour markers are almost always negative in the serum. By contrast, a-fetoprotein (AFP) and/or beta-human chorionic gonadotropin (beta-hCG) are elevated in 80-90% of malignant GCTs [1764]. AFP positivity is more frequent (~73%) than increased serum levels of beta-hCG (~27%) [1955]. In adults, tumour marker levels at first presentation are criteria for the risk grouping (good, intermediate, poor) of GCT according to the IGCCCG system [4] as given in Table 3.09. In addition, unsatisfactory decline of AFP and/or beta-hCG levels during the early phase of chemotherapy appears to herald lack of tumour responsiveness and is therefore associated with a worse outcome [1273]. On the other hand, decline of tumour markers in spite of persistence or enlargement of a mediastinal GCT on repeated imaging can be due to the “growing teratoma syndrome” or somatic-type malignancy accompanying a chemosensitive GCT.

**Tumour spread and staging**

When all mediastinal GCT are considered, metastasis has been observed in ~20% of cases [1356,1359]. While mature teratomas do not metastasize, mediastinal seminomas show metastasis in up to 41% of cases [197,199]. In mediastinal NSGCT, metastasis to at least one site is present in 85-95% of patients at presentation, and hematogenous metastasis is the predominant type of dissemination. In contrast, lymph node metastasis is particularly common in seminomas. Haematogenous metastases typically involve lung (38%), bone, liver, brain [518], retroperitoneum and heart [40]. Metastasis is a major criterion for staging and is an adverse prognostic factor in seminomas [790] and NSGCT [199, 790].

A modification of the TNM classification of soft tissue tumours is recommended for staging of mediastinal GCTs.

**Genetics**

As indicated above, most GCT at extragonadal sites have been demonstrated to arise in primordial germ cells that have undergone erasure of imprinting prior to migration [1766]. The factors responsible for the aberrant migration pathways and the ability of the germ cells to survive at the extragonadal sites are largely unknown. However, primordial germ cell migration has been shown to be determined by the ckit, stem cell factor receptor ligand pair. Abnormalities in expression of either the receptor or the ligand at any site in this pathway may result in abnormal migration or survival [1004].

The genetic changes that have been documented in primary mediastinal germ cell tumours vary with age at presentation and parallel the genetic changes found in germ cell tumours arising at gonadal sites in comparable age groups. This results in three categories of genetic changes within mediastinal germ cell tumours:

- **Malignant mediastinal germ cell tumours in infants and young children** almost exclusively show yolk sac tumour histology. These tumours may be diploid or near-tetraploid and are uncommonly aneuploid [1517,1765]. Cytogenetic and comparative genomic hybridization (CGH) analysis of such tumours demonstrate gain of chromosomes 1q, 3, and 20q and loss of chromosomes 1p, 4q, and 6q [1765]. The same genetic changes have been identified in infantile yolk sac tumours of the sacral region and testis [1572,1573]. The two loci that have received additional attention and study are loss of distal 1p and loss of distal 6q [874,1574,1881]. Loss of distal 1p has been identified in 80% of infantile YST and is particularly intriguing due to its established role in another embryonal tumour of infancy, neuroblastoma. While candidate tumour suppressor genes have been identified at this site, these have not been substantiated or confirmed. Loss of distal 6q is of interest due to the location of the potential tumour suppressor gene insulin growth factor type II receptor. IGF2R has multiple activities, one of which is to degrade IGF2, a potent growth promoter. Specific deletions, mutations, or imprinting abnormalities of IGF2R have not been documented.

- **Malignant mediastinal germ cell tumours in adolescents and adults** demonstrate ploidy and genetic features similar to those described in their gonadal counterparts. In contrast to the tumours of young children, tumours in this category are usually aneuploid and demonstrate gain of chromosome12p, regardless of the histologic subtype [316,1765]. This observation correlates with the presence of an isochromosome 12p [1057,1392,2230], which has been found in 84% of 25 malignant mediastinal germ cell tumours in adults reported to date [316].

The isochromosome 12p is formed by the duplication and centromeric fusion of the short arm of one chromosome, and loss of the long arm. In other patients amplification of fragment of the chromosome12p, regardless of the histologic subtype [316,1765]. This observation correlates with the presence of an isochromosome 12p [1057,1392,2230], which has been found in 84% of 25 malignant mediastinal germ cell tumours in adults reported to date [316].

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**Table 3.09**

IGCCCG criteria for the prognostic factor-based clinical “risk grouping” of malignant GCT in adults [4].

<table>
<thead>
<tr>
<th>IGCCCG Group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Seminoma: No non-pulmonary visceral metastases AND normal AFP, any HCG, any LDH. Non-Seminoma: no patients classified as good prognosis</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Seminoma: non-pulmonary visceral metastases AND normal AFP, any HCG, any LDH. Non-Seminoma: no patients classified as intermediate prognosis</td>
</tr>
<tr>
<td>Poor</td>
<td>Seminoma: no patients classified as poor prognosis. Non-Seminoma: all patients with mediastinal Non-Seminoma are classified as poor prognosis</td>
</tr>
</tbody>
</table>

IGCCCG= International Germ Cell Cancer Collaborative Group
Histology

Clinical behaviour

M=F

Recurrent genetic aberrations

Pure mediastinal teratomas (immature and mature) arising in all ages have demonstrated no genetic gains or losses (258,860,1765). This observation is similar to those described in mature teratomas of the ovary, the infant testis, and other extragonadal sites in infants. However, it is distinctly different from genetic reports of mature teratomas in the adult testis, in which aneuploidy and the isochromosome 12p have been identified. Therefore, due to the extreme rarity of mature mediastinal teratomas in post-puberty males, caution is recommended prior to assuming a benign clinical behaviour in such cases. Supporting this is evidence provided by tumours that contain a mixture of teratoma and malignant germ cell histologies. In those cases for which it was possible to analyze the teratoma component separately from the malignant component, these tumours demonstrated similar abnormal CGH profiles within both the teratomatous and the malignant components (1765). Similar findings have been reported at other sites (1205).

In addition to the above changes, post-pubertal malignant mediastinal GCTs have long been associated with Klinefelter syndrome (480,793,795,1459,2246). The majority of adolescent and adult mediastinal malignant germ cell tumours arise in males (1359), and up to half of these patients show an additional X chromosome within their peripheral blood lymphocytes (258,1765). Therefore, adolescent males presenting with malignant mediastinal GCT should be evaluated for Klinefelter syndrome. No genetic differences between mediastinal GCT in individuals with and without Klinefelter syndrome have been described, and the underlying cause of the increased frequency of GCT in patients with Klinefelter syndrome is unknown. Constitutional sex chromosomal abnormalities have not been identified in mediastinal germ cell tumours of young children.

Prognostic factors

In the era of cisplatin-based chemotherapy for malignant GCTs, the most important “natural” prognostic factors in extragonadal GCTs are histology and localization of the primary tumour (997,1461,1955).

In NSGCTs, mediastinal localization is associated with a worse prognosis compared to their counterparts at other extragonadal and gonadal sites (105,790,1159,1233,1764). However, recent neoadjuvant strategies achieved dramatically improved outcomes also in NSGCTs of children (1764) and adults (198,199,588).

Initial AFP levels >10,000 ng/ml indicate a worse prognosis in children (105) while elevated beta-hCG is an independent adverse prognostic factor for survival in adults (199).

Seminomas show a favourable response to radiotherapy and cisplatin-based chemotherapies, and their excellent prognosis (~90% survival) is not different from the prognosis of seminomas in other locations (198,199,790,1159,1955). Adverse prognostic parameters in seminomas are liver metastasis or metastases to multiple other sites (790).

Mature mediastinal teratomas have an excellent prognosis after complete resection in all age groups. In infants, tumours may be quite large and associated with developmental abnormalities due to compression of adjacent structures during development. Tumour-related deaths almost never occur when the tumour is able to be resected (721,1159,1955).

Following preoperative cisplatin-based chemotherapies of malignant GCTs, completeness of resection (786,787,1764) less than 10% viable cells (588) and low-risk features according to the IGCCCG grouping system (4) are favourable prognostic factors. Decreased survival is associated with failure to respond to cisplatin and higher rates of relapses (790). Unsatisfactory decline of AFP and/or beta-hCG levels during the early phase of chemotherapy appears to herald a worse outcome (1273). Treatment failure is among the worst prognostic factors and is more common in mediastinal than other GCTs and is significantly associated with non-seminomatous histology and metastasis to liver, lung and brain (790).

Table 3.10

<table>
<thead>
<tr>
<th>Age at clinical presentation</th>
<th>Histology</th>
<th>Sex predilection</th>
<th>Clinical behaviour</th>
<th>Recurrent genetic aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>Teratoma (mature and immature)</td>
<td>M=F</td>
<td>Benign if resectable</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Yolk sac tumour</td>
<td>F&gt;M</td>
<td>Malignant (80% survival)</td>
<td>del(6q), del(1p), gain 20q, gain 1p diploidy or tetraploidy</td>
</tr>
<tr>
<td>Adolescents and Adults</td>
<td>Teratoma (mature and immature)</td>
<td>M&gt;&gt;F</td>
<td>Benign</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Malignant GCT (all histologic subtypes)</td>
<td>M&gt;&gt;F</td>
<td>Malignant (50% survival)</td>
<td>i(12p), gain 21, loss 13, loss of Y, +Xc*, aneuploidy</td>
</tr>
</tbody>
</table>

* +Xc, constitutional gain of the X-chromosome (Klinefelter syndrome)
Seminoma

Definition
A primitive germ cell tumour composed of fairly uniform cells with clear or eosinophilic, glycogen-rich cytoplasm, distinct cell borders, and a round nucleus with one or more nucleoli, resembling primordial germ cells. Mediastinal seminomas are morphologically indistinguishable from their gonadal counterparts.

ICD-O code
9061/3

Epidemiology
Seminomas are rare mediastinal germ cell tumours first described in 1955 (2170). Only 2 to 5% of all adult germ cell tumours arise in the mediastinum. Among extragonadal germ cell tumours, primary mediastinal seminomas account for 8% of cases (197,198). In a large series reported from Japan, only 1.6% of primary mediastinal neoplasms are pure seminomas (1955). The reported frequency of pure seminomas among primary mediastinal germ cell tumours ranges from 9% to 39% (520,1356,1371,1955), ranking seminoma second in frequency following teratoma (520,1356,1371). The size of the tumour may be rather large due to slow constant growth with overall little clinical symptoms. Moderate serum beta-hCG elevation (≤100 IU/L in adults and ≤25 IU/L in children) may be found in up to one third of patients and is still compatible with the diagnosis of pure seminoma (197,696).

At the time of diagnosis, the majority of mediastinal seminomas are localized, circumscribed masses without macroscopic or microscopic evidence of invasion into neighbouring organs such as pleura, pericardium, and great vessels (1371). The preferential sites of distant spread, if present, are the lung, chest wall, brain, pleura, liver, adrenal gland, and bone (1349,1356). Lymph node metastases most commonly occur in cervical and abdominal lymph nodes (in one series in 25% and 8%, respectively) (197).

Clinical features
Mediastinal seminomas typically arise in the anterior mediastinum, although a few cases have been reported to arise in the posterior mediastinum (1955). Clinical symptoms are non-specific. Patients may present with symptoms related to a mediastinal mass, e.g. chest pain, dyspnoea, cough, superior vena cava syndrome. Some patients are asymptomatic, with the tumour being detected by routine X-ray or during unrelated thoracotomy (1371). The size of the tumour may be rather large due to slow constant growth with overall little clinical symptoms. Moderate serum beta-hCG elevation (≤100 IU/L in adults and ≤25 IU/L in children) may be found in up to one third of patients and is still compatible with the diagnosis of pure seminoma (197,696).

Etiology
The cellular origin of mediastinal seminomas is controversial (316). Apart from gonads, seminomas may occur at other sites in the human body along the midline, such as the pineal gland, retroperitoneum, or the sacral area. During embryogenesis, migratory primordial germ cells may become misplaced along the midline on their way from the yolk sac to the embryonic gonadal ridge (293,1356). A derivation from thymic myoid cells or from occult testicular intratubular germ cell tumour has been discussed (316,1689). Yet, in contrast to patients with retroperitoneal seminomas, no testicular intraepithelial neoplasia is observed in patients with mediastinal germ cell tumours (193,440,441).

The histogenetic relationship between mediastinal and gonadal seminoma is controversial. Genetic analysis of mediastinal seminomas have shown similar patterns of non-random chromosomal changes, in particular the presence of i(12p), as in gonadal seminoma (314,316), suggesting a very close pathogenetic relationship between seminomas at either sites. However, other studies...
report significant differences between the two. Compared with testicular seminomas, in one series, mediastinal seminomas are reported to more frequently express CAM5.2 (80% vs 21%), keratin (68% vs 0%), PLAP (93% vs 50%) and vimentin (70% vs 46%), possibly reflecting a more mature degree of tumour cell differentiation in the latter [1920]. KIT mutational analysis showed a different mutational pattern in mediastinal seminoma compared with testicular seminoma [1623].

While Klinefelter syndrome is a risk factor for nonseminomatous mediastinal germ cell tumours, seminomas have not been observed [794].

Morphology

Mediastinal seminomas are morphologically identical to their gonadal counterparts. Macroscopically, they are mostly well-circumscribed, fleshy tumours with a homogeneous, slightly lobulated to multinodular, tan-grey or pale cut surfaces. Punctate focal hemorrhage and yellowish foci of necrosis may be observed. The tumour size ranges from 1 to 20 cm (median size 4.6 cm) [197, 1371].

Microscopically, mediastinal seminomas are composed of round to polygonal, fairly uniform tumour cells with round to oval, central, slightly squared, non-overlapping nuclei and one or more large central nucleoli. The tumour cells commonly have abundant glycogen-rich, clear to lightly eosinophilic cytoplasm and distinct cell membranes. Rarely, the tumour cells may show a dense eosinophilic cytoplasm or a greater degree of cellular pleomorphism. The tumour cells grow in confluent multinodular clusters, sheets, cords, strands or irregular lobules displaying a nesting pattern. Between the tumour cell aggregates, delicate fibrous septa are often observed.

Frequently, there is a prominent inflammatory cellular background infiltrate of small mature lymphocytes, plasma cells and occasional eosinophils. The infiltrate is typically most dense in and around the fibrous septa, but is also intermingled with the tumour cells. A granulomatous reaction ranging from ill-defined clusters of epithelioid histiocytes to well-defined epithelioid granulomas with Langhans giant cells may be present. Occasionally, germinal centers are present. The brisk inflammatory, granulomatous reaction and scar formation may obscure the underlying seminoma [1354,1371].

In some cases, large syncytiotrophoblastic cells are scattered throughout the tumour, often in close proximity to capillaries and/or focal microhaemorrhage. These giant cells are multinucleated, with abundant basophilic cytoplasm and occasional intracytoplasmic lacunae. However, there are no cytotrophoblast cells or confluent nodules as in choriocarcinoma.

**Fig. 3.72 Seminoma.** A Large tumour cells with broad clear cytoplasm, large nuclei and conspicuous nucleoli. A light infiltrate of lymphocytes is present among the tumour cells and in the septa. B Mediastinal seminoma accompanied by lymphocytes and epithelioid cells including multinucleated giant cells. C Syncytiotrophoblast in mediastinal seminoma. D Immunoreactivity for CD117 in thymic seminoma.
In a quarter of cases, remnants of thymic tissue can be found within or at the periphery \cite{1356,1371}. In 10%, the thymic remnants undergo prominent cystic changes similar to multicellular thymic cysts, probably reflecting cystic transformation of remnant thymic epithelium induced by seminoma cells \cite{1354}. In some cases, the thymic epithelium undergoes hyperplasia, and may lead to a misdiagnosis of thymic epithelial tumour. Seminoma can also occur as a component in mixed germ cell tumours. Spermatocytic seminomas have not been described in the mediastinum. Mediastinal seminomas commonly show diastase-labile PAS staining due to the presence of abundant glycogen.

**Immunohistochemistry**

Immunohistochemically, 80-90% of mediastinal seminomas are reported to be positive for PLAP, and 70% show vimentin positivity. CD117 positivity in a cell membrane or paranuclear Golgi pattern is common \cite{1623}. Although up to 70% of cases show staining for pankeratin, the staining is often only focal, weak, and paranuclear. Immunostaining for beta-hCG highlights the scattered syncytiotrophoblastic cells, if present, and also isolated seminoma cells in about 5% of cases. CEA, EMA, and AFP are negative \cite{1356,1371,1920}.

While it is prudent to rule out metastatic disease from a primary gonadal seminoma, mediastinal metastases are rare in gonadal seminomas, in particular in the absence of retroperitoneal lymph node metastasis \cite{996}. Other differential diagnoses include metastatic melanoma, lymphoma, thymoma, thymic carcinoma, and in particular clear cell carcinoma (primary or metastatic).

**Genetics**

The genetic changes that have been described in mediastinal seminomas are the same as those reported in testicular seminomas, with 69% demonstrating the isochromosome i(12p) characteristic of post-pubertal malignant germ cell tumours at all sites. Mediastinal seminomas are most commonly aneuploid, with a minority having near-tetraploid DNA content.

**Prognosis**

Compared with mediastinal nonseminomatous germ cell tumours, pure mediastinal seminomas are associated with a favourable prognosis. A 5-year survival rate of 90% can be achieved with cisplatin-based combination chemotherapy which has largely replaced radiotherapy as the initial treatment in patients with mediastinal seminoma \cite{197,198}. Primary radiotherapy seems to be associated with a higher recurrence rate, but most patients have been salvaged with subsequent chemotherapy \cite{197}. After completion of chemotherapy residual lesions detectable by radiographic studies frequently persist, in most cases consisting of necrotic masses that will ultimately shrink over time. In contrast to mediastinal nonseminomatous germ cell tumours, surgical resection is usually not indicated. Investigation by positron emission tomography (PET) is helpful in distinguishing viable from necrotic tumour residuals in seminoma patients \cite{460}. In a large international study on mediastinal seminomas, liver metastases, two or more metastatic sites, and the presence of non-pulmonary visceral metastases have been identified as negative prognostic factors. Metachronous testicular germ cell tumours in patients with mediastinal seminoma are exceedingly rare \cite{198}.
Embryonal carcinoma

Definition
A germ cell tumour (GCT) composed of large primitive cells of epithelial appearance with abundant clear or granular cytoplasm, resembling cells of the embryonic germ disk and growing in solid, papillary and glandular patterns.

IDC-O code
9070/3

Synonym
Malignant teratoma, undifferentiated

Epidemiology
Embryonal carcinoma (EC) of the mediastinum is a tumour of young males (M/F ratio, >10:1) [1033,1955]. It occurs in pure form or as a component in mixed germ cell tumours at about equal frequencies [1033,1369,1955]. ECs (pure or mixed) account for up to 12% of all mediastinal GCTs [1033,1356] and for 30-65% of all NSGCT [997,1356,1955]. The mean age of adult patients is 27 years (range: 18-67 years) [1032,1955]. In the literature, EC in childhood is very rare before the age of 1 year and peaks (usually as part of a mixed GCT) between 1 and 4 years of age and again after the age of 14 years [1764]. However, as the pathologic features of solid yolk sac tumour (YST), and its distinction from EC is increasingly recognized, it is evident that the vast majority, if not all, the tumours in prepubertal patients previously classified as EC are better classified as YST. In adults, EC as a component of mixed GCTs accounts for 9% of all mediastinal GCTs and for 75% of all NSGCT [1955]. EC is commonly associated with teratoma (56%), choriocarcinoma (22%) or seminoma (22%) [1032,1954]. The association with yolk sac tumour is very rare in adults [1955] but more common in adolescents [1369]. In adolescents, combined EC accounts for 15% of all GCT [1764] and for 27-33% [1111,1764] or even more [1111] of the non-seminomatous subgroup. EC in this group is a component of most mixed GCT (77%) [1111,1764]. The association with seminoma is equally frequent in children after puberty and adults (20-30%) [1764,1955].

Tumour spread
Local tumour spread is common and can lead to compression and infiltration of the lung. About 25% of pure or combined ECs already show pulmonary metastasis at presentation [1955]. Further specific information on tumour spread in mediastinal EC is not available. However, since pure or combined ECs are among the most frequent malignant mediastinal GCTs, it is reasonable to assume that spread of ECs is similar to that of the whole NSGCT group, in that there is a high rate (~50%) of haematogenous metastasis (to lung, liver, brain and bones), while lymphogenous metastasis is apparently much rarer [199].

Clincal features
Patients present with thoracic or shoulder pain (60%), respiratory distress (40%), hoarseness, cough or fever (<10%), or superior vena cava syndrome (12%) [1955]. Gynaecomastia is uncommon and asymptomatic patients are rare [1808]. A quarter of patients have pulmonary metastasis at presentation and virtually all patients exhibit increased serum AFP levels, while ßHGG levels are elevated in cases with a choriocarcinoma component [1955]. Imaging findings are not specifically different from those reported for other NSGCT [1684]. A minority of patients show features of Klinefelter syndrome [150,1290].

Etiology
The etiology of EC is unknown. The rare association with Klinefelter syndrome [150,1290] suggests a similar (but unresolved) etiology as in other mediastinal NSGCT. A single reported familial case [34] might indicate a fortuitous coincidence rather than a genetic predisposition. Risk factors for testicular GCTs [1204] appear largely irrelevant for the development of mediastinal GCTs [793].

Macroscopy
ECs are described as large tumours with invasion of the surrounding organs and structures. Grossly, the cut surface often reveals large areas of necrosis and haemorrhage. Viable tumour tissue is soft, fleshy, grey or white to pink or tan. In mixed GCT cystic spaces may be conspicuous.

Histopathology
Pure ECs show a more solid growth pattern than other NSGCTs. ECs form sheets, tubules or vague papillary structures composed of large polygonal or...
columnar cells. The nuclei are large, round or oval, often vesicular, and can be hyperchromatic or have a light chromatin. They can be crowded and overlapping. Prominent single or multiple nucleoli are common. The cell borders are often indistinct, especially in the solid areas. The cytoplasm is often amphophilic, but can be basophilic, eosinophilic, pale or clear (1808). As in seminoma, scattered single or small groups of syncytiotrophoblasts can occur in EC. Mitoses are numerous and often atypical. Extensive necrosis can occur, and is particularly prominent in ECs combined with yolk sac tumour. The stroma is usually scant in viable tumour areas, but fibrotic adjacent to areas with regressive changes. Scattered lymphocytes and a granulomatous reaction are uncommon.

In mixed GCTs, the EC component may be combined with a yolk sac tumour, teratoma, seminoma, choriocarcinoma, or combinations of these GCTs, and uncommonly somatic-type malignancies (1230).

**Immunohistochemistry**

CD30 (Ki-1) is expressed in 85-100% of pure EC or EC components of mixed germ cell tumours (1135,1534), while other germ cell tumours (with the exception of rare cases of seminomas and yolk sac tumours (855,1369)) and other non-haematopoietic neoplasms are CD30-negative (1369). There is distinct cell membrane staining with variable cytoplasmic positivity.

In addition, ECs are uniformly and strongly reactive with antibodies to low-molecular weight cytokeratins, while EMA, carinoembryonic antigen (CEA), and vimentin are usually negative. Alpha-fetoprotein (AFP) (1369,1920) and placental alkaline phosphatase (PLAP) (1808,1920) can occur in scattered tumour cells or small foci in about 30% of cases. One third of cases show beta-hCG expression in scattered syncytiotrophoblastic cells.

**Differential diagnosis**

When syncytial areas are extensive, EC can mimic choriocarcinoma (1369). However, a biphasic plexiform pattern produced by a mixture of syncytiotrophoblasts and cytotrophoblasts is lacking, and pure ECs lack the extensive beta-hCG immunoreactivity of choriocarcinoma (1369). Yolk sac tumours can be distinguished from EC by a more varied growth pattern (most commonly microcystic and reticular), smaller cell size, presence of Schiller-Duval bodies, and lack of CD30 expression. EC can be distinguished from seminoma by showing a greater degree of nuclear pleomorphism, at least focal definite epithelial characteristics (such as gland formation), uniform strong staining for cytokeratin, frequent CD30 expression, and usual lack of CD117 expression (1920). Mediastinal metastasis from large cell carcinoma of the lung can be a morphologic mimic (1369). The young age of most EC patients, CD30 expression, and the tumour markers in the serum (such as AFP and beta-hCG) are distinguishing features. Metastasis to the mediastinum from a testicular EC or mixed GCT (932,996) has to be excluded.

**Genetics**

The genetic changes that have been described in mediastinal EC are the same as those reported in their testicular counterparts and demonstrate the isochromosome 12p characteristic of post-pubertal malignant germ cell tumours at all sites. Mediastinal EC is rarely associated with Klinefelter syndrome (150,1290). A single familial case (34) cannot be taken as evidence for a genetic predisposition.

**Prognostic factors**

There are no reports focussing on the prognostic factors of mediastinal EC. However, since EC histology has not been shown to be an adverse prognostic factor in several large clinical studies (199,237,1462), it is likely that the prognostic factors described for NSGCT apply to EC. This conclusion is supported by a recent study: the long-term survival rate of ~50% in adult patients with mediastinal EC after cisplatin-based chemotherapy (1955) was very similar to the rates published for large series of adult NSGCT. Similar conclusions appear justified for children with EC, although 5-year survival rates are significantly better (>80%) than for adults (1764).

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Fig. 3.74 Embryonal carcinoma. A High power. Cytological details of a tumour with glandular growth pattern. B Strong membranous CD30 staining.
Yolk sac tumour

**Definition**
A tumour characterized by numerous patterns that recapitulate the yolk sac, allantois and extra-embryonic mesenchyme.

**ICD-O code** 9071/3

**Synonym**
Endodermal sinus tumour

**Epidemiology**
Mediastinal yolk sac tumours (YST) present in two distinct age groups. In infants and young children, YST is virtually the only malignant germ cell tumour histologic subtype seen and there is a strong predominance of females (F:M, 4:1) [1765]. In these patients it is usually the sole histologic subtype, however it may occasionally be accompanied by teratomatous elements. The age at presentation ranges from the newborn period to 7 years of age, with over 75% of these patients presenting within the first three years of life [1764]. In contrast, in post-pubertal patients YST is identified as the sole histologic element in approximately 10% of mediastinal tumours [1356,1369]. This is a much higher frequency than is seen in testicular sites, which may be due to the different cellular environments in which the tumours develop [316]. In addition, YSTs are often seen as one element within a mixed germ cell tumour [1369,1765,1955]. Like other mediastinal malignant GCT in post-pubertal patients, YST presents exclusively in males. The age at presentation ranges from 14 to 63 years [1369,1955].

**Clinical features**
Patients with mediastinal YST often present with chest pain, dyspnoea, chills, fever, and superior vena cava syndrome [1369,1955]. The site of involvement is almost invariably the anterior mediastinum. Regardless of the age, alpha fetoprotein (AFP) levels are elevated in over 90 percent of cases.

**Macroscopy**
Macroscopically, pure YSTs are solid, soft, and the cut surface is typically pale grey or grey-white and somewhat gelatinous or mucoid. Large tumours often show haemorrhage and necrosis.

**Histopathology**
The histology of YST is the same regardless of the age of the patient or the site of presentation. For detailed discussions of the protean manifestations of endodermal sinus tumour, several excellent reviews are available [1102,1963,2050]. Cytologically, YSTs are composed of small pale cells with scant cytoplasm and round to oval nuclei with small nucleoli. Uncommonly, the cells may be larger with prominent nucleoli, and may therefore be difficult to distinguish from embryonal carcinoma or germinoma. The virtual nonexistence of the latter two histologic subtypes in young children lessens this diagnostic difficulty in this setting. A number of different histologic patterns have been described; microcystic (reticular), macrocystic, glandular-aloeveral, endodermal sinus (pseudopapillary), myxomatous, hepatoid, enteric, polyvesicular vitelline, and solid [1102, 1963,1990]. The majority of yolk sac tumours show more than one histologic subtype, and the different subtypes often merge subtly from one to another. These many different histologic types have not been shown to have prognostic or biologic significance, but aid in the recognition of unusual YSTs. The reticular or microcystic variant is the most common histologic subtype, and is characterized by a loose network of spaces and channels with small cystic spaces lined by flattened or cuboidal cells with scant cytoplasm. A variant of the microcystic pattern is the myxomatous pattern in which the epithelial-like cells are separated by abundant myxomatous stroma. The endodermal sinus pattern has a pseudopapillary appearance and typically shows numerous Schiller-Duval bodies. These are glomeruloid structures with a central blood vessel covered by an inner rim of tumour cells, surrounded by a capsule lined by an outer (parietal) rim of tumour cells. The polyvesicular vitelline pattern is composed of compact connective tissue stroma containing cysts lined by cuboidal to flat tumour cells. The solid pattern is uncommon, and is usually...
Germ cell tumours

...seen only in small foci. This pattern may be difficult to distinguish from embryonal carcinoma or germinoma, however, the cells of yolk sac tumour are smaller and less pleomorphic. Unfortunately, these foci may be negative or only weakly positive for cytokeratin but usually retain their AFP positivity. Hepatoid and enteric variants are other less common forms of yolk sac tumour. The hepatoid pattern contains cells with abundant eosinophilic cytoplasm resembling fetal or adult liver. The enteric and endometroid patterns show glandular features resembling the fetal human gut and endometrial glands, respectively. If these patterns are seen within an immature teratoma it may be difficult to determine whether they represent immature fetal tissue or YST. Fortunately, these unusual patterns of YST are usually accompanied by other more common patterns.

Special studies

Schiller-Duval bodies are present in only 50 to 75% of YST, and are seen predominantly in the microcystic and endodermal sinus patterns. Therefore, these are not required for the diagnosis. Hyaline droplets are commonly present in YST. However, these may also be found in a minority of embryonal carcinomas, as well as in some other epithelial tumours. These are composed of a variety of proteins, and are PAS positive, resistant to diastase digestion. The droplets may be positive for AFP as well as alpha-1-antitrypsin, but often are not.

Genetics

The genetic changes identified in YST depend on the age at presentation. Prepubertal YST demonstrate the same recurrent genetic abnormalities described in infantile sacral and testicular YST, including loss of the short arm of chromosome 1 (in particular the 1p36 region), loss of the long arm of chromosome 6, and gain of the long arm of chromosomes 1, and 20, and the complete chromosome 22. In contrast, mediastinal YST following puberty are aneuploid and often demonstrate the isochromosome 12p characteristic of testicular malignant germ cell tumours in the same age group.

Prognosis and predictive factors

It is difficult to accurately provide prognostic information due to the rarity of these lesions, the variability in staging parameters utilized, and the variability in the chemotherapy provided. However, the most important predictive factor of both pre- and post-pubertal YST is the resectability of the primary lesion. This is more often possible in prepubertal patients due to a greater frequency of presentation at earlier stages. With cisplatin based chemotherapy these children have an overall survival of over 90%. In contrast, over half of post-pubertal mediastinal YST have metastatic disease at presentation and the majority of these die of their disease; stage 1 and 2 patients are uncommon but often survive, particularly following aggressive chemotherapy.
Definition
Choriocarcinoma is a highly malignant neoplasm displaying trophoblastic differentiation. It is composed of syncytiotrophoblast, cytotrophoblast and variably intermediate trophoblast cells. Mediastinal choriocarcinomas are morphologically indistinguishable from their gonadal or uterine counterparts.

ICD-O code 9100/3

Epidemiology
Pure mediastinal choriocarcinomas are exceedingly rare and virtually non-existent in children. Only 2.5 to 5% of mediastinal germ cell tumours are pure choriocarcinomas [997,1033,1356]. Pure choriocarcinoma constitute 9% of malignant mediastinal nonseminomatous germ cell tumours, and 4.3% of nonseminomatous germ cell tumours [1033,1349,1356].

Clinical features
The patients’ ages range from 17 to 63 (most commonly the 3rd decade of life), and almost all reported cases were male patients [520,1821,1955]. At diagnosis, mediastinal choriocarcinomas are mostly large anterior mediastinal masses (average size 10 cm) [1357]. Primary choriocarcinomas have also been observed in the posterior mediastinum [1357]. The patients present with symptoms due to the mediastinal mass, such as chest pain, dyspnoea, cough, superior vena cava syndrome. Patients may show gynecomastia due to elevated beta-hCG levels [1356,1821]. Mediastinal choriocarcinomas are highly aggressive neoplasms with early haematogeneous dissemination. In a series of 8 cases, metastases were observed in the lungs (88%), liver (50%), kidney (38%) and spleen (25%). Metastatic disease to the brain, heart, adrenals and bone has also been observed [1033,1357,1821].

Morphology
Mediastinal choriocarcinomas are large tumours with soft consistency and extensive hemorrhage and necrosis. Microscopically, they are composed of syncytiotrophoblast, cytotrophoblast and intermediate trophoblastic cells. Syncytiotrophoblasts are large multinucleated cells with numerous, pleomorphic, dark-staining nuclei, distinct nucleoli, and abundant densely eosinophilic cytoplasm which may contain cytoplasmic lacunae. Cytotrophoblasts are uniform, polygonal cells with round nuclei, prominent nucleoli, and clear cytoplasm.

Syncytiotrophoblasts and cytotrophoblasts may grow intermingled in a bilaminar plexiform pattern or in disordered sheets. Occasionally, scattered clusters of syncytiotrophoblasts cap cytotrophoblast nodules. Atypical mitosis and cellular atypia are common. There can be sheets of nondescript mononuclear cells that resemble intermediate trophoblast. Choriocarcinomas are typically intimately associated with dilated vascular sinusoids. Partial or complete replacement of the walls of blood vessels are common. There are often vast areas of haemorrhage and necrosis. Mediastinal choriocarcinoma cannot be distinguished morphologically from metastatic choriocarcinoma. Since gonadal choriocarcinoma often displays extensive regressive alterations but still may give rise to widespread metastasis, the exclusion of a primary gonadal choriocarcinoma is particularly difficult, although mediastinal metastasis of gonadal choriocarcinoma seem to be very rare [997,1356].

Trophoblastic neoplasms other than choriocarcinoma, such as monophasic choriocarcinoma and placental site trophoblastic tumour have not been reported in the mediastinum.

Fig. 3.78 Choriocarcinoma. A High power showing multinucleated and eosinophilic syncytiotrophoblastic cells intertwined with mononuclear cytotrophoblastic cells. B beta-hCG staining of syncytiotrophoblastic cells.
Immunohistochemistry
Syncytiotrophoblasts and cytotrophoblasts react with pan-keratin markers and CAM5.2, whereas they are negative for PLAP, AFP, CEA, CD30 and vimentin. The syncytiotrophoblasts additionally express beta-hCG, while the cytotrophoblasts are variably positive for human placental lactogen (1357,1920). Apart from metastasis of an extramediastinal choriocarcinoma, the differential diagnoses include mediastinal mixed germ cell tumour (in which a further germ cell tumour component is found), sarcomatous component in teratoma, and mediastinal metastasis from a carcinoma with choriocarcinoma-like features/dedifferentiation.

Genetics
The genetic changes that have been described in mediastinal choriocarcinoma are the same as those reported in the testis and demonstrate the isochromosome (12p) characteristic of postpubertal malignant germ cell tumours at all sites [316]. Such tumours are most commonly aneuploid, with a minority having near-tetraploid DNA content.

Prognosis
In most of the reported cases, patients died of disseminated disease shortly after diagnosis (average survival time 1 to 2 months) {520,1357,1821}. However, treatment with cisplatin-based chemotherapy may improve the prognosis {1955}.

Teratoma

Definitions
A germ cell tumour (GCT) that is composed of several types of organoid mature and/or immature somatic tissues derived from two or three germinal layers (ectoderm, endoderm and mesoderm).

Mature teratomas are tumours composed exclusively of mature, adult-type tissues. Dermoid cyst is a variant consisting of one or more cysts lined predominantly by keratinizing squamous epithelium with skin appendages. Monodermal teratomas analogous to struma ovarii have not been described in the mediastinum.

Immature teratomas contain immature, embryonic or fetal tissues exclusively or in addition to mature tissues. Mature and most immature mediastinal teratomas are benign tumours {1053,1244,1764,1808}.

Teratomatous component is the term used to describe differentiated somatic tissues associated with a seminoma, embryonal carcinoma, yolk sac tumour or choriocarcinoma. The teratomatous component of mixed GCTs is very often immature {1808}.

Teratoma with somatic-type malignancy is a teratoma containing one or more components of non-germ cell malignant tumour, which may be a sarcoma or a carcinoma (ICD-O code 9084/3).

ICD-O codes
Mature teratoma 9080/0
Immature teratoma 9080/3

Epidemiology
Mediastinal teratomas account for 7-9.3% of mediastinal tumours {708,1171} and 50-70% of all mediastinal germ cell tumours {466,520,759,1356,1458,1888,2116}. Among teratomas of all sites, up to 27% occur in the mediastinum in adults, and 4-13% in children {708,1053,1763}. Overall, there is an equal sex distribution {1171} or a slight female preponderance (M:F =1.1.4) {1808}, but immature teratomas occur almost exclusively in males {1808}.

The mean age of adults is 28 years (range 18-60) {1171}. In children, teratoma is the predominant mediastinal tumour during the first year and has been detected in fetuses as young as 28 weeks of gestation {708}. The proportion of immature teratomas (up to 40%) is much higher in the first year of life than at older age (~4-6%) {1053,1356,2116}. Mature teratoma can be associated with classical (47, XXY) and very rarely, mosaic Klinefelter syndrome (480).

Clinical signs and symptoms
30-59% of mediastinal mature teratomas, particularly those in adults {1955}, are asymptomatic {708,1171,1337}. Other cases can be associated...
with chest, back or shoulder pain, dyspnoea, cough, and fever due to chronic pneumonia \cite{708,1764}. Rare symptoms include superior vena cava syndrome, erosion of bronchi or vessels, Horner syndrome, or pneumothorax \cite{696,708,1764,1808}. Due to the occurrence of exocrine pancreatic tissue, rupture is more common in mediastinal teratomas than teratomas of other sites \cite{1808,2038} and can result in pleural effusions or cardiac tamponade. Endocrine pancreatic component can cause hyperinsulinism and hypoglycaemia \cite{1808}. Hydrops fetalis is a complication of congenital intra- and extrapericardial mediastinal teratoma \cite{708}.

**Imaging**
Mature teratomas show multilocular cystic structures in almost 90% of cases \cite{1888}. Attenuation is heterogeneous with varying combinations of soft tissue, fluid, fat and calcium \cite{1337}. Calcifications occur in in 26% \cite{1171} to 53% \cite{1337}. A shell-like tumour wall calcification or identifiable bone and teeth occur in up to 8% each \cite{1171,1337}. Immature teratomas appear more often solid \cite{1888}. With rare exceptions \cite{1244}, the usual serum tumour markers (AFP; beta-hCG) are not elevated.

**Site of involvement**
More than 80% of mature teratomas occur in the anterior mediastinum, 3-8% in the posterior mediastinum and 2% in the middle mediastinum, while 13-15% involve multiple mediastinal compartments \cite{963,1337,1829}. Teratomas can extend deeply into one or both thoracic cavities and elicit atelectasis.

**Macroscopy**
Mature mediastinal teratomas are usually encapsulated masses with a mean diameter of 10 cm (range 3-25 cm) \cite{1655,2008,2116}. There can be adhesions to the surrounding lung or great vessels. The cut surface is variegated, showing cystic spaces with fluid or grumous materials, hair, fat, flecks of cartilage, and rarely teeth or bone \cite{1808,1888}. Immature teratomas are often very large (up to 40 cm) \cite{1975} and solid. They exhibit a soft to fleshy consistency or are extensively fibrous or cartilaginous \cite{1808}. Haemorrhage and necrosis can be present.

**Histology**

*Mature teratomas*
These are characterized by a haphazard admixture of organoid mature tissues derived from 2 or 3 germinal layers. Skin and cutaneous appendages are consistent constituents and form cyst linings. Bronchial, neural, gastrointestinal, smooth muscle and adipose tissue com-

Fig. 3.81 Mature teratoma. A Dermoid cyst-like area (left), mature cartilage (top, right), mature intestinal type glands and villi (bottom, right). B High power of pancreatic tissue, including islets.

Fig. 3.82 Immature teratoma. A Immature neural tissue forming tubes. B Immature cartilage.
ponents are very frequent (>80%), while skeletal muscle, bone and cartilage are less common {708,1808}. Salivary gland, prostate, liver and melanocytes are even less frequent; thyroid tissue has not been reported {1808}. Pancreatic tissue is typical of mediastinal teratomas and found in up to 60% of cases, but is rare or absent in teratomas of other sites {521, 1808}.

Regressive changes, such as rupture of cystic structures, can be accompanied by a granulomatous inflammation {1808, 2116}. Remnant thymic tissue is found outside the capsule in 75% of mature teratomas {708}.

**Immature teratoma**

These lesions are characterized by embryonic or fetal tissues derived from the various germinal layers, such as immature glands lined by tall columnar epithelial cells, fetal lung, immature cartilage and bone, rhabdomyoblasts, blastema-like stromal cells. The most common immature components are neuroectodermal tissues, with neuroepithelial cells forming tubules, rosettes or retinal anlage {708,1808,2116}. By definition, pure immature teratoma should not harbour a morphologically malignant component.

**Immunohistochemistry**

The main role of immunohistochemistry in teratomas is: (i) to define the nature of immature components, such as rhabdomyoblasts (desmin, myogenin), neural components (S100; NSE) or immature cartilage (S100; GFAP) {1490}, and (ii) to exclude other germ cell or somatic malignancies. Pure teratomas are negative for PLAP, beta-hCG and CD30. AFP is usually negative, although liver cells and immature neuroepithelium in teratomas may express AFP.

**Grading of immature teratoma**

There are insufficient data to support a particular grading system for immature teratomas of the mediastinum. Grading according to Gonzalez-Crussi {708} was of no prognostic significance in children {696,1244,1764,1808}. However, it is important to realize the following: 1) the more immaturity is present in a teratoma, the higher the risk to find a yolk sac tumour component; 2) immaturity in a teratoma in an adolescent male is highly suspicious of a malignant i(12p)-containing germ cell tumour. Therefore, the pathologist should communicate clearly in the report the quantity (rough percentage) of immaturity.

**Genetics**

The pure mature and immature teratomas analyzed and reported to date do not show recurrent genetic gains and losses. This is in contrast to malignant germ cell tumours {1765}. Mature teratoma can be associated with classical and very rarely mosaic Klinefelter syndrome {480}.

**Differential diagnosis**

The main differential diagnosis is mixed germ cell tumour with a teratomatous component. Immature teratoma may be difficult to distinguish from teratoma with somatic type malignancy; the latter usually shows frank cytologic atypia and invasiveness that are absent in pure immature teratomas.

**Prognostic factors**

Mature teratoma is a benign tumour irrespective of the patient’s age. The prognosis of pure immature teratoma is age-dependent. In children, pure immature teratoma has an excellent prognosis with no risk of recurrence and metastasis {1244,1764}. The presence of an admixed malignant germ cell tumour component (detected in up 30% of immature teratomas after extensive sampling {1244}, and most commonly yolk sac tumour) is associated with a recurrence rate of 25%. In children, such mixed GCTs have a good prognosis after cisplatin-based chemotherapy (>80% 3-years-survival) {695,1244}.

In adults, the prognosis of pure immature teratoma is more guarded but experience is limited {2116}. Apparently pure immature teratomas with pulmonary metastases have been reported in adults, with only the metastasis showing a germ cell and/or somatic type malignancy {1808}.
Mixed germ cell tumours

Definition
A neoplasm composed of two or more types of germ cell tumours (GCTs). The diagnosis should be complemented by listing each component and its approximate proportion.

Polyembryoma represents a variant with a unique growth pattern that is characterized by the predominance of embryoid body-like structures. Embryonal carcinoma, yolk sac tumour, syncytiotrophoblastic cells and teratomatous components can usually be recognized in polyembryoma.

Embryonal carcinomas or seminomas containing scattered syncytiotrophoblastic cells do not qualify as mixed GCTs, but are classified as the respective “pure” GCTs.

ICD-O code
Polyembryoma 9072/3

Synonyms
Malignant teratoma intermediate, terato-carcinoma. The use of terms that do not precisely qualify the type and quantity of tumour components is discouraged.

Epidemiology
In adults, mixed GCTs account for 13-25% of all mediastinal GCTs [466,520, 1005,1033,2116], second only to teratomas (40-60%) and as common as seminomas (15-20%) [520,1005,1356, 1808,2116]. Virtually all patients are male [1005,1356].

In children, mixed GCTs account for about 20% of cases, and yolk sac tumour with mature or immature teratoma is the characteristic constellation. Other types of mixed GCTs are virtually nonexistent during the first four years of life [1764]. Among children <8 years of age, some authors [1005,1765] but not others [167] see a preponderance of females, while almost all adolescent patients > 8 years are males [1765].

After the onset of puberty, mixed germ cell tumours can be associated with Klinefelter syndrome [150,795,1106, 1290,1765].

Clinical features
Only ~10% of mixed GCTs are asymptomatic at diagnosis [1955]. Most patients present with general and local symptoms identical to those in other mediastinal GCT: chest pain, cough, dyspnoea, hoarseness, superior vena cava syndrome and cardiac tamponade [757, 1955]. Precocious puberty and gynecomastia are rare in polyembryoma [150] and other mixed GCTs [1106,1808]. In some cases, endocrinologic symptoms induced by beta-hCG production may precede tumour diagnosis by years [1769].

A minority of patients present with symptoms attributable to metastases [709, 757,1955]. Clonally related leukaemias are rare (~2%) [40,729,789,1518]. Imaging studies typically show a large inhomogeneous mass with necrosis, hemorrhage and infiltration of adjacent structures. Cystic spaces or adipose tissue hint to the presence of a teratomatous component [757,1888].

Most cases (~90%) show elevated serum tumour marker levels [1005].

Raised AFP (~80%) is strongly correlated with a yolk sac tumour component, although teratomatous hepatoid cells and teratomatous neuroepithelium can also produce small amounts of AFP. Increased beta-hCG (~30%) levels occur in mixed GCTs with a choriocarcinoma component or with syncytiotrophoblast cells [2169].

Post-chemotherapy findings, including the Growing Teratoma Syndrome
During or following chemotherapy, patients with GCT can alternatively show [2169]: (1) Normalization of tumour markers and resolution of the tumour mass (10%), (2) persistence of elevated tumour markers and the tumour mass due to resistance to chemotherapy (10%), or (3) normalization of tumour markers with residual tumour mass (80%).

In the latter group, 10-20% of patients exhibit tumour enlargement. This phenomenon can be due to a) chemotherapy-resistant GCT components that do not secrete AFP or beta-hCG; b) development of somatic-type malignancies; c) the “growing teratoma syndrome” (GTS). GTS is a rare complication of mixed GCTs [24] and defined by 1) an increase in tumour size during or after chemotherapy; 2) normalization of serum tumour markers; 3) identification exclusively of mature teratoma on histological analysis of the resected tumour specimen [1199]. The growing mediastinal mass is usually asymptomatic but can be accompanied by fever and dyspnoea [24,1256]. Lymphatic spread can involve mediastinal and supraclavicular lymph nodes [56]. Late GTS complications are local or metastatic development of malignant non-seminomatous GCTs and development of GCT-related sarcomas, carcinomas or leukaemias [56,1256]. The pathogenesis of GTS is largely unknown.

Tumour spread
Most mixed GCT exhibit extensive infiltration into mediastinal structures and adjacent organs. Rates of metastasis at time of diagnosis vary widely in different reports, from 20-36% [520,1356,1764, 1955] up to >80% [997,2169]. Metastasis to lung, pleura, lymph node, liver, bone and brain have been reported [156,1005,1765,1955]. Metastases to supraclavicular lymph nodes and lung due to occult mediastinal mixed GCTs are rare [708].

Macroscopy
The tumours are often poorly circumscribed or frankly infiltrative, and show a heterogeneous cut surface with solid areas, haemorrhage and necrosis. Cystic spaces usually indicate presence of a teratomatous component. The size ranges between 3 and 20 cm (mean 10 cm) [908]. Tumours in the context of the “growing teratoma syndrome” measure up to 28 cm [24].

Histopathology
Various types of GCTs can occur in any combination in mediastinal mixed GCTs. Their morphologies are identical to those

Mixed germ cell tumours

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of pure GCTs. The reported frequencies of the various GCT subtypes vary widely in the literature, but the following conclusions can be drawn:

In adults, the two most frequent components are teratoma (50-73%; mean 65%) and embryonal carcinoma (22–100%; mean 66%) {237,520,1005,1356,1955}. Less common are yolk sac tumour (0-83%; mean 48%), seminoma (22-50%, mean 38%), and choriocarcinoma (10–67%, mean 28%) {520,1005,1033,1356,1955}. The teratoma components are more often immature than mature {17,1033,1808}. The most common combination is teratoma and embryonal carcinoma (previously called teratocarcinoma), encountered in 15-56% of cases (mean 40%) {237,1005,1808,1955}.

In children, a yolk sac tumour component occurs in most (>90%) mixed GCTs, followed by teratoma (~30%), and, in adolescents, seminoma, choriocarcinoma and embryonal carcinoma (~20% each) {709,1764}. In contrast to adults, the teratoma components in paediatric mixed GCTs are more often mature than immature {167,1725,1765}.

Polyembryomas {150} show a unique growth pattern mimicking embryoid bodies. These GCTs are composed of EC, YST, syncytiotrophoblast cells and teratoma. Adult, but not childhood, mediastinal mixed GCTs are frequently associated with non-germ cell malignancies (sarcomas, carcinomas, and/or leukaemias).

**Histology of metastasis**

The histology of metastases usually reflects the histology of the primary GCT or one of its components {17} but other GCT histologies and somatic type malignancies may occur, particularly after chemotherapy {56,406,1230,1256,2046}.

**Postchemotherapy histology**

After chemotherapy, viable non-teratomatous tumour occurs in up to 50% of cases even after normalization of serum tumour markers {1808,2049}. In the remaining cases, areas of necrosis, teratoma structures, inflammatory infiltrates including xanthogranulomatous reactions, and fibrosis can be encountered. Chemotherapy may unmask a previously overlooked somatic-type tumour or a teratomatous component. Metastases do not necessarily reflect the histology of remnant viable tumour cells in the primary location {56,1256}.

**Immunohistochemistry**

The immunohistochemical profiles reflect those of the various germ cell tumour components contributing to a given mixed GCT, AFP is expressed in virtually all mixed GCTs, at least focally, due to the frequent occurrence of yolk sac tumour components.

**Genetics**

In adults and children > 8 years old, gain of 12p and sex chromosomal abnormalities (often associated with Klinefelter syndrome) are the most common recurrent abnormalities of mediastinal mixed GCTs {258,1765}, including polyembryoma {150}. Additional recurrent changes include gain of chromosome 21 and loss of chromosome 13. These abnormalities are also encountered in the mature teratoma component and/or somatic-type malignant components of mixed GCTs, while pure teratomas are typically devoid of genetic imbalances {1394,1765}.

In children < 8 years old, i(12p) does not occur {1765}, and gain of the X chromosome and trisomy 21 {258,1765} are rare findings. Instead, gain of 1q, 3, and 20q and loss of 1p, 4q, and 6q are common {258,1765} in yolk sac tumour; teratomatous elements show no chromosomal abnormalities.

**Postulated cell of origin**

Toti- or pluripotent primordial germ cell.

**Differential diagnosis**

Embryonal carcinoma components may be difficult to recognize against a background of yolk sac tumour due to the heterogeneity of yolk sac tumour growth patterns. CD30 staining is a helpful diagnostic adjunct to resolve this differential. Due to the lack of cytrophoblastic cells, scattered syncytiotrophoblasts in “pure” seminomas and embryonal carcinomas can be distinguished from the choriocarcinoma components of mixed GCTs.

**Prognostic factors**

In adults, mixed GCTs exhibit a long-term survival rate of 40-45% {1359} and there appears to be no significant difference between mixed and pure NSGCTs {1955}. Therefore, tumour stage, particularly metastasis to brain, liver, lung, and bone, and elevated beta-hCG levels might be major risk factors for mixed GCTs as for NSGCTs {199,790}. Modern cisplatin-based chemotherapies and resection are the treatment of choice {199,236,1462,2172}.

In children, mixed GCTs usually harbour only yolk sac tumour and teratomatous components and their prognosis is not different from the prognosis of pure yolk sac tumour {1764}, suggesting that 5-year overall survival rates of >80% can be achieved with modern therapies {1764}. Local stage, distant metastasis and AFP levels have not been shown to be of prognostic significance in a recent paediatric series of NSGCTs that includes 24% mixed GCTs {1764}. In young children, mixed GCTs exhibiting microscopically small foci of NSGCTs in teratomas have a good prognosis after complete resection and chemotherapy {1244}. Small series suggest that histology, specifically an extensive seminoma component of mixed GCTs, has a beneficial impact on survival {1349,1359}, while a choriocarcinoma component might indicate a more aggressive clinical course {466,2116}.

**Postchemotherapy prognostic factors**

Postchemotherapy findings are the most important prognostic factors in the era of multimodality treatments. Primary complete response, i.e. normalization of tumour marker levels and disappearance of the mediastinal mass after chemotherapy occurs in 10% of NSGCT patients and is associated with 80% long-term survival {587}. 20% of such patients relapse usually within 2 years after chemotherapy and may be amenable to salvage therapy after early detection of the relapse {2169}.

Among patients that show normalization of tumour markers and a residual tumour mass (80% of cases) {587,588,2169,2172}, completeness of resection is the most important prognostic factor in adults {199} and children {11,1764}: salvage rates after incomplete resection are <10% in adults and <50% in children. In addition, postchemotherapy histology has a bearing on prognosis {660,1655}: complete lack of viable tumour cells is associated with a 90% disease-free survival rate, while the rate drops to 60% if viable teratoma, including the growing teratoma syndrome, is encountered. Viable non-teratomatous GCT tumour or somatic-type malignant cells are associated with a 30% and <10% survival rate, respectively.
Patients with persistently elevated tumour markers have a worse prognosis than patients with normalization of tumour markers, although viable tumour cells are detectable in only half of the respective resection specimens [997]. Relapses after chemotherapy and surgery and primary resistance to chemotherapy are poor prognostic factors due to low salvage rates [199].
Germ cell tumours with somatic-type malignancy

Definition
A germ cell tumour (GCT) accompanied by a somatic-type malignant component of sarcoma, carcinoma or both. Leukaemias or lymphomas are also somatic-type neoplasms that can accompany mediastinal GCTs.

Synonyms
Teratoma with malignant transformation (1394); Malignant teratoma with non-germinatal malignant tumour (1808); Teratoma with non-germ cell malignancy.

Comments
Tumours included in this category have been collectively called “Teratomas with malignant components” etc. in the literature. However, since somatic-type malignancies are more common in mixed germ cell tumours than in teratomas (709, 1230, 1515, 1808, 2046) and can also occur in pure yolk sac tumours (2048) and seminomas (879, 2047), the germ cell tumour component that accompanies the somatic malignancy should be specified accordingly. A minimum size of one low-power field has been suggested as the threshold for the diagnosis of somatic-type malignancy in GCTs (1655, 2047). However, this size criterion is arbitrary. More important is the independent growth pattern demonstrated by the somatic-type malignancy. It would be helpful to estimate the size and percentage areas occupied by the somatic malignancy and give this information in the pathology report.

Epidemiology
GCTs with somatic-type malignancies are rare (~ 2% of all male GCTs) (30). About 25-30% of cases occur in the mediastinum (2047). They account for up to 29% of all mediastinal GCTs of adults (40, 199, 1230, 1394, 1450, 1808, 1955), but are almost non-existent in children (277, 406, 428, 1005, 1232, 1764). With few exceptions (277, 428, 1033), the tumours occur in males. The age range is from 4-66 years (277, 406, 1005, 1033, 1230, 1356, 1385), with most cases occurring between 20-40 years.

The somatic-type malignancies may arise in the mediastinum or only in the metastases (277, 1394, 1808). They are more common after chemotherapy and in tumours of late recurrences (1665). After removal of apparently mature teratomas, metastases with pure sarcomatous features have been rarely reported (277, 1808).

Clinical features
Signs and symptoms
The tumours show the same local symptoms as other mediastinal GCTs, but they are more frequently symptomatic (~90%) than pure teratomas (~50%) (1808). Symptoms due to metastatic disease may accompany or follow local symptoms (1394). Most but not all cases show elevated AFP and/or beta-hCG levels in the serum. Other tumour markers (e.g. carcinoembryonic antigen [CEA] or neuron-specific enolase [NSE]) may be elevated according to the malignant components that are present.

Imaging studies typically reveal a solid mass (representing the sacoma or carcinoma component) associated either with a cystic teratomatous structure or with a lesion showing heterogeneous attenuation, predominant areas of enhancing soft tissue elements, calcifications and massive necrosis (1888).

Tumour spread
Sarcoma and carcinoma components can infiltrate into the mediastinal structures and the lung (1230). Metastases have been reported in the majority of cases (1230, 1505) and can be composed either of the somatic-type tumour (406, 1230), the GCT or one of its components (1230), or of both somatic-type and germ cell tumour (1230, 2046). Metastatic spread may involve lung (406, 1394), regional lymph nodes (40, 997), bone (1515, 2186), brain (2046, 2186), liver (40, 2046) and spleen (1394, 2046).

### Table 3.11
Mediastinal germ cell tumours and associated somatic-type malignancies.

<table>
<thead>
<tr>
<th>Germ cell tumour component</th>
<th>Frequency</th>
<th>Somatic-type malignancies</th>
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<tbody>
<tr>
<td>Teratoma (mature; immature)</td>
<td>~ 10-20%</td>
<td>Sarcomas/Neurogenic Tumours</td>
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<td></td>
<td></td>
<td>Rhabdomyosarcoma</td>
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<td>Angiosarcoma</td>
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<td>Neuroblastoma</td>
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<td>Liposarcoma</td>
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<td></td>
<td>Leiomyosarcoma</td>
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<tr>
<td>Non-teratomatous GCT of one histological type (most commonly seminoma or yolk sac tumour)</td>
<td>&lt; 5%</td>
<td>Osteo-, Chondrosarcoma, Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>Mixed germ cell tumours (almost all cases contain teratoma components)</td>
<td>&gt; 75%</td>
<td>Malignant fibrous histiocytoma</td>
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<td>MPNST^4</td>
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<td>Glioblastoma</td>
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<td>Epithelial Malignancies</td>
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<td>Adenocarcinoma</td>
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<td>Adenosquamous carcinoma</td>
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<td>Squamous cell carcinoma</td>
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<td>Undifferentiated carcinoma</td>
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<td></td>
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<td>Haematological malignancies</td>
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</table>

^Percentage of all mediastinal GCTs with somatic-type malignancies

More than one type of sarcoma and/or carcinoma can occur in a single GCT, and haematologic neoplasias can accompany sarcomas (1394)

^PNET, primitive neuroectodermal tumour; ^MPNST, malignant peripheral nerve sheath tumour
Germ cell tumours with somatic-type malignancy

Germ cell tumours with somatic-type malignancy

Macroscopy
The tumours range in size from 6 to 30 cm [1230,1356]. They usually exhibit a partially cystic and often variegated cut surface with focally necrotic areas. The carcinoma or sarcoma areas are firm and gray or haemorrhagic (e.g. angiosarcoma) and often adherent to adjacent mediastinal structures [2046].

Histopathology
Mature [277,428,1033,1385] and immature [520,1195,1505,2186] teratomas, in addition to seminomas, yolk sac tumours or mixed germ cell tumours can be associated with various sarcomas (63% of cases) [428,2046,2047], carcinomas (37%) [1385,1808], combinations of both [1033,1808,2047] or carcinosarcoma [1808]. The somatic malignancy can be intimately intermingled with the GCT component, or forms an expansile nodular proliferation of atypical cells, often with increased mitotic rate and necrosis. Embryonal rhabdomyosarcoma [428,1230,1450] is the single most frequent somatic-type malignancy. Angiosarcoma [1230,2046], leiomyosarcoma [1450] and neuroblastoma [397,1505] are also common. Any other type of sarcoma or combinations [1230] may occur, including chondrosarcoma, osteosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumour, glioblastoma [1808], and liposarcoma [1359].

The non-mesenchymal component can be adenocarcinoma (usually of colonic type) [1385,1394,1808,2047], adenosquamous carcinoma [2047], squamous cell carcinoma [1655] or primitive neuroectodermal tumours (PNET) [1655]. Melanocytic neuroectodermal tumours [49] and carcinoids [1707] are rare.

Immunohistochemistry
Somatic-type malignancies stain like their counterparts occurring elsewhere in the body. PLAP, AFP, beta-hCG, and CD30 are generally not expressed, while they can be detected in “pure” GCTs and the respective components of mixed GCTs. One should keep in mind that rhabdomyoblasts, embryonal rhabdomyosarcomas and leiomyosarcomas can express PLAP [700] and that hepatoid carcinomas can be AFP-positive.

Genetics
An isochromosome i(12p) genotype shared by the somatic-type neoplasia and the associated germ cell tumour component is typical [789,1113,1394]. In a case of teratoma-associated rhabdomyosarcoma, an add(2)q35-q37 genetic abnormality that is characteristic...
for rhabdomyosarcoma was detected in the sarcoma but not the germ cell component [1394]. Thus, tissue-specific secondary chromosomal aberrations may be necessary for the development of somatic-type tumour components in GCTs. Klinefelter syndrome has been reported in association with GCT with somatic-type malignancy [2186].

**Postulated cell of origin**

Malignant transformation of mature teratoma cells or divergent differentiation of a pluripotent primordial germ cell towards a germ cell tumour and the somatic-type malignancy have been suggested [314]. The latter hypothesis is favoured by the finding that “pure” mature mediastinal teratomas show no chromosome 12 abnormalities [1765] while a shared i(12p) abnormality is characteristic of teratomas that are clonally related with somatic type malignancies, including leukaemias [1394].

**Differential diagnosis**

Immature teratoma may be difficult to distinguish from teratoma with somatic-type malignancy. Frank atypia and infiltrative growth favour the latter interpretation. Likewise, chemotherapy-induced atypia is usually diffusely distributed throughout the tumour, while somatic-type malignancy is a focal process often forming a recognizable mass and invading adjacent structures [1888]. Scattered rhabdomyoblasts are a frequent feature of mature and immature teratomas and do not justify a diagnosis of rhabdomyosarcoma unless they show nodular tumour formation and/or infiltration of adjacent structures. Rhabdomyoblasts can rarely occur in thymic carcinomas. The thymic carcinoma is morphologically different from GCT and commonly expresses CD5, while the rhabdomyoblasts are devoid of atypia and proliferative activity.

**Prognostic factors**

Presence of somatic-type malignancy in a GCT confers a dismal prognosis [406,520,709,1005,1230,1394,1515,1655,2047]. There is no response to chemotherapy used for treatment of germ cell tumours. Only a minority of patients will survive after chemotherapy and complete surgical removal of mediastinal tumour remnants [879,1394,2047]. Advanced local infiltration, metastatic disease, and incomplete resection are bad prognostic factors [997,1230,2047], while the type of somatic malignancy in the primary biopsy has no major impact on survival [1394]. Persistence of viable tumour after chemotherapy heralds an unfavourable outcome [660,997,2169]. The median survival is only approximately 9 months [406,520,709,997,1005,1230,1394,1515,1655,2047].

Fig. 3.86 Germ cell tumour with somatic-type malignancy. A Angiosarcoma component of the case shown in Fig. 3.85. B CD31 expression of the same case. C Immature teratoma and rhabdomyosarcoma. D Adenocarcinoma component in immature teratoma.
Germ cell tumours with associated haematologic malignancies

Definition
Germ cell tumours associated with haematologic malignancies that are clonally related to the underlying GCTs. The association represents a variant of somatic-type malignancy that is unique to mediastinal GCTs. The haematologic malignancies can involve the mediastinum or present as infiltration of bone marrow or lymphatic organs, leukaemia or myelosarcoma. Haematopoietic malignancies that arise due to chemotherapy are not included in this category.

Historical annotation
The association between mediastinal GCTs and hematologic malignancies has been recognized since the 1970s [2599,2477]. Derivation from a GCT-derived pluripotent cell [2592,1681,1698] and independence from previous radio-chemotherapy [1681,1698] were suggested since the 1980s. Genetic studies [1698,1735,1737] demonstrated chromosomal aberrations that were shared between GCTs and associated haematologic malignancies, providing evidence for a clonal relationship. Extra-medullary haematopoeisis in a subgroup of mediastinal GCTs {1310} suggests that committed haematopoietic precursors can be an alternative origin. The predilection of the syndrome for mediastinal GCTs has remained unexplained.

Epidemiology
Haematologic malignancies develop in 2-6% of malignant nonseminomatous mediastinal GCTs [789, 1450] (i.e. 0.5–1.5% of all mediastinal GCTs) but virtually never in GCTs of other sites [1243]. Patients are typically adolescents or young adults (age range 9–48 years) and virtually all are males [315, 474,1461]. About 10-20% of cases have been associated with Klinefelter syndrome [129, 490,1461].

Clinical signs and findings
In a series of 17 patients the most common clinical features at the diagnosis of the haematologic disorder include pancytopenia, spleno-/hepatomegaly, or thrombocytopenia in a range of 20 to 35% each. Bleeding complications and infections arise due to cytopenias in myelodysplastic syndromes and acute leukaemias are also common events. Thromboembolic complications due to thrombocytosis and megakaryocytic hyperplasia [1461], and mediastinal mass formation due to myelosarcoma is rare [1723]. Other clinical signs are leukaemic skin lesions, and flushing [789], and the development of haemo-phagocytic syndromes [2055]. Haematological complications can accompany, follow [199,2055,2087] or precede local symptoms. Leukaemias most often become apparent within the first year after the diagnosis of GCTs (range 0–122 months; median 6 months) [474,789,1394,1518]. There is no increased overall risk for other second tumours in mediastinal GCT patients [199,789].

Etiology and pathogenesis
The etiology is unresolved. It has been speculated that expression of haematopoietic growth and differentiation factors in some mediastinal GCTs could drive differentiation of primordial germ cells into haematopoietic progeny. The profile of differentiation factors expressed may also underlie the preferred commitment of transformed precursors to the megakaryocytic and monocytic lineage [1450, 1518]. Concomitant mediastinal and extramediastinal leukaemias show a comparable immunophenotype and genotype, suggesting spread of haematopoietic tumour cells from GCTs to blood, bone marrow, and extra-medullary sites [1113,1394].

Macroscopy
Gross findings are identical to those of non-seminomatous malignant GCTs.

Histopathology
The GCTs underlying the haematologic malignancies typically are non-seminomatous malignant GCT, most often yolk sac tumours or mixed germ cell neoplasias with a yolk sac component, though immature teratomas and mixed germ cell tumours with somatic-type sarcomas have been observed [83,315,1112,1394,1461]. In a series of 287 patients with nonseminomatous mediastinal germ cell tumours, yolk sac and teratocarcinoma histology have been significantly associated with the occurrence of haematologic neoplasias [789]. Categories of haematological malignancies reported are: acute leukemias [199,1132], malignant (and rarely benign [2246]) histiocytosis [83,129,474,1112,1461], myelodysplastic syndromes [1450,1846,2087], myeloproliferative diseases [315,1113,1461], and mastocytosis [335]. Among acute leukaemias, acute megakaryoblastic leukaemia (AML M7) and “malignant histiocytosis” (including AML M4 [729,1113] and M5 [2074]) are most common and account for about half of the cases [199,1461,1518]. In addition, AML M2 [2087], M6 [1450,1729], acute undifferentiated leukaemia (AUL) [1461], and acute lymphoblastic leukaemia [1132,1461] have been described. Myelodysplastic syndromes (MDSs) include refractory anaemia with excess blasts [1846] or cases with megakaryocytic hyperplasia [1460], suggesting the 5q- syndrome [1394]. Myelodysplasia can precede AMLs [2087].

Essential thrombocytemia and chronic idiopathic myelofibrosis are the characteristic myeloproliferative disorders encountered in association with mediastinal GCTs [663,814,1461]. Leukaemias may diffusely or focally infiltrate the underlying GCT [1518] or can form tumorous lesions (granulocytic sarcomas) in the mediastinum [1723]. Extramediastinal manifestations (organomegaly, leukaemia) can occur in the presence or absence of detectable haematopoietic malignancy in the mediastinal GCT [1518].

Immunohistochemistry
Interpretation of cytochemical findings in blood or bone marrow smears, and immunophenotypic profiles follows the
criteria of the WHO classification of tumours of haematopoietic and lymphoid tissues [919]. Useful immunohistochemical stainings include myeloperoxidase (MPO), lysozyme, CD10, CD20, CD34, CD68, CD61, CD117, TdT, and glycophorin.

**Genetics**
Isochromosome 12 [i(12p)] is the most specific and most common chromosomal marker shared by GCTs and the associated haematologic malignancies [315, 1394, 1461]. In addition, the haematologic malignancies can harbour genetic alterations that are typical for specific haematologic malignancies in general (del(5q); trisomy 8), suggesting that GCT-unspecific aberrations determine the phenotype of the associated haematologic malignancy [1394].

**Postulated cell of origin**
Toti- or pluripotent primordial germ cell. Alternatively, the detection of non-neoplastic extramedullary haematopoeisis in the yolk sac tumour component of some GCTs suggests that some haematologic malignancies can arise from more committed, somatic-type haematopoietic cells by malignant transformation [1518].

**Differential diagnosis**
Clonally-related haematologic malignancies must be distinguished from secondary MDSs and AMLs that are related to salvage chemotherapy regimens including etoposide in patients with mediastinal GCT [100, 1047]. Secondary MDSs occurred in 0.7%, and AMLs in 1.3 % of cases in a large series [1047]. Chemotherapy-related AMLs do not show i(12p) and usually manifest later (25–60 months after chemotherapy) than germ cell-related AMLs (median time to onset 6 months, range 0–122) [789, 1461].

**Prognostic factors**
The occurrence of a clonally related acute leukaemia in a patient with mediastinal GCT is among the most adverse prognostic factors. In a recent series, none of the reported patients has survived for more than 2 years after the onset of leukemia (median survival time: 6 months) [789]. These leukaemias appear to be refractory to current treatment protocols including aggressive induction chemotherapy and allogeneic bone marrow transplantation. However, the clinical course in patients with myeloproliferative diseases may be more protracted [663, 814].
Mediastinal lymphomas and haematopoietic neoplasms: Introduction

Principles of classification
The classification of haematological malignancies has undergone significant reappraisal in recent years. These changes have resulted from insights gained through the application of immunological and genetic techniques, as well a better understanding of the clinical aspects of lymphoid and myeloid neoplasms through advances in diagnosis, staging and treatment. A multifaceted approach to both disease definition and diagnosis, as proposed by the Revised European and American Lymphoma (REAL) classification {783} and updated in the WHO classification {919}, is now considered the state of the art.

While morphology is still the starting point for pathologic diagnosis, immunologic and genetic techniques have been crucial in defining disease entities, and are often useful in differential diagnosis. The pathologist must also be cognizant of the clinical history, as the site of presentation and other clinical parameters are an important aspect of both disease definition and diagnosis. Finally, in many instances, lymphoid and myeloid neoplasms can be related to a normal cellular counterpart in the haematopoietic and lymphoid systems.

Mediastinal lymphomas arise in either mediastinal lymph nodes or the thymus gland. Thymic lymphomas are unique in many respects, as they reflect the function of the thymus gland as an organ involved in T-cell generation and differentiation {1863}. Precursor T-lymphoblastic lymphoma/leukaemia presents as a mediastinal mass in 85% of cases, and the immunophenotype of the neoplastic cells reflects the stages of cortical thymocyte differentiation {157,1604}. There are also rare reports of natural killer (NK)-cell tumours with an immature phenotype arising in the thymus gland {1046}, and the fetal thymus is one site of NK-cell development {1863}. B-cell lymphomas of the thymus gland are relatively rare. The most common of these is mediastinal large B-cell lymphoma (PMLBCL), of proposed origin from specialized thymic B-cells found in the medullary perivascular space {22,906}. Classical Hodgkin lymphoma, nodular sclerosis type, (HLNS) also arises in the thymus gland, and is genotypically of B-cell origin, although B-cell markers may be absent. Lymphomas of mucosa-associated lymphoid tissue (MALT)-type may arise in the thymus gland, as well as in other mucosal or epithelial sites, and reflect the intimate functional relationship between epithelial and lymphoid components in the thymus gland {891}. A functionally related lesion is the multilocular thymic cyst seen in autoimmune disease and HIV-infection {1051,1326,1923}. Lymphomas involving the mediastinal lymph nodes reflect to some extent the spectrum of systemic nodal lymphomas. However, because of its inaccessibility as a biopsy site, the primary diagnosis of lymphoma is uncommonly made in mediastinal lymph nodes. Myeloid neoplasms rarely have primary presentations in the mediastinum. A recent described entity, precursor T-lymphoblastic lymphoma with eosinophilia and t(8;13) typically presents with a mediastinal tumour with the immunophenotype of T-LBL, but is associated with development of acute myeloid leukaemia in the bone marrow {2179}. Acute myeloid leukaemias, often with megakaryoblastic differentiation may develop in the mediastinum and bone marrow in association with non-seminomatous germ cell tumours with an i(12)p {159,315,474,506,729,1113,1460,1461,1723}.

Histiocytic and dendritic cell tumours are rare tumours that occasionally may present in mediastinal lymph nodes and the thymus gland. However, as with myeloid neoplasms, most histiocytic neoplasms presenting in the mediastinum are related to teratomatous germ cell tumours, indicative of the capacity of germ cell neoplasms to differentiate along many cell lines {159,729,1052,1518,1723}.

Epidemiology
The epidemiology of haematopoietic and lymphoid neoplasms of the mediastinum and thymus gland is heterogeneous, reflecting the diversity of disease entities presenting in this site. Precursor T-cell and NK-cell neoplasms are for the most part diseases of children and young adults, with an increased male:female ratio. Mediastinal large B-cell lymphoma and nodular sclerosis Hodgkin lymphoma share many epidemiological features, including prevalence in young adult females, and propensity to present with localized disease. This observation, plus the fact that synchronous and metachronous instances of mediastinal large B-cell lymphoma and nodular sclerosis Hodgkin lymphoma may be encountered, has suggested that these neoplasms may share a common cell of origin {710,1575}. In addition, there are rare grey zone lymphomas with features intermediate between both entities {1270,1704}.

Clinical features
With the exception of the relatively rare MALT-type lymphomas, most mediastinal lymphomas and haematopoietic neoplasms are clinically aggressive; patients typically present with symptoms related to a large mediastinal mass, or with pericardial or pleural effusions in lymphoblastic lymphoma. Other clinical features vary with the type of lymphoma.

Genetic features
The genetic features of these neoplasms for the most part are similar to their counterparts presenting in other sites. One exception is mediastinal large B-cell lymphoma, which has genetic features distinct from that of other diffuse large B-cell lymphomas {148,404,1756}.
Primary mediastinal large B-cell lymphoma

Definition
Primary mediastinal large B-cell lymphoma (PMLBCL) is a type of diffuse large B-cell lymphoma arising in the mediastinum, of putative thymic B-cell origin, with distinctive clinical, immunophenotypic and genotypic features.

ICD-O code 9679/3

Synonyms
Primary mediastinal clear cell lymphoma of B-cell type {1341}, mediastinal large-cell lymphoma of B-type with sclerosis {1296}. REAL: Primary mediastinal (thymic) large B-cell lymphoma {783}

Epidemiology
It accounts for about 2-3% of non-Hodgkin lymphomas and occurs predominantly in young adults (third and fourth decade), with a slight female predominance {3,305,783,1143}. Both of these factors distinguish PMLBCL from other types of diffuse large B-cell lymphoma, which have a median age in the 7th decade and a male predominance.

Etiology
It is unrelated to EBV or other known tumour viruses {1340,2034}. It might be driven by a still elusive oncogene, probably located on chromosome 9p {941}.

Localization
At presentation, the disease affects the antero-superior area of the mediastinum without superficial lymphadenopathy or hepatosplenomegaly. The thymus is typically involved and rare cases of lymphoma confined to the thymus have been reported, suggesting that the tumour arises in the thymus and secondarily involves mediastinal lymph nodes {918,1121}. The mass is often “bulky” (>10 cm in diameter) and is often locally invasive, infiltrating lung, pleura, thoracic wall and pericardium. Supraclavicular extension is sometimes observed {22, 1296,1341}. At progression, PMLBCL disseminates predominantly to extranodal sites, including lung and extrathoracic organs {305}; liver, kidney, and adrenal are the most frequent sites of parenchymal involvement; gastro-intestinal tract, ovary, CNS, and pancreas {171} are other reported sites. Bone marrow involvement is extremely rare.

Clinical features
Signs and symptoms are related to the mediastinal mass: superior vena cava syndrome (most frequently), airway obstruction, pleural and/or pericardial effusion. B symptoms may be present {1143}. Traditional or more sophisticated imaging techniques are important in detecting the mass, in documenting the involvement of other intra-thoracic structures and in deciding on the best approach to obtain a diagnostic biopsy.

Macroscopy
Radical surgery or debulking is rarely performed, because the mass is typically widely infiltrative at the time of the diagnosis. In resected specimens, the cut surface has a fleshy appearance, often with necrotic areas. Thymic cysts may be present. Diagnostic features may be lacking in small (e.g., trans-thoracic needle) biopsies when only sclerosing and/or necrotic tissue is obtained.

Tumour spread and staging
PMLBCL most probably arises intrathymically {22} and then aggressively invades adjacent structures and tissues, including regional lymph nodes, whereas distant lymph nodes are rarely affected. Leukaemia is never observed; however, haematogenous dissemination occurs during progression, as evidenced by distant organ involvement {305}. Staging procedures must exclude a secondary mediastinal involvement by a systemic diffuse large B-cell lymphoma; extrathoracic lymph nodes or bone marrow involvement would suggest this diagnosis.

Histopathology
The growth pattern is diffuse. PMLBCL has a broad range of cytomorphology; however, individual cases tend to be monomorphic. The cells range from...
Primary mediastinal large B-cell lymphoma

medium-sized to large (2-5 times the size of a small lymphocyte), have abundant, frequently clear cytoplasm and irregularly round or ovoid (occasionally multilobated) nuclei, usually with small nucleoli. Some cases may have more pleomorphic nuclei and abundant amphophilic cytoplasm and may resemble Hodgkin lymphoma or nonlymphoid tumours. Mitotic activity is high, similar to other large cell lymphomas. The centre of the lesion contains predominantly neoplastic cells. However, at periphery of the mass, a variable number of reactive cells such as lymphocytes, macrophages and granulocytes may be present. A frequent but not consistent feature is a distinctive fibrosis made up of irregular collagen bands compartmentalizing cellular areas of varying size (1296,1341,1558,2224). The combination of different architectural patterns and cellular morphology might raise the differential diagnosis of thymoma, seminoma or Hodgkin lymphoma.

Fig. 3.90 Mediastinal large B-cell lymphoma. A High power view of mediastinal large B-cell lymphoma. B Note the clear cytoplasm and the very irregular nuclei with inconspicuous nucleoli. C Polymorphic tumour cells including Hodgkin-like cells. D Silver stain highlights the pseudoalveolar compartmentalization of the neoplastic tissue by collagen fibrils and fibers. E CD20 expression. F CD30 expression.
Depending on the surgical approach and specimen size, thymic remnants can be observed, usually better highlighted by immunohistology. Cystic change may be present in the thymic remnant. Lung, pleura and pericardium can be included. Rare cases of composite PMLBCL and Hodgkin lymphoma are reported [1704].

**Immunophenotype**

PMLBCL expresses B-cell lineage-specific surface molecules such as CD19, CD20, CD22 [1344], and the immunoglobulin-associated CD79a [1595] molecule, but not lineage-restricted T-cell antigens, except for MAL [404], which is regarded as T-cell restricted and is not observed in other diffuse large B-cell lymphomas. CD10 has been detected in some studies in 20-25%, similar to its frequency in other large B–cell lymphomas [448,1595], but has not been detected in other studies [1343,1344]. CD15 and CD21 are always negative. BCL6 protein may be detected by immunohistochemistry in 50-60% of the cases. Molecules often found in/on PMLBCL cells like CD38, PC-1, MUM1 and PAX5 [1595] in the absence of CD138 favour a post-germinal centre stage of maturation. The majority of PMLBCL do not express Ig [1296,1341]. In fact, the discrepancy between the lack of Ig and the constitutive CD79a [953] is characteristic of this disease. The lack of Ig expression is likely not related to a defect in the Ig transcriptional machinery since the Ig transcription factors Oct2 and BoB.1 are expressed [1595]. Furthermore, there is frequently a defect of HLA class I and/or II molecule expression [1342]. CD30 expression, often weak and restricted to a subset of the tumour cells, is often observed in PMLBCL, especially when antigen retrieval techniques are used [829]. CD30 expression is typically low compared with the strong CD30 expression in neoplastic cells of classic Hodgkin lymphoma (HL) or in diffuse large B-cell lymphoma (DLBCL) of anaplastic type. This may result in differential diagnostic problems between PMLBCL, Hodgkin disease, and the so-called “grey zone” lymphomas of the mediastinum, which have features intermediate between HL and DLBCL [1704].

**Histogenesis**

Histologically, PMLBCL has been attributed to the asteroid variant of thymic medullary B-cells [862]. Genetically, PMLBCL seems to be derived from B-cells that have been activated by a specific antigen, passed through the germinal centre and have shut down their mutational machinery before neoplastic transformation is completed [1158]. Immunophenotypically, PMLBCL are at post-germinal centre stage [1158,1344,1595].

**Somatic genetics**

Antigen receptor genes and BCL6. As in other diffuse large B-cell lymphomas, Ig heavy-chain and light-chain genes are rearranged and have high loads of mutations [872,1098,1158,1753]. Further, the vast majority of heavy-chain V genes are potentially functional by showing evidence of selection for a functional antibody. No bias towards particular gene families (such as VH4) were observed, so selection by an autoantigen or superantigen is unlikely. Intrachromosomal variation was not detected in the PMLBCL cases analysed so far, indicating that continuing mutational activity is not a prominent feature [1158]. The data on frequencies of BCL-6 mutations in PMLBCL are conflicting, ranging from 6-50% [448,1532,1595,2034].

Genetic abnormalities. BCL-2 is germine, suggesting that the regular expression of bcl-2 protein in PMLBCL is regulatory [1595,2034]. BCL-1 and N-ras are not altered while p16, c-MYC, and TP53 occasionally carry mutations [1595,1754,1755]. Different genetic approaches, including comparative genomic hybridization, FISH, arbitrarily primed PCR fingerprinting and classical cytogenetics have yielded a highly characteristic pattern of genomic alterations in PMLBCL: chromosomal gains (2p, 6p, 7q, 9p, 12, and X) are much more frequent than losses [941,1661,1756]. Most important is gain of chromosome arm 9p (9p+), which is detectable in up to 75% of cases [148]. This aberration is a chromosomal marker in PMLBCL, since 9+ is very rare in other nodal and extranodal B-cell lymphomas but, interestingly, is detectable in about 25% of classic Hodgkin disease [940]. In both tumours, the consensus region of the recurrent aberrations on 9p is subtelomeric. A second essential genomic region in PMLBCL is the long arm of chromosome X. Aberrations of Xq, including high levels of DNA amplification, are present in up to 89% of cases of PMLBCL [148]. Recent molecular studies applying gene expression profiling show that classical Hodgkin lymphoma and PMLBCL are closely related [1694,1752].

**Prognosis and predictive factors**

There are no histological [1558], immunophenotypic or genotypic features that have prognostic potential. Similarly to other DLBCL, response to initial therapy is a good marker for prognosis. The survival with aggressive therapy is similar to that of other localized DLBCL [305,918,1143].
Thymic extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)

Definition
Primary thymic extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue is a lymphoma consisting predominantly of small B-cells with a centrocyte-like or monocytoid appearance, which surround reactive follicles and infiltrate the thymic epithelium to produce lymphoepithelial lesions.

ICD-O code 9699/3

Synonyms
Mucosa-associated lymphoid tissue (MALT) lymphoma; MALToma

Epidemiology
Primary thymic extranodal marginal zone B-cell lymphoma is rare, with less than 30 cases having been reported in the literature [493,778,891,1209,1279,1426,1556,1700,1945,2188]. Most patients are in the fifth and sixth decades. There is female predominance (M:F = 1:3), and >60% of the reported cases are Asians.

Etiology
Primary thymic extranodal marginal zone B-cell lymphoma is strongly associated with autoimmune disease (>50% of the cases), especially Sjögren syndrome [891]. The autoimmune disease-associated reactive lymphoid hyperplasia may provide a fertile ground for emergence of the lymphoma. There is no association with Epstein Barr virus [891]. There is currently no evidence for a histogenetic link with mediastinal large B-cell lymphoma.

Localization
The bulk of the disease is in the anterior mediastinum, but the regional lymph nodes and other extranodal sites (e.g. stomach, salivary gland, lung) may be involved concurrently.

Clinical features
Patients are usually asymptomatic, with the mediastinal tumour being discovered incidentally on chest radiograph. A minority of patients present with chest pain, shortness of breath, haemoptysis or back pain. In patients associated with autoimmune disease, the time interval between the onset of autoimmune disease and the discovery of the thymic tumour ranges from 2-25 years [891]. Monoclonal gammopathy (frequently IgA, occasionally IgG or IgM) is common, and may sometimes result in hyperviscosity syndrome [891,1209]. An association with Sjögren disease is frequently observed.

Macroscopy
Grossly, the tumour is often encapsulated and comprises solid greyish-white fleshy tissue commonly interspersed with multiple variable-sized cysts. Invasion into the adjacent pericardium and pleura is sometimes found.

Tumour spread and staging
Most tumours (>75%) are of low stage (Stage I/II) at presentation [891]. Concurrent extranodal marginal zone B-cell lymphoma in other MALT sites (e.g. salivary gland, stomach, lung) occurs in about 20% of cases, probably related to the homing characteristics of extranodal marginal zone B-cell lymphomas [891].

Histopathology
The normal thymic lobular architecture is effaced by an abnormal dense lymphoid infiltrate, but residual Hassall corpuscles can still be identified. There are commonly many interspersed epithelium-lined cystic spaces. Reactive lymphoid follicles are scattered within the lymphoid infiltrate. There is a proliferation of small lymphocytes and centrocyte-like cells around and between these follicles. The centrocyte-like cells have small to mediumsized irregular nuclei, indistinct nucleoli, and a moderate amount of pale cytoplasm. They show extensive invasion of the Hassall corpuscles or the thymic epithelium lining the cystic spaces, forming lymphoepithelial lesions. The lymphoid cells within and immediately around the epithelial structures usually possess an even greater amount of clear cytoplasm, reminiscent of monocytoid B-cells. There are often interspersed aggregates of plasma cells, which are shown on immunohistochemical staining to be...
part of the neoplastic clone. Scattered centroblast-like cells or immunoblasts are frequently found. Transformation to diffuse large B-cell lymphoma has only been rarely reported [1209].

**Immunophenotype**
Immunohistochemically, the tumour cells express B-cell specific markers, such as CD20 and CD79a. They are negative for CD3, CD5, CD10, CD23, CD43, and cyclin D1. They commonly express BCL2. More than 75% of the cases express IgA [891].

**Differential diagnosis**
The main differential diagnosis is reactive lymphoid hyperplasia of the thymus. In reactive lymphoid hyperplasia, which is most frequently associated with myasthenia gravis, the thymic lobular architecture is preserved, and there is no band-like or sheet-like proliferation of centrocyte-like cells and monocytoïd cells [1556].

**Histogenesis**
This lymphoma is derived from post-germinal centre marginal zone B-cells.

**Somatic genetics**
Immunoglobulin genes are clonally rearranged [950]. Although API2-MALT1 fusion resulting from t(11;18) is present in up to 50% of extranodal marginal zone B-cell lymphomas in general, this chromosomal translocation is not detected in thymic extranodal marginal zone B-cell lymphomas [891]. Only one case has been studied by cytogenetics, with the finding of 46,X,dup(X)(p11p22) [778].

**Genetic susceptibility**
There is no known genetic susceptibility. It remains unclear whether this lymphoma type shows a predilection for Asians.

**Prognosis and predictive factors**
Thymic extranodal marginal zone B-cell lymphoma is associated with an excellent outcome. Only one documented tumour-related death has been reported [891]. High tumour stage at presentation or concurrent involvement of other MALT sites is not necessarily associated with a poor prognosis. Most patients have undergone surgical resection both for diagnosis and treatment of low stage disease. Chemotherapy and radiotherapy have also resulted in complete remission in some cases.

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Fig. 3.94 Primary extranodal marginal zone B-cell lymphoma of the thymus. A The thymic epithelium lining the cysts is extensively infiltrated by the lymphoma cells. Note also the presence of small clusters of plasma cells. B The lymphomatous infiltrate comprises small lymphocytes, centrocyte-like cells and cells resembling monocytoïd B cells. C Immunostaining for CD20 shows sheets of positive cells, confirming the B-cell lineage of the lymphoma. A residual Hassall corpuscle is seen in the left middle field. Note that plasma cells do not react. D Many plasma cells are highlighted by immunostaining for immunoglobulin (lambda light chain in this case).
Definition
Precursor T-lymphoblastic lymphoma/leukaemia is a neoplasm of lymphoblasts committed to the T-cell lineage, typically composed of small to medium-sized blast cells with scant cytoplasm, moderately condensed to dispersed chromatin and indistinct nucleoli, variably involving bone marrow and blood (precursor T-cell acute lymphoblastic leukaemia), thymus and/or lymph nodes (precursor T-cell lymphoblastic lymphoma).

ICD-O code
Precursor T-lymphoblastic lymphoma 9729/3
Precursor T-lymphoblastic leukaemia 9837/3

Synonyms
Precursor T-cell acute lymphoblastic leukaemia (ALL) / Precursor T-cell lymphoblastic lymphoma (LBL); T-cell lymphoblastic lymphoma; T-cell acute lymphoblastic leukaemia; convoluted lymphocytic lymphoma (Lukes-Collins); lymphoblastic lymphoma, convoluted cell type (Kiel, Working formulation); poorly-differentiated lymphocytic lymphoma (Rappaport); leukosarcoma (Sternberg sarcoma) (historical term) [1878]

Epidemiology
Precursor T-cell neoplasms occur most frequently in late childhood, adolescence, and young adulthood, with a male predominance. Fifteen percent of childhood and 25% of adult ALL are of precursor T-cell type [206]. Cases presenting without bone marrow and peripheral blood involvement (lymphoblastic lymphoma) comprise 85% of lymphoblastic lymphomas, 25-30% of childhood non-Hodgkin lymphomas and only 2% of adult non-Hodgkin lymphomas worldwide [3]. Some studies indicate an increased prevalence of precursor T-cell neoplasia in underdeveloped countries, while precursor B-cell neoplasms are more common in industrialized countries [2016].

Etiology
The etiology is unknown. No association with viruses or immune status has been demonstrated. Patients with ataxia telangiectasia are at increased risk for development of T-ALL, but the ATM gene has not been implicated in sporadic T-precursor neoplasia [1959]. In early childhood T-ALL, the neoplastic clone can be detected at birth by clone-specific T-cell receptor gene rearrangement, suggesting that the transforming event occurs in utero [559].

Localization
The tumour typically involves the mediastinum, specifically the thymus, and often mediastinal lymph nodes. Supradiaphragmatic lymph nodes may also be involved, and tumour cells are often shed into the pleural fluid. The bone marrow and peripheral blood are involved in the majority of the cases. Central nervous system involvement is also common. Clinically, a case is defined as lymphoma if there is a mediastinal or other mass and <25% blasts in the bone marrow, and as leukaemia if there are >25% bone marrow blasts, with or without a mass. This is an arbitrary distinction and should be regarded as staging rather than classification.

Clinical features
Patients typically present acutely with symptoms related to a large mediastinal mass, often with pleural or pericardial effusions. Airway compromise is common, and the presentation is often as a medical emergency

Histopathology
The thymus and mediastinal soft tissue as well as adjacent lymph nodes are involved. The epithelial meshwork is destroyed, septa are effaced, and the tumour cells spread through the capsule into adjacent mediastinal tissue. In tissue sections, the cells are small to medium-sized, with scant cytoplasm, round, oval, or convoluted nuclei, with fine chromatin and indistinct or small nucleoli. Occasional cases have larger cells. In lymph nodes the pattern is infiltrative rather than destructive, often with partial preservation of the subcapsular sinus and germinal centres. A starry-sky pattern may be present, but is usually less prominent than in Burkitt lymphoma. Pleural or pericardial fluid may be the initial diagnostic specimen. On smears, lymphoblasts vary from small cells with

Fig. 3.95 Infiltration of the heart by a T-lymphoblastic lymphoma.

Fig. 3.96 Precursor T-lymphoblastic lymphoma
A Monomorphous infiltrate with a starry-sky pattern. B Tumour cells have dispersed chromatin, small nucleoli, and scant cytoplasm, such that the nuclei appear to overlap.
scant cytoplasm, condensed nuclear chromatin, and indistinct nucleoli to larger cells with a moderate amount of cytoplasm, dispersed chromatin, and multiple nucleoli. Azurophilic granules may be present. Recently, cases of mediastinal precursor T-cell lymphomas with increased tissue and bone marrow eosinophils have been described. Patients typically developed acute leukemia with myeloid antigen expression. These cases were found to have a translocation t(8;13) in both the myeloid and lymphoid cells, indicating a true biphenotypic malignancy [2179].

**Immunophenotype**

The lymphoblasts are positive for terminal deoxynucleotidyl transferase (TdT) in virtually all cases, and variably express CD2, CD7, surface or cytoplasmic CD3, CD5, CD1a, CD4 and/or CD8. Only surface CD3 is considered lineage-specific. Minimal criteria for classification as T-LBL are CD7+ and cytoplasmic CD3+. The constellation of antigens defines stages of differentiation, ranging from early or pro-T (CD2, CD7 and cytoplasmic CD3), to “common” thymocyte (CD1a, sCD3, CD4 and CD8), to late thymocyte (CD4 or CD8).

Although there is some correlation with presentation and differentiation stage (cases with bone marrow and blood presentation may show earlier differentiation stage than cases with thymic presentation [157,725]) there is overlap [1632]. Among cases that express T-cell receptor proteins, the majority are of the alpha/beta type and a minority express gamma/delta type; the latter appear to have a more immature phenotype [1938]. Rare cases of lymphoblastic lymphoma presenting in the mediastinum have the immunophenotype of immature natural killer (NK) cells [325,1046,1795].

**Differential diagnosis**

On biopsy specimens, the differential diagnosis may include thymoma with a prominent immature T-cell population (B1 or B2 thymoma). The immunophenotype of T-LBL and of the normal precursor T-cells in thymoma can be identical. The infiltrative growth of the lymphoblasts with destruction of the epithelium and demonstration of clonality by molecular genetic analysis can be helpful in confirming the diagnosis of lymphoma. In a patient with a mediastinal mass and lymphocytosis, a diagnosis of peripheral T-cell lymphocytosis associated with thymoma has to be included among the differential diagnoses [116,445].

**Histogenesis**

Precursor T lymphoblasts at varying stages of differentiation.

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**Somatic genetics**

Rearrangement of antigen receptor genes is variable in lymphoblastic neoplasms, and may not be lineage-specific; thus, precursor T-cell neoplasms may have either or both T-cell receptor (TCR) beta or gamma chain gene rearrangements and immunoglobulin heavy chain gene rearrangements [1939]. The majority have T-cell receptor gamma chain rearrangements, with either beta or delta rearrangements in the majority of the cases [1938].

Chromosomal translocations involving the TCR alpha and delta loci at chromosome 14q11 and beta and gamma loci at 7q34 are present in about one-third of the cases [998,2044]; the partner genes are variable and include the transcription factors c-MYC (8q24), TAL1/SCL (1p32), RBTN1 (11p35), RBTN2 (11q13), and HOX11 (10q24) and the cytoplasmic tyrosine kinase LCK (1p34). In an additional 25%, the TAL1 locus at 1p32 has deletions in the 5’ regulatory region [136]. Deletions of 9p involving deletion of the p16INK4a tumour suppressor gene (CDK4 inhibitor) is also seen in T-lymphoblastic neoplasms [901,1601]. Cases associated with eosinophilia and myeloid neoplasms have a t(8;13) involving the fibroblast growth factor receptor gene on chromosome 8 and a novel zinc-finger gene on chromosome 13 [2179].

Analysis by gene expression array has shown that acute leukaemias of lymphoid and myeloid types can be distinguished, as can precursor T and precursor B-cell lymphoblastic leukemias. The utility of these studies in diagnosis remains to be determined, however, some differentially expressed genes, such as TAL1/SCL can be detected by immunohistochemistry and may provide a marker for T-precursor neoplasia [552,706].

**Prognostic factors**

The prognosis with aggressive therapy is similar to that of precursor B-cell neoplasms, and is not affected by immunophenotype or genetic abnormalities. In children, treatment is generally more aggressive than that for precursor B-ALL, and is typically the same for lymphomatous and leukemic presentations [1361]. The median disease-free survival in one recent study of adult T-ALL was 28 months [206,2044].
**Anaplastic large-cell lymphoma and mature T and NK cell lymphomas of the mediastinum**

**Definition**
Mature T-cell and NK-cell neoplasms are derived from mature or post-thymic T cells and NK cells, respectively. Because they share some immunophenotypic and functional properties, these two classes of neoplasms are considered together.

**ICD-O code**
Anaplastic large-cell lymphoma 9714/3

---

**Anaplastic large-cell lymphoma (ALCL)**

ALCL mainly occurs in children and young adults, involving a variety of sites. The incidence of a mass presentation in the thymus and/or mediastinum varies from 8-39% with or without lymphadenopathy [231,1775,1930]. The higher figure of 39% likely results from inclusion in some series of “Hodgkin-like” ALCL, which is now thought to be a variant of Hodgkin lymphoma in most cases [919]. ALCL involving the thymus may be associated with cyst formation, evident on gross or microscopic examination. ALCL usually shows a cohesive growth pattern and cytologic features as follows: the cells are large, with round or indented nuclei, often described as reniform, embryo-, and horseshoe-shaped, multiple nucleoli that vary in size, and abundant cytoplasm. The so-called “hallmark cell” has an indented nucleus with a paranuclear, eosinophilic region corresponding to the Golgi region. Reactive cells may be numerous in rare cases, usually histiocytes or neutrophils; eosinophils are not common. The tumour cells are strongly and consistently positive for CD30. Although they show T-cell receptor gene rearrangement on a molecular level, phenotypically their derivation from the T-cell lineage may be difficult to prove. CD2 and CD4 are the markers most frequently positive. CD3 is often but not always positive. Most cases express cytotoxic molecules such as granzyme B and TIA-1. They also may exhibit positivity for other T-cell markers (CD43, CD45R0), EMA, while CD5 and CD7 are frequently negative. Anaplastic lymphoma kinase (ALK) is expressed in 40-70% of ALCL in various series. It may be nuclear and cytoplasmic or cytoplasmic only, depending on the translocation; it is more commonly expressed in pediatric cases, and is associated with an excellent prognosis [919]. ALCL may pose differential diagnostic problems from carcinoma, mediastinal large B-cell lymphoma or Hodgkin lymphoma. Immunophenotyping for CD15, CD30, pan-B and pan-T antigens, cytotoxic molecules, EMA, keratin, and ALK protein may be essential for their exact diagnosis.

**Somatic genetics**
ALCL is associated with characteristic chromosome translocations involving the ALK gene on chromosome 2, with the partner being the NPM gene on chromosome 5 in most cases, and other genes in a minority of the cases [919].

**Mature T cell lymphomas**

Mature T-cell neoplasms are very rare in the thymus, despite the importance of the thymus in T-cell ontogeny [1402, 1610,1827,2195]. Only 0.2% of peripheral T-cell lymphomas are diagnosed from mediastinal biopsies. Although there is no documented case of mature NK cell lymphoma primarily affecting the thymus, 5 of 142 cases registered in the NK Cell Tumour Study Group in Japan showed mediastinal involvement (unpublished). In a patient with a mediastinal mass and lymphocytosis, a diagnosis of peripheral T-cell lymphocytosis associated with thymoma has to be included among the differential diagnoses [116,445].

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**Fig. 3.98** Anaplastic large-cell lymphoma. **A** Hallmark cells with embryoform or kidney shaped nuclei, broad cytoplasm, and pale staining Golgi region; numerous apoptotic bodies and mitoses. **B** CD30 expression in the membrane and Golgi region.

**Fig. 3.99** High power magnification of typical ‘hallmark’ cells in ALCL.
Hodgkin lymphoma of the mediastinum

Definition
Hodgkin lymphoma (HL) is a neoplasm derived from B-cells in most cases, characterized by large tumour cells scattered in a characteristic inflammatory background. It encompasses two entities distinguishable by their phenotype and clinical presentation, namely nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and classical Hodgkin lymphoma (cHL) [50,496]. Since HLs other than nodular sclerosis are exceedingly rare in biopsies from the mediastinum, these should be referred to in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [919].

ICD-O code
Hodgkin lymphoma, nodular sclerosis 9650/3

Synonyms
In older publications, thymic HL was often designated as granulomatous thymoma [968]. Since the tumour cells are of lymphoid origin, the term Hodgkin lymphoma is preferred over Hodgkin's disease.

Epidemiology
Nodular sclerosis Hodgkin lymphoma (NSHL) is especially predominant in industrialized countries, in high socioeconomic groups and in urban areas [782]. The age distribution shows a peak at the third decade, and probably also a second smaller peak in late life. The disease more commonly affects women than men. Patients with a history of infectious mononucleosis have a slightly higher incidence of HL. Both familial and geographical clustering have been described [1270].

Macroscopy
The thymus or mediastinal lymph nodes involved by NSHL show multiple firm greyish-white nodules, with or without visible fibrous bands. The thymus commonly exhibits interspersed cystic spaces [988].

Localization
NSHL of the anterior mediastinum often takes origin from the thymus or mediastinal lymph nodes, or both may be involved [988,1080].

Clinical features
The patients present with symptoms due to the presence of a large anterior mediastinal mass, such as chest discomfort or dyspnoea, or occasionally are asymptomatic, being incidentally found to have a mass lesion on chest radiograph. Some patients have simultaneous involvement of supraclavicular or lower cervical lymph nodes. A proportion of patients also have systemic symptoms. Myasthenia gravis has been described in one case of thymic HL [1494].

Histopathology
The architecture of the lymph node or the thymus is effaced by a nodular infiltrate that comprises variable numbers of...
Hodgkin and Reed-Sternberg cells associated with a rich inflammatory background. Classical Reed-Sternberg cells are large cells with apparently double or multiple nuclei and abundant eosinophilic or amphophilic cytoplasm. The nuclei are often rounded in contour, with thick nuclear membrane, pale chromatin, at least 2 eosinophilic nucleoli in 2 separate lobes, and perinucleolar clearing. Mononuclear variants are termed Hodgkin cells. Some tumour cells may have condensed cytoplasm and pyknotic nuclei, and are known as mummified cells. The lacunar variant of Reed-Sternberg cells is characterised by relatively small, lobated nuclei, often with small nucleoli, and abundant, pale cytoplasm that is retracted in formalin-fixed tissues.

NSHL invariably shows sclerosis, which in lymph nodes begins in the capsule, and divides the tumour into nodules of varying size. At least one fibrous band encapsulating a tumour nodule is considered to be the minimal criterion for the nodular sclerosis subtype. The inflammatory background of NSHL comprises lymphocytes, plasma cells, and granulocytes, especially eosinophils. Geographic necrosis is common, frequently accompanied by neutrophil infiltration and concentration of tumour cells around the necrotic areas.

Involvement of the thymus by cHL often results in cystic changes, and pseudo-epithelial hyperplasia of thymic epithelium mimicking thymoma on small biopsies. The cysts are lined by flat epithelium which is frequently non-keratinizing-squamous, but may be columnar, ciliated or mucus producing (988,1080). Tumour may be detected within cyst walls, sometimes producing bulges into the lumen. Similar cystic changes can also occur in the thymus not involved by the lymphoma itself.

In small biopsies, both the characteristic pattern and tumour cells may be difficult to identify. To establish the primary diagnosis of cHL, either classical multinucleated Reed-Sternberg cells or lacunar cells showing the typical immunophenotype should be identified, and this may require examination of multiple levels of the biopsy. If fibrous bands cannot be identified, the case may be classified as cHL not further classified, with a note that the small specimen size precludes definitive subclassification. Composite lymphomas with CHL and diffuse large B cell lymphoma infiltrates side by side are rare.

**Immunohistochemistry**

In cHL, tumour cells strongly and consistently express CD30. CD15 is detectable in more than 85% of the cases, although sometimes only focally (2090). CD20 may be expressed in up to 20% of cHL (1760,2090,2248), but it is usually weaker than in accompanying B-cells and staining intensity varies among tumour cells (1705). CD79a is negative in the majority of cases. EBV is expressed in about 20% of NSHL, and may be detected by immunohistochemistry for its latent

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**Table 3.12**

Synopsis of mediastinal Hodgkin lymphomas

<table>
<thead>
<tr>
<th>Classification of Hodgkin lymphomas</th>
<th>Abbreviation</th>
<th>Frequency diagnosed from mediastinal biopsies with HL*</th>
<th>ICD-O code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular lymphocyte predominant Hodgkin lymphoma</td>
<td>NLPHL</td>
<td>1%</td>
<td>9659/3</td>
</tr>
<tr>
<td>Classical Hodgkin lymphoma</td>
<td>CHL</td>
<td>99%</td>
<td>9650/3</td>
</tr>
<tr>
<td>Nodular sclerosis classical Hodgkin lymphoma</td>
<td>NSHL</td>
<td>80%</td>
<td>9663/3</td>
</tr>
<tr>
<td>Mixed cellularity classical Hodgkin lymphoma</td>
<td>MCHL</td>
<td>18%</td>
<td>9652/3</td>
</tr>
<tr>
<td>Lymphocyte-rich classical Hodgkin lymphoma</td>
<td>LRCHL</td>
<td>0%</td>
<td>9651/3</td>
</tr>
<tr>
<td>Lymphocyte-depleted classical Hodgkin lymphoma</td>
<td>LDHL</td>
<td>1%</td>
<td>9653/3</td>
</tr>
</tbody>
</table>

* German Hodgkin Study Group data based on 169 mediastinal biopsies, unpublished data.
membrane antigen or EBER probes (692), while EBNA2 is not expressed (1991). The incidence of EBV association in NSHL is generally lower than in other subtypes and varies geographically (692,782). Vimentin (1705) and fascin (1600) are generally expressed in cHL, but rare in large B-cell lymphomas. The reactive background contains variable numbers of B- and T-lymphocytes, with the latter forming rosettes around individual tumour cells.

**Histogenesis**

Post germinal center activated B cells are the presumed cells of origin.

**Somatic genetics**

On a single cell level, rearrangement of the immunoglobulin genes can be demonstrated in almost all cases, indicating B cell derivation of the Reed-Sternberg cells and variants (1096A). In cHL, the rearranged immunoglobulin gene is not transcribed, either due to non-functional mutations in the immunoglobulin genes (1099,1873) or due to a lack in essential transcription factors (such as OCT-2, BOB-1) (1874). Rare cases with rearranged T-cell receptor genes have been observed (1414,1776).

In CGH-analysis, gains on the short arms of chromosomes 2 and 9, and on the long arm of chromosome 12 are frequently detected. An overrepresentation of the REL-protooncogene (2p15-p16) and the JAK/STAT signal transduction pathway may play a major role in the pathogenesis (115,939,940,1249).

Recent molecular studies applying gene expression profiling show that classical Hodgkin lymphoma and PMLBCL are closely related (1694,1752).

**Prognostic factors**

Patients are usually treated with chemotherapy with or without radiotherapy, adapted to clinical stage. Stage is the single most important prognostic factor. The various subtypes of cHL do not differ in their prognosis, which has greatly improved with recent protocols (495). In one study, cases that lacked CD15 expression had a worse prognosis than CD15+ cases (2090). Grading systems for nodular sclerosis have been shown in some studies, but not others, to predict prognosis (574,825,1221,2069,2091).
Grey zone between Hodgkin lymphoma and non-Hodgkin lymphomas (NHL)

Definitions
The term grey zone lymphoma has been assigned to neoplasms exhibiting indeterminate features between classical Hodgkin lymphoma (cHL) and large cell non-Hodgkin lymphoma (NHL), such that a definitive classification as cHL or NHL is not possible.

Composite lymphomas exhibit clearly separable lymphoma infiltrates with typical features of cHL and NHL side by side. They may or may not be clonally related. The different components and their proportions should be stated in the diagnosis.

ICD-O code
Composite Hodgkin and non-Hodgkin lymphoma 9596/3
This code may also be used for grey zone lymphomas.

Some tumours can exhibit indeterminate features of both cHL and large B cell lymphoma, such that definitive classification as cHL or NHL is impossible even after extensive immunophenotypic and molecular studies (1270,1704). These lymphomas are termed grey zone lymphomas. Their occurrence is not surprising. Since Hodgkin lymphoma is a lymphoid malignancy derived from B-cells in nearly all cases (1097,1099,1237), its interface to B-cell NHL may not always be clear-cut. The interface between NSHL and primary mediastinal large B-cell lymphoma (PMLBCL) is currently felt to comprise a biological transition: apart from their frequent mediastinal presentation, both tumours frequently lack functional expression of HLA class I and immunoglobulin genes. CHL is always CD30 positive, and primary mediastinal large B cell lymphoma is also frequently CD30 positive. CGH studies suggest that they share an overrepresentation of genomic material on the short arms of chromosomes 2 and 9 (148,1752).

Finally, microarray-based studies have documented largely overlapping gene expression profiles in cHL and PMLBCL, stressing their close keenship (1694, 1752). However, as HL is treated differently than NHL, it is important to distinguish between them, if possible.

Histopathology.
Grey zone lymphomas, by definition, have no specific morphology. They may manifest a vaguely nodular infiltrate with focal fibrosis. There are sheets of malignant cells, some of which resemble Reed-Sternberg cells or lacunar variants. The inflammatory background may be sparse or absent. The tumor cells typically all express CD20, and in addition strongly express CD30. CD79a and CD15 may be variably expressed. Retrospective clinical data suggest that the mostly male patients respond poorly to radiotherapy alone, and relapses in abdominal and extranodal locations are common (1704).
Histiocytic tumours rarely occur as a primary tumour in the mediastinum. Details are available in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues [919]. This section focuses on cases located in the thymus or mediastinum. Exceptionally, Rosai-Dorfman disease (Sinus Histiocytosis with Massive Lymphadenopathy, SHML) can also involve these sites.

**Langerhans cell histiocytosis and sarcoma**

**Definitions**
Langerhans cell histiocytosis is a neoplastic proliferation of Langerhans cells, with expression of CD1a, S100 protein, and the presence of Birbeck granules by ultrastructural examination. Langerhans cell sarcoma differs from Langerhans cell histiocytosis in showing overtly malignant cytologic features; it can present de novo or progress from antecedent Langerhans cell histiocytosis.

**ICD-O codes**
- Langerhans cell histiocytosis: 9751/1
- Langerhans cell sarcoma: 9756/3

**Synonym**
Langerhans cell sarcoma was previously termed malignant histiocytosis X.

**Epidemiology and clinical features**
Involvement of the thymus or mediastinal lymph node by Langerhans cell histiocytosis or Langerhans cell sarcoma is rare [1181]. It usually occurs in the setting of disseminated disease [143,210,945, 1596,1761]. Rare cases of Langerhans cell histiocytosis presenting with thymic involvement have been reported [219,683,1491, 1578,2096]. In children, the thymus is often markedly enlarged and extensively infiltrated by Langerhans cells; there can be invasion of the surrounding mediastinal structures. In adults, the thymic involvement is usually subtle, and is discovered incidentally in thymus removed primarily for another indication; thus the reported association with myasthenia gravis is probably fortuitous [219,683, 1578,2096].

**Histopathology**
The key histologic feature of Langerhans cell histiocytosis is a diffuse infiltrate of non-cohesive Langerhans cells with grooved or markedly contorted nuclei, thin nuclear membranes, fine chromatin and eosinophilic cytoplasm. There are commonly admixed multinucleated giant cells and eosinophils. Necrosis can be present. The Langerhans cells typically express S-100 protein and CD1a. The thymus can be involved diffusely or focally. The involved areas show destruction of the normal thymic parenchyma, damage to Hassall corpuscles, interlobular connective tissue infiltration, and scattered calciospherites [1761,1823]. Localized thymic involvement in adults often takes the form of scattered small nodular aggregates of Langerhans cells.
This can be accompanied by reactive lymphoid hyperplasia or multilocular thymic cyst [2096].

**Differential diagnosis**
An important differential diagnosis is histioeosinophilic granuloma of the mediastinum, which is a reactive lesion resulting from iatrogenic pneumomediastinum, akin to reactive eosinophilic pleuritis [762,1304]. Although both histioeosinophilic granuloma and Langerhans cell histiocytes feature histiocytes and eosinophils, the histiocytes in the former are confined to the capsule or septa of the thymus with sparing of the parenchyma, the nuclei are uncommonly grooved, and S-100 protein and CD1a immunostains are negative.

**Somatic genetics**
In contrast to pulmonary eosinophilic granuloma, which in most cases is a non-neoplastic, reactive process in smokers, most cases of Langerhans cell histiocytosis occurring in non-pulmonary sites are believed to be clonal neoplasms, as demonstrated by X-chromosome inactivation [2149]. Thymic cases have not, however, been specifically studied.

**Histiocytic sarcoma and malignant histiocytosis**

**Definition**
Histiocytic sarcoma is a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes. There is expression of one or more histiocytic markers without accessory/dendritic cell markers. Tumourous masses of acute monocytic leukaemia are excluded. The term ‘malignant histiocytosis’ is sometimes applied for histiocytic sarcoma showing systemic disease, often with liver, spleen and bone marrow involvement.

**ICD-O code**
- Histiocytic sarcoma 9755/3
- Malignant histiocytosis 9750/3

**Synonyms**
- True histiocytic lymphoma, histiocytic medullary reticulosis (obsolete)

**Epidemiology**
Among the recent series on histiocytic sarcoma diagnosed using strict criteria (including over 50 cases) [405,774,949, 1140,1596], there is only a single case with predominant involvement of the mediastinum [949]. There are reports on malignant histiocytosis or histiocytic sarcoma associated with mediastinal non-seminomatous germ cells tumours, but they lack vigorous documentation regarding the true histiocytic nature of the neoplasm [83,473,474,789,1460, 1461,2246].

**Histopathology**
Histiocytic sarcoma is characterized by a diffuse infiltrate of large cells with voluminous eosinophilic, and sometimes finely vacuolated, cytoplasm. The nuclei are round, oval, indented, grooved or irregularly folded, often with vesicular chromatin and small nucleoli. Nuclear pleomorphism can be significant. The diagnosis has to be confirmed by immunohistochemical staining: positive for CD68 and lysozyme; frequently positive for CD45, CD4, CD43, CD45RO and HLA-DR; occasionally positive for S100 protein; and negative for myeloid markers, dendritic cell markers (CD1a, CD21, CD35), T lineage-specific markers, B lineage-specific markers and CD30 [1596].
**Follicular dendritic cell tumour / sarcoma**

**Definition**

Follicular dendritic cell (FDC) tumour/sarcoma is a neoplastic proliferation of spindle to ovoid cells showing morphologic and phenotypic features of follicular dendritic cells. The terms tumour and sarcoma are both used because of the variable cytologic grade and indeterminate clinical behaviour of these neoplasms.

**ICD-O code**

- Follicular dendritic cell tumour 9758/1
- Follicular dendritic cell sarcoma 9758/3

**Clinical features**

These neoplasms are uncommon, with only a small number of cases having been reported to show primary involvement of the thymus or mediastinal lymph nodes [58,323,482, 560,1571,1596]. The patients are adults with a mean age of 46 years, being comparable to that of the same tumour occurring in other sites [323,1571]. However, they differ in showing marked male predominance, but this may be due to bias from the small number of cases. The patients are asymptomatic, or present with cough, haemoptysis or chest discomfort.

**Etiology and precursor lesions**

A proportion of cases of follicular dendritic tumour/sarcoma arise in the setting of hyaline-vascular Castleman disease, often through an intermediary phase of follicular dendritic cell proliferation outside the follicles [320,323,1186]. Both components of hyaline-vascular Castleman disease and follicular dendritic cell tumour/sarcoma may be identified in the same tumour mass in the mediastinum [482].

**Histopathology**

Tumours are often large, with a broad histologic spectrum. The growth pattern can be storiform, whorled, fascicular, nodular, diffuse or even trabecular. The individual tumour cells are spindle or ovoid, and the lightly eosinophilic cytoplasm often exhibits indistinct cell borders. The nuclei are elongated or oval, with thin nuclear membrane, vesicular or granular chromatin, and small distinct nucleoli. There is often an irregular clustering of the nuclei, and occasional multinucleated tumour giant cells can be seen. Some cases can exhibit significant nuclear pleomorphism, mitotic activity and coagulative necrosis. The tumour is typically sprinkled with small lymphocytes, which can show clustering around blood vessels. A diagnosis of follicular dendritic cell sarcoma should be confirmed by immunohistochemical studies (positive for CD21 and CD35, and variably CD23), and preferably also by ultrastructural studies (numerous long slender cytoplasmic processes and mature desmosomes).

**Differential diagnosis**

Mediastinal follicular dendritic cell sarcoma can be mistaken for type A thymoma because of the mediastinal location, spindle cell growth and lymphocytic infiltration. To add to the confusion, follicular dendritic cell sarcoma can exhibit jigsaw puzzle-like lobulation and perivascular spaces as commonly seen in thymomas [359]. In contrast to type A thymoma, there is no focal glandular differentiation, cytokeratin is negative, and follicular dendritic cell-associated markers are expressed.

**Histogenesis**

Follicular dendritic cells of the B-cell follicle.

**Prognosis and predictive factors**

Among 5 patients with mediastinal FDC tumour/sarcoma with follow-up information, two developed pulmonary metastases after two years, one developed local recurrence at 3 years, and two were alive without evidence of disease after surgery and radiochemotherapy.
**Interdigitating dendritic cell tumour / sarcoma**

**Definition**
Interdigitating dendritic cell sarcoma/tumour is a neoplastic proliferation of spindle to ovoid cells with phenotypic features similar to those of interdigitating dendritic cells.

**ICD-O code**
- Interdigitating dendritic cell tumour 9757/1
- Interdigitating dendritic cell sarcoma 9757/3

**Epidemiology, localization and clinical features**
Interdigitating dendritic cell sarcomas are very rare, and mediastinal involvement is even rarer. The few reported cases have involved the mediastinal lymph nodes as a component of disseminated disease [569,1309,1635,1698, 2067]. There is a reported case of mediastinal tumour showing hybrid features of follicular dendritic cells and interdigitating dendritic cells [499].

**Histopathology**
The tumour shows a fascicular, storiform, whorled or diffuse growth pattern, comprising spindle or plump cells with indistinct cell borders and abundant eosinophilic cytoplasm. The nuclei often exhibit finely dispersed chromatin and distinct nucleoli. Cytologic atypia is variable.

**Differential diagnosis**
The diagnosis should always be confirmed by immunohistochemical staining, with or without ultrastructural studies (complex interdigitating cell processes lacking well-formed macula adherens-type desmosomes and lacking Birbeck granules). The neoplastic cells strongly express S-100 protein, and often show variable weak staining for CD68, lysozyme, CD4 and CD45. They should be negative for CD1a, follicular dendritic cell markers (CD21, CD35), myeloperoxidase, T lineage specific markers, B-cell-specific markers and CD30.
Myeloid sarcoma and extramedullary acute myeloid leukaemia

**Definition**
Myeloid sarcoma is a mass forming neoplastic proliferation of myeloblasts or immature myeloid cells occurring in an extramedullary site. It may occur de novo or simultaneously with acute myeloid leukaemia (AML), myeloproliferative disorders, or myelodysplastic syndromes, but may also be the first manifestation of leukaemic relapse in a previously treated patient [1518]. Interstitial infiltration of myeloid blasts without a nodular mass can be termed extramedullary AML.

**ICD-O code**
9930/3

**Synonyms**
Extramedullary myeloid tumour; granulocytic sarcoma; chloroma

**Clinical features**
Mediastinal myeloid sarcoma has been reported in association with a superior vena cava syndrome [1643]. Most mediastinal cases occur simultaneously with AML or are followed by AML shortly. Patients who presented with “primary” mediastinal granulocytic sarcoma without concurrent AML, all eventually relapsed as frank leukaemia [369].

**Histopathology**
The most common type of myeloid sarcoma occurring in the mediastinum is known as granulocytic sarcoma [2193], a tumour composed of myeloblasts and promyelocytes. The degree of maturation is variable in different cases. The blastic subtype is entirely composed of myeloblasts; in the more differentiated subtypes, promyelocytes are also present [919,2108]. Rare cases composed of monoblasts (termed monoblastic sarcoma), can also occur in this location. Cases associated with acute transformation of an underlying myeloproliferative disorder may show foci of trilineage extramedullary hematopoiesis associated with the blastic proliferation. In patients with mediastinal germ cell tumours with mediastinal myeloid sarcoma or extramedullary myeloid leukaemia, the possibility of a “local” origin of the tumour should also be considered.

**Cytochemistry and immunophenotype**
Cytochemical stains to detect myeloid differentiation in AML can be applied to imprints of biopsy material. Flow cytometry may demonstrate myeloid antigen expression. Myeloid associated markers which can confirm the diagnosis include lysozyme, myeloperoxidase, CD43, CD117, CD68, and CD61. The lack of expression of lymphoid associated antigens helps in the differential diagnosis versus large cell lymphomas and lymphoblastic lymphoma. The histochemical stain for chloroacetate esterase may be helpful in identifying promyelocytes and more differentiated myeloid elements in differentiated myeloid sarcoma subtypes.

**Differential diagnosis**
The major differential diagnosis is with non-Hodgkin lymphomas, lymphoblastic lymphoma and diffuse large cell lymphoma. In children, the differential includes various metastatic small round cell tumours. Cases of myeloid sarcoma with prominent sclerosis may closely mimic sclerosing mediastinal (thymic) large B-cell lymphoma. In patients with mediastinal germ cell tumours, the possibility of a “local” origin of the myeloid sarcoma from haematopoietic precursor cells occurring within the germ cell tumour should also be considered [1278].

**Somatic genetics**
AML with t(8;21) has an increased frequency of granulocytic sarcomas, as do monocytic and monoblastic leukemias with 11q23 abnormalities. The presence of genetic abnormalities in myeloid sarcoma, can be detected by reverse transcriptase-polymerase chain reaction, conventional cytogenetics, or fluorescence in-situ hybridization studies.

**Prognosis and predictive factors**
Mediastinal myeloid sarcoma is an aggressive disease. Patients who presented with a “primary” mediastinal MS and were treated by local irradiation only (prior to developing AML), eventually all relapsed as frank leukaemia and died soon afterwards [369]. In contrast, patients who were considered to have AML and given upfront systemic chemotherapy achieved better outcomes, their prognosis being that of the underlying leukaemia [369,919].

Fig. 3.109 Myeloid sarcoma (monoblastic). Sclerotic bands divide the neoplasm into irregular alveolar clusters and cords. Note the kidney shaped immature nuclei with vesicular or granular chromatin, multiple small nucleoli, and pale abundant cytoplasm.
A variety of mesenchymal and neurogenic tumours can arise in the mediastinum. For those that occur in the anterior mediastinum, it is often difficult to ascertain whether they are of thymic origin or derived from other mediastinal constituents (1529). An exception is thymolipoma, since the intimate admixture of lipomatous tissue with thymic parenchyma strongly supports its thymic derivation. Some sarcomas arise in mediastinal germ cell tumours (1230, 1932).

Principles of the classification
The classification of mesenchymal and neurogenic tumours of the thymus and mediastinum follows the WHO classifications of tumours of soft tissues and bone (590) and of tumours of the nervous system (1026). Since thymolipoma is a unique thymic tumour with a predominant mesenchymal component, it is described and discussed here in more detail.

Epidemiology
Mesenchymal and neurogenic tumours of the thymus and mediastinum are all very rare, constituting less than 10% of all mediastinal neoplasms. Almost all neurogenic neoplasms of the mediastinum occur in the posterior mediastinum.

Clinical features
Mesenchymal and neurogenic tumours of the anterior mediastinum or thymus are frequently detected incidentally, but may present as cough, chest pain, pleural effusion, respiratory distress or the superior vena cava syndrome. Hypoglycaemia is a rare complication of solitary fibrous tumour (2164). Tumours in the middle and posterior mediastinum, which are mostly neurogenic neoplasms, often produce symptoms due to compression of large vessels, heart, nerves or spinal cord.

Thymolipoma

Definitions
Thymolipoma is a well-circumscribed tumour consisting of mature adipose tissue with interspersed islands of non-neoplastic thymic tissue.

ICD-O code
8850/0

Synonym
Thymolipomatous hamartoma

Epidemiology
Thymolipomas are rare tumours (about 80-100 published cases) that may occur at any age, but are most commonly encountered in young adults (10-30 years, mean age 33 years) (1352,1683). There is no sex predilection.

Localization
All documented cases arose in the anterior mediastinum.

Clinical features
Thymolipomas may remain asymptomatic for a long period. The majority of cases are incidental findings on routine chest radiographs and may simulate cardiomegaly (44,1818) or other mediastinal neoplasms. Thymolipomas may become symptomatic either due to the size of the lesion, or, less frequently, due to associated autoimmune phenomena. Among these, myasthenia gravis is the most frequent (about 7% of cases (1352)), but single cases with other manifestations such as aplastic anaemia (113) and Graves disease (147) have been reported.

Macroscopy
The size of thymolipoma ranges from 4 to over 30 cm (1352). The tumours are yellow, soft, fairly well circumscribed with scattered white streaks or focal solid areas on the cut surface.

Histopathology
Histologically, they consist of abundant mature adipose tissue admixed with areas containing remnants of thymic tissue. The fat cells show no cytologic atypia or mitotic activity (1352). The thymic tissue component may vary from strands of atrophic thymic epithelium to large

Fig. 3.110 Thinly encapsulated thymolipoma in a 6-year-old male child. The cut surface is yellow, bulging, and lobulated, resembling lipoma. From Y. Shimosato and K. Mukai (1808).

Fig. 3.111 Thymolipoma. A Thymolipoma showing a delicate but distinct fibrous capsule and thin septae of atrophic thymic tissue. B Strands of thymic epithelial cells within thymolipoma. The lymphocyte content is virtually absent in this case, possibly related to the age of the patient. The content of fibrous tissue may be extensive: ‘Thymofibrolipoma’ (1372). Note single melanocytes scattered among thymic epithelial cells.
areas containing inconspicuous thymic parenchyma containing numerous, often calcified, Hassall’s corpuscles (1352). Myoid cells are present (907). The thymic compartment may show single lymph follicles.

**Differential diagnosis**
Diagnosis of thymolipoma is usually not problematic. However, due to the large size of some lesions, careful sampling is necessary in order to rule out the possibility of atypical or malignant areas. In rare cases, thymomas may arise within thymolipomas (69). Histologically, the main differential diagnoses include lipoma of the thymus (no thymic epithelial component) and mediastinal liposarcomas (scattered lipoblasts).

**Histogenesis**
The pathogenesis and biological nature of thymolipoma are controversial, but most authors favour a benign neoplasm (69, 763,1352). An origin from specialized thymic stroma has been postulated (69, 763).

**Prognosis and predictive factors**
There have been no reports on recurrences, metastasis or tumour-related deaths, and local excision is curative.

**Thymoma in thymolipoma**
There is a single case report about thymoma within a thymolipoma occurring in a 67 years old female patient without myasthenia gravis (69). The thymoma was classified as “cortical” (type B2). There was no recurrence within 10 years after radical surgery. We observed an almost identical case.

**Lipoma**
ICD-O code 8850/0
Lipoma is the most common benign mesenchymal tumour of the mediastinum (1529,1932). In contrast to thymolipoma it does not contain foci of thymic parenchyma. Other rare benign lipomatous tumours are lipoblastoma/lipoblastomatosis (517), hibernoma (31), and angiolipoma (1031).

**Liposarcoma**
ICD-O code 8850/3
Liposarcoma is the most common sarcoma in the anterior mediastinum, and some cases may represent thymic stromal sarcomas (801,938), i.e. malignant counterparts of thymolipoma (thymoliposarcoma) (1030). Mediastinal liposarcoma usually occurs in adults (mean age 43 years), and is rare in children (357). In some cases, there is synchronous}

![Fig. 3.112 Thymoliposarcoma. A Macroscopy of a recurrent tumour (2 years after first treatment): well circumscribed and partially encapsulated tumour from the anterior mediastinum. B Bland looking well differentiated (lipoma-like) liposarcoma adjacent to thymic remnant tissue with some lipoblasts (arrows). C Multinucleated neoplastic lipoblasts and a heavy inflammatory reaction in the more fibrotic stroma of the recurrent tumour. D Higher magnification demonstrating multinucleated tumour cells and the inflammatory reaction.](image-url)
involvement of other sites such as the retroperitoneum. Well-differentiated liposarcoma is the most frequent subtype (60% of cases), including lipoma-like, inflammatory (1030) spindle cell (1138,1835), leiomyomatous and dedifferentiated variants (601), followed by myxoid liposarcoma (28%), and other subtypes (12%) (1030), such as the highly aggressive pleomorphic liposarcoma (513). In some cases, the presence of heavy lymphoid infiltration may result in mimicry of lymphoma or an inflammatory process (1030).

Like the same tumour occurring in other sites, mediastinal myxoid liposarcoma shows TLS/FUS-CHOP fusion transcripts (1762).

The tumours are curable by surgical excision in some patients (47,256, 357,740), but recurrences develop in up to 32% of cases after a mean interval of 36 months. Myxoid liposarcoma has a worse prognosis than well-differentiated liposarcoma (1030).

Solitary fibrous tumour

Definition

Solitary fibrous tumour (SFT) is an uncommon, locally aggressive mesenchymal neoplasm with highly variegating morphologic appearance, characterized by two basic elements encountered in varying proportions: a solid spindle cell component and a diffuse sclerosing component.

ICD-O code 8815/0

Epidemiology

Mediastinal SFT is a rare tumour of adults (28-78 years of age) (999). Mediastinal SFT on average account for 15% of all SFT, and about 25% of extrapleural SFT (772,791,999,1384).

Localization

Some mediastinal SFT may represent extensions from pleural SFT, but others arise from the mediastinal (including thymic) stroma (1685).

Macroscopy

Mediastinal SFT can reach a large size, of up to 16 cm (2164).

Table 3.13

Comparison of immunophenotype of solitary fibrous tumour (SFT) with other spindle cell tumours of the thymus and mediastinum.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CD34</th>
<th>Bcl-2</th>
<th>CD99</th>
<th>CK</th>
<th>S100</th>
<th>Desmin</th>
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<tbody>
<tr>
<td>SFT</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-/-</td>
</tr>
<tr>
<td>Type A Thymoma</td>
<td>-</td>
<td>-</td>
<td>-/2</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spindle Cell Liposarcoma</td>
<td>+++</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
<td>-</td>
<td>+++</td>
<td>+/-</td>
<td>+/++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fibromatosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>+++ &gt;</td>
<td>-</td>
<td>.5</td>
<td>++++8</td>
<td>-</td>
</tr>
</tbody>
</table>

Histopathology

Solitary fibrous tumour (SFT) of the mediastinum is identical to SFT of the pleura in terms of morphology and immunophenotype [CD34+(>90%), CD99+ (>90%), bcl2+ (80-90%), cytokeratin+] (772,791,999,1384,2063).

In contrast to the usually bland-looking pleural or thyroid SFT (1674,2164), high mitotic activity (> 1-4/10HPF), cytologic atypia and coagulative necrosis occur in more than 50% of mediastinal SFT, suggesting a high propensity for sarcomatous transformation (637,772,2164). In such cases there is sometimes an identifiable component of bland-looking SFT.

Differential diagnosis

The typical collagenous stroma around individual tumour cells and the charac-
teristic immunophenotype distinguish SFT from type A thymoma, synovial sarcoma, low-grade spindle cell liposarcoma, leiomyomatous tumours and neural tumours [1908].

**Somatic genetics**
Genetic findings in mediastinal SFT have not been reported.

**Prognosis and predictive factors**
Primary mediastinal SFT are more aggressive than pleural or thyroid SFT [1674]. Local recurrences and tumour-related deaths occur in about 50% and 25% of cases, respectively [2164]. SFT may recur late (13 years after surgery) and can rarely develop intrathoracic metastases [2164]. High mitotic activity (>1/10 HPF) and necrosis herald an aggressive course.

**Rhabdomyosarcoma (RMS)**

ICD-O code 8900/3

RMS most commonly arise in thymic germ cell tumour [1932], or may occur as a component of sarcomatoid thymic carcinoma [1509], but can also rarely arise de novo. Embryonal, pleomorphic and alveolar RMS of the thymus, one with unusual clear cell features, have been reported [135, 1922, 1932]. The tumours can occur in adults and children, and follow a very aggressive clinical course [135, 1922]. The t(2;13)(q35; q14) translocation resulting in a PAX3/FKHR fusion gene has been observed in an example of mediastinal alveolar RMS of the solid variant [1742]. “Rhabdomyomatous thymomas” [1351, 1730] with myoid cells, should not be mistaken for RMS.

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**Fig. 3.114 Embryonal rhabdomyosarcoma.** A Embryonal rhabdomyosarcoma of the mediastinum. B Desmin expression with occasional cells showing cross-striations.

**Fig. 3.115 Synovial sarcoma (SS).** A Monophasic spindle cell SS focally with gaping vessels resembling haemangiopericytoma. B Spindle cell component calcifying SS (30% of all SS cases). Unusual biphasic type: solid epithelial cords and few spindle cells. C Round cell component. High power of the solid epithelial component (if single component: = "monophasic epithelial SS").
Fig. 3.117  A Capillary haemangioma of the anterior mediastinum. The tumour forms distinct lobules separated by a loose stroma.  
B Epithelioid haemangiendothelioma. Cords of tumour cells with abundant eosinophilic cytoplasm. Occasional tumour cells show vacuolation. Some primitive vascular channels contain blood. This case also shows interspersed osteoclastic giant cells.

Fig. 3.118  Angiosarcoma.  
A The tumour forms anastomosing channels, and the lining cells show significant nuclear pleomorphism and atypia.  
B Angiosarcoma can show a solid growth, obscuring the vascular nature of this malignant tumour.  
C Typical immunostaining of tumour cell membranes for CD31.  
D Immunostaining of remnant thymic epithelial cell network for cytokeratin 19.
**Synovial sarcoma (SS)**

**ICD-O code** 9040/3

Several cases of SS have been reported (871,2033,2163). The tumours usually occur in adults but rarely in children (871) and manifest by pain, dyspnoea or superior vena cava syndrome. Most cases followed an aggressive clinical course, with 3 of 5 patients dying of tumour on follow-up of 10 months to 4 years. Detection of SYT-SSX chimeric RNA transcripts, resulting from the t(X;18) translocation is often essential to distinguish SS from mesothelioma, sarcomatoid (thymic and other) carcinomas, malignant peripheral nerve sheath tumour with glandular differentiation, germ cell tumour-associated sarcomas or metastases (71,2033).

**Vascular tumours**

Mediastinal lymphangioma is a common mediastinal tumour in children (1932). Hemangiomas of the cavernous, and less frequently, capillary subtype have been reported and may be complicated by the Kasabach-Merritt syndrome (838,1353,1932). Hemangioendothelioma, epithelioid hemangioendothelioma and angiosarcoma (the latter usually arising from a thymic germ cell tumour (1230,1356)) have also been described (962,1921,1932).

**Leiomyomatous tumours**

Leiomyomas, probably derived from the aortic arch (1789), and even rarer, leiomyosarcomas (96,1370) have been reported in the mediastinum, including its anterior compartment. They should be distinguished from liposarcomas with leiomyomatous differentiation (601), and angiomatoid fibrous histiocytomas (AFH) of the mediastinum. AFH can exhibit spindle cell features, and half of the cases show desmin expression. However, it is often accompanied by an infiltrate of lymphocytes and plasma cells, particularly in the peripheral portion. Frequent coexpression of CD99, CD68 and EMA, and a characteristic t(12;16)(q13; p11) translocation generating FUS/ATF1 fusion transcripts distinguish AFH from leiomyoma and leiomyosarcoma (590).

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**Fig. 3.119** Paraganglioma. A Macroscopy of a well encapsulated paraganglioma of the anterior mediastinum with central scar formation. B The tumour comprises packets of cells with abundant eosinophilic cytoplasm, traversed by a delicate vasculature. C Low power histology showing the “Zellballen-Pattern” of a mediastinal paraganglioma. D High power of the same case shows marked variability of cell and nuclear size. E Typical strong cytoplasmic granular immunostaining for synaptophysin. F Immunostaining for S100 protein reveals the delicate sustentacular cells that wrap around the tumour cell packets.

**Fig. 3.120** Angiomatoid fibrous histiocytoma of the central mediastinum involving the ascending aorta and thymus. A The tumour typically comprises spindle cells that may raise the differential diagnosis of leiomyoma. In contrast to leiomyoma, AFH is typically accompanied in the tumour periphery by a dense inflammatory infiltrate composed of lymphocytes and plasma cells. B Desmin positivity in the neoplastic cells. Inflammatory cells are negative.
Neurogenic tumours

Neurogenic tumours of the mediastinum occur almost exclusively in the middle and posterior compartments, where they constitute the most frequent neoplasms. However, benign schwannomas [1597], and malignant peripheral nerve sheath tumours, including malignant Triton tumours [1525] have also been described in the anterior mediastinum, mainly in patients with neurofibromatosis [1726,1851]. About 20% of mediastinal paragangliomas occur in the anterior compartment [1365] and they may be pigmented [1350]. They tend to occur in older individuals (mean age 46 years). The patients are asymptomatic, or present with compression symptoms, or rarely with Cushing syndrome [1548]. Posterior mediastinal paragangliomas tend to occur in younger patients (mean age 29 years), and about half of the cases have hypertension or other symptoms due to release of catecholamines by the tumours [1350]. They recur locally and metastasize in 55% and 26% of cases, respectively [1123]. Paragangliomas typically show a nesting pattern associated with a prominent vasculature. The tumour cells are immunoreactive for synaptophysin, and S100 protein positive sustentacular cells are often demonstrable around tumour cell nests. In contrast to neuroendocrine carcinomas, paragangliomas do not form ribbons or rosette-like structures, and cytokeratin is usually negative.

Tumours related to the sympathetic ganglia include neuroblastoma, ganglioneuroblastoma and ganglioneuroma. They occur almost exclusively in the posterior mediastinum, although neuroblastomas [70] and ganglioneuroblastomas have also been rarely described in the thymus [76,1964,2141]. In fact, neuroblastoma is the most common malignant tumour of the posterior mediastinum in young children. Ganglioneuroblastoma and ganglioneuroma occur mostly in adults. Primary ependymoma of the posterior mediastinum in adults, is typically associated with a prolonged indolent course [503,2153].

Other rare neoplasms

Other thymic/mediastinal soft tissue tumours include Ewing sarcoma which usually extends into the mediastinum from the thoracic wall [690], malignant rhabdoid tumour [166,1160,1691], inflammatory myofibroblastic tumour (inflammatory pseudotumour) [422,467], calcifying fibrous tumour [1443], giant cell angiofibroma [636], elastofibrolipoma [455], desmoid fibromatosis [1036], benign mesenchymoma [2054], rhabdomyoma [1315], alveolar soft part sarcoma [593] and malignant fibrous histiocytoma [344,1932]. Primary malignant melanoma [42,642,1804,2088] probably arises from thymic nevus cell aggregates [642,1552]. Other rare tumours include meningioma [553,2150], osteosarcoma [454,739,888], chondrosarcoma [1592], giant cell tumour [622], chordoma [32,1675,1910], myelolipoma [1008,1706,1884], and extramedullary haematopoietic tumours [449,834,1366,1400,1481,1788].

Fig. 3.121 A Ganglioneuroma of the posterior mediastinum. Clusters of ganglion cells merge into a spindle cell component that resembles neurofibroma or schwannoma. Calcification is common. By definition, there should not be identifiable neuroblasts. B Differentiating neuroblastoma of the posterior mediastinum with abundant neuropil. The latter should not be confused with the schwannian stroma required for a diagnosis of ganglioneuroblastoma.

Fig. 3.122 Fibromatosis (desmoid tumour) of the thoracic wall and pleura.

Fig. 3.123 A Ewing sarcoma of the mediastinum with B CD99 (MIC-2) expression.
Ectopic thyroid and parathyroid tumours

Ectopic thyroid tumour

Definition
Ectopic thyroid tumour is a thyroid neoplasm that occurs in sites other than the cervical thyroid gland proper.

Thyroid tumours occurring in the mediastinum are often of cervical thyroid gland origin with extension into the mediastinum. Ectopic thyroid tumours arising in the mediastinum without connection to the cervical thyroid gland are very rare. They are either discovered incidentally, or present with symptoms referable to a mediastinal mass. The nomenclature and diagnostic criteria of these thyroid tumours should follow those of the World Health Organization classification of tumours of endocrine organs [9]. Follicular adenoma and papillary carcinoma are the commonest, but other tumour types have also been described, such as follicular carcinoma, oncocytic (Hürthle cell) carcinoma and poorly differentiated insular carcinoma [507,966,1191,1328,1527,1889,2133]. If there are uncertainties as to whether the tumour is of thyroid origin, positive immunostaining for thyroglobulin would provide a strong support for the diagnosis.

Histogenesis
Thyroid tissue that has aberrantly migrated to the mediastinum during embryologic development is the cell of origin for the ectopic thyroid tumours in the mediastinum.

Ectopic parathyroid tumour

Definition
Ectopic parathyroid tumour is a parathyroid cell neoplasm occurring in sites other than the usual locations of the parathyroid glands in the neck [1889].

Epidemiology, clinical features
Approximately 10-20% of all parathyroid adenomas (including lipoadenomas) occur in the mediastinum, most commonly the anterosuperior mediastinum in the vicinity or within the thymus gland [376,399,1444,2103,2141]. The patients present with symptoms due to hyperparathyroidism. Ectopic parathyroid carcinomas of the mediastinum are very rare, and they may or may not be functional [990,1412,1627].

Histopathology
The nomenclature and diagnostic criteria for ectopic parathyroid tumours should follow those of the World Health Organization Classification of endocrine tumours (see “World Health Organization Classification of Tumours: Pathology and Genetics of Turnours of Endocrine Organs”). Parathyroid adenomas are circumscribed or thinly encapsulated tumours comprising sheets, cords and acini of polygonal cells traversed by a delicate vasculature. There is often a mixture of tumour cells with clear, lightly eosinophilic and oxyphilic cytoplasm. Some tumours have abundant interdispersed adipose cells (lipoadenomas) [1444,2167]. Mitotic figures are absent or rare, and focal nucleomegaly is acceptable. Parathyroid carcinomas often show capsular or vascular invasion, sclerotic bands, and mitotic figures. If there are uncertainties whether a neoplasm is of parathyroid origin, positive immunostaining for parathyroid hormone would provide a strong support for the diagnosis.

Histogenesis
Ectopic or supernumerary parathyroid gland in the anterosuperior mediastinum is the cell of origin for the ectopic parathyroid tumours. Such a localization for the parathyroid gland is not surprising since the inferior parathyroid glands share a common origin with the thymus from the third branchial pouch [2141].
Metastases to thymus and anterior mediastinum

Definition
Malignant tumours that metastasize to the thymus or anterior mediastinum from distant primary tumours. Neoplasms that extend directly from adjacent organs or tissues are also included in this category.

The most common primary tumours involving these sites are lung, thyroid, breast and prostatic carcinomas [948, 1188, 1287, 1288, 1305], while melanoma and various sarcomas (liposarcoma, osteosarcoma, rhabdomyosarcoma, Kaposi sarcoma and malignant fibrous histiocytoma) are rare primary tumours [33, 702, 843, 1852, 1865].

The distinction between squamous and neuroendocrine carcinomas of the thymus and mediastinal metastases with this differentiation can be difficult. In about 50% of carcinomas, morphological and immunohistochemical features can clarify the thymic derivation, while clinical staging procedures are required to clarify the derivation of the other cases. The different genetic characteristics of carcinomas of the thymus [896, 2238, 2242] compared to those of lung and the head and neck region [188, 1582, 1585, 1866] are of diagnostic value. Clinical data is also necessary to distinguish primary thymic melanomas [42, 642, 1804, 2088] or sarcomas [256, 1742, 1932] from metastasis with a respective differentiation.

Table 3.14
Morphological and immunohistochemical criteria for the differential diagnosis of features of primary thymic carcinomas from metastases to the anterior mediastinum arising from carcinomas of the lung and head and neck region.

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Primary of the thymus</th>
<th>Primary of lung or head and neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell, basaloid, lymphoepithelioma-like carcinoma</td>
<td>Lobular growth pattern 70%</td>
<td>Lobular growth pattern rare</td>
</tr>
<tr>
<td></td>
<td>Perivascular spaces 50%</td>
<td>Perivascular spaces very rare</td>
</tr>
<tr>
<td></td>
<td>CD5 expression 50%</td>
<td>CD5 not expressed</td>
</tr>
<tr>
<td></td>
<td>CD70 expression 50%</td>
<td>CD70 not expressed</td>
</tr>
<tr>
<td></td>
<td>CD117 expression 40-100%1</td>
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<tr>
<td>Neuroendocrine carcinoma2</td>
<td>TTF-1 expression absent2</td>
<td>TTF-1 expression frequent</td>
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