Tumors of the Thymus

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6.1 Introduction

The thymus is a primary lymphoid organ of the immune system granting generation and maturation of T lymphocytes throughout life [1]. Neoplasms of the thymus show a wide range of histology and biological behaviour, potentially involving both adjacent and distant structures. Imaging is paramount for diagnosis, staging and management of thymic malignancies [1].

6.1.1 Embryology

The thymus arises from the third and fourth branchial pouches, during the sixth gestational week. After the eighth gestational week, it migrates downwards to the anterosuperior mediastinum. The thymus is a purely epithelial organ until the ninth gestational week. Glandular lobulations develop since the tenth week when small lymphoid cells migrate from the foetal liver and bone marrow into the thymus.

6.1.2 Histology

The thymus displays a cortical and a medullar component. On the one hand, the cortex is mainly composed of lymphocytes (named thymocytes), with fewer epithelial and mesenchymal cells. On the other hand, the medulla features fewer thymocytes and a larger amount of epithelial cells. The interaction between the cortical and medullar component grants synergistic maturation of thymocytes under the paracrine action of epithelial cells, the latter also differentiating into macrophages and myoid cells. Moreover, epithelial cells also evolve into a peculiar structure of thymus: the "Hassall's corpuscles" defined by round and keratinized formations of mature epithelial cells [1].

6.1.3 Gross Anatomy and Normal Imaging Findings

The thymus lies in the retrosternal region occupying the anterosuperior mediastinum (from sternal manubrium to the level of the fourth costal cartilage). Since 2017, a three-compartment (prevascular, visceral and paravertebral) computed tomography (CT)-based classification of mediastinum is provided by the International Thymic Malignancy Interest Group (ITMIG) (Fig. 6.1). According to the ITMIG scheme, the thymus is located within the adipose tissue of prevascular compartment, along with lymph nodes and the left brachiocephalic vein. Macroscopic shape is determined by adjacent structures as thymus moulds against the trachea, left brachiocephalic vein, aortic arch and its branches, and pericardium [2]. Bilobate morphology is seen at complete maturation, each lobe is enclosed in its own thin fibrous capsule [2]. The right lobe shows quite simple and homogeneous shape and is located near the superior vena cava. Conversely, the left lobe features two components, namely, the main part (anterior to the ascending aorta) and the accessory limb (lateral to the pulmonary artery trunk, with variable size among individuals). Rarely, another small projection of the left lobe extends upwards behind the left brachiocephalic vein in front of the trachea; it is seen as a small tapering cranial extensions reaching the thyroid cartilage [3]. Such anatomic distribution reflects the most common spots of primary thymic

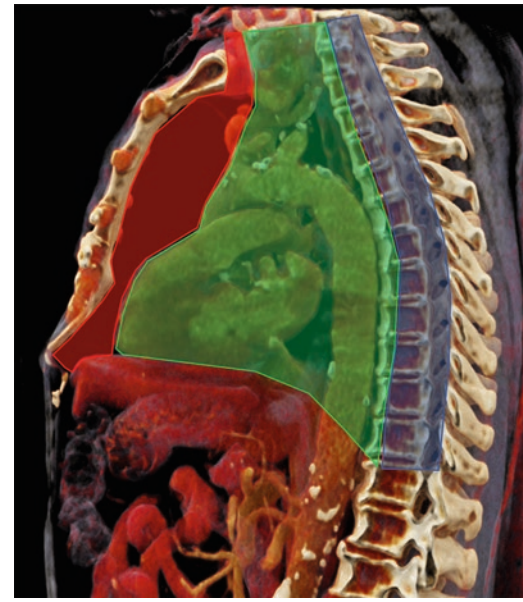

Fig. 6.1 ITMIG definition of mediastinal compartments. Cinematic CT image showing prevascular (red), visceral (green) and paravertebral (blue) compartments. (Carter et al. [14])

Table 6.1 Predictive features for anterior mediastinal mass diagnosis [4–6, 90–93]

	Thymic epithelial neoplasms	Lymphoma	Germ cell tumors	Benign lesions
Age	Thymoma: >35 years	<35 years	<35 years	Thymic hyperplasia: 20–30 years
	Thymic carcinoma: the portion tends to gradually increase as age increases			Thymic bed cyst: >50 years
Size	Thymoma: 5–10 cm	Bulky > 5 cm	Larger	Thymic cyst: 0.5–16 cm
	Thymic carcinoma: 5.00 ± 2.29 cm		(The largest ever mixed germ cell tumor of the mediastinum reported was 21 × 20 × 16 cm)	
Shape	Thymoma: round, oval, lobulated	Lobulated/amorphous	Lobulated/amorphous	Thymic hyperplasia: bipyramidal
				Thymic cyst: round, oval, saccular
Smooth contour CT	Only thymoma		Only mature teratoma	+
Lobulated contour CT	++	++		
Internal mammary lymphadenopathy	Rarely observed	+++	Not seen	Not seen
Mediastinal and supraclavicular lymphadenopathy	Rarely observed	+++	+	
Mediastinal encasement – lung invasion	Rarely observed	++	Rarely observed	
Marbled fat[a]	Occasionally seen	Occasionally seen		+
Globular fat			+	
Calcification	+	+	++	
Low CT attenuation (<40)				++
Midline location				+
Pleural effusion	+	++	+	Not seen

[a]Several malignant lesions could contain interspersed intralesional fat that could simulate the marbled fat appearance; for this reason, radiologists should exercise caution and evaluate the characteristics of the lesion as a whole before concluding that it is benign
+++ very frequent; ++ frequent; + possible

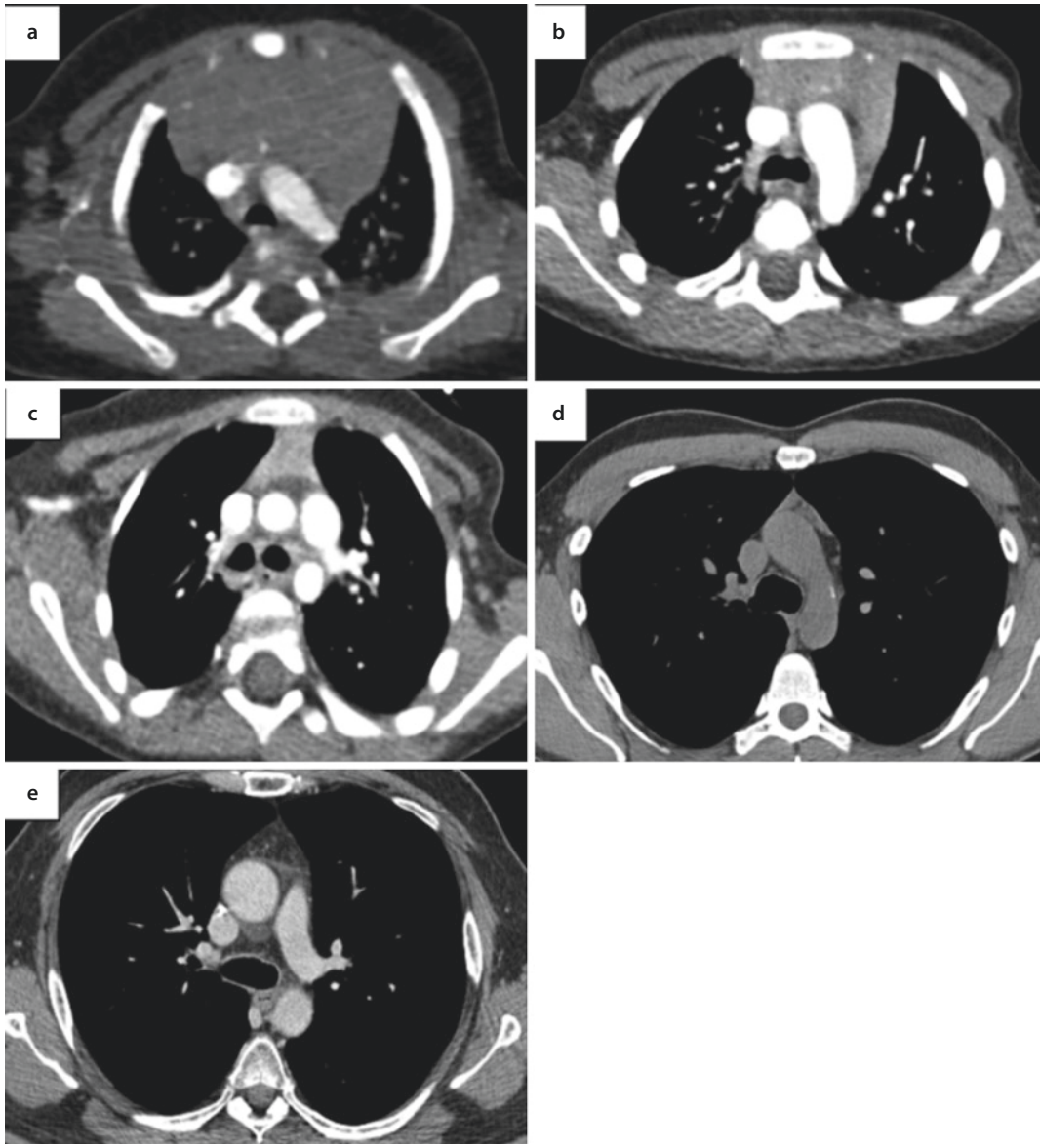

Fig. 6.2 Physiological modifications of thymic morphology throughout age. Chest CT in axial plane at the age of 2 months **a**, 3 years **b**, 4 years **c**, 39 years **d** and 48 years **e**. **a** The thymus appears as a bilobed homogeneous soft-tissue density structure, without compression of vascular structures or airway. **b**, **c** The thymus shows a quadrangular shape in early childhood. **d**, **e** In adult age, the thymus displays a triangular shape, with progressive reduction of its volume and density (almost complete adipose tissue replacement in older individuals)

malignancy, exploited for systematic differential approach to imaging of mediastinal masses. Various neoplasms may arise from this anatomic region; still, the differential can be narrowed based on both clinical and radiological features [4–6] (Table 6.1). Thymic composition varies with age and so does its appearance at imaging: at younger age, thymus density by computed tomography (CT) is similar to muscle, whilst in elderly it shows almost adipose density (Fig. 6.2). Homogeneous thymic density is the most common appearance on CT; nonetheless, lobular architecture with partial fatty replacement is occasionally seen [2].

Table 6.2 Diagnostic criteria of thymomas in the 2015 World Health Organization (WHO) classification

Thymoma subtype	Obligatory criteria	Optional criteria
Type A	Occurrence of bland, spindle-shaped epithelial cells (at least focally); paucity or absence of immature (TdT+) T cells throughout the tumor	Polygonal epithelial cells CD20+ epithelial cells
Atypical type A variant	Criteria of type A thymoma; in addition: comedo-type tumor necrosis; increased mitotic count (>4/2 mm^2); nuclear crowding	Polygonal epithelial cells CD20+ epithelial cells
Type AB	Occurrence of bland, spindle-shaped epithelial cells (at least focally); abundance of immature (TdT+) T cells focally or throughout tumor	Polygonal epithelial cells CD20+ epithelial cells
Type B1	Thymus-like architecture and cytology: abundance of immature T cells, areas of medullary differentiation (medullary islands); paucity of polygonal or dendritic epithelial cells without clustering (i.e. <3 contiguous epithelial cells)	Hassall's corpuscles; perivascular spaces
Type B2	Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells	Medullary islands; Hassall's corpuscles; perivascular spaces
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of intermingled TdT+ T cells	Hassall's corpuscles; perivascular spaces
Micronodular thymoma with lymphoid stroma	Nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma	Lymphoid follicles; monoclonal B cells and/or plasma cells (rare)
Metaplastic thymoma	Biphasic tumor composed of solid areas of epithelial cells in a background of bland-looking spindle cells; absence of immature T cells	Pleomorphism of epithelial cells; actin-, keratin- or EMA-positive spindle cells

6.2 Thymic Epithelial Tumors

Thymic epithelial malignancies are rare entities (incidence 1.3 to 3.2/1.000.000 individuals in Europe) [7]. Various classifications of thymic malignancies have been proposed by variable perspectives.

Histological findings are accounted in the World Health Organization (WHO) classification system (last updated in 2015), which features both obligatory and optional diagnostic criteria (Table 6.2). Notably, WHO stratifies thymoma into five subtypes, as follows: A, AB, B1, B2 and B3 [8]. The latter two subtypes are described as "high-risk thymomas", as opposed to the remainder "low-risk thymomas". Besides the five subtypes of thymoma, a further category C is applied to thymic carcinoma [8].

Description of surgical findings is articulated within the Masaoka-Koga staging system (Table 6.3), where the stratification of risk is obtained by signs of local invasion and presence of metastases [9]. A similar (yet different) approach is provided by the International Association for the Study of Lung Cancer (IASLC) and ITMIG. This system is endorsed by the eighth edition of the TNM classification of malignant tumors (Table 6.4a). Noteworthy, the similarities between the IASLC-ITMIG approach and the Masaoka-Koga system allow a detailed translation between each other (Table 6.4b).

6.2.1 Epidemiology

Thymic malignancies may affect all ages; nonetheless, mean age at diagnosis is around 50–60 years. Slight female predominance is seen in categories A, AB and B1; otherwise, thymoma

Table 6.3 Masaoka-Koga staging system for thymoma

Stage	Descriptor
I	Complete encapsulation of tumor
IIa	Microscopic tumor invasion through capsule
IIb	Macroscopic tumor invasion into surrounding fat
III	Invasion of the pericardium, great vessels or lung
IVa	Pleural or pericardial dissemination
IVb	Lymphatic/hematogenous metastasis

shows an overall balanced by-gender representation [10].

There is no confirmed evidence about environmental or infectious risk factors through the pathogenesis of thymic epithelial tumors. Rarely, thymoma was reported in subjects with solid-organ transplantation, HIV infection or after mediastinal radiation therapy [9]. Thymoma is found in association with cancer susceptibility syndromes (e.g. multiple endocrine neoplasia type I (MEN1)) as well as extra-thymic hematopoietic and solid cancers [11].

Five-year survival of thymic malignancies was 64% overall, with large variations across WHO subtypes ranging from 69% in malignant thymoma to 13% in undifferentiated thymic cancer [10].

6.2.2 Local Growth

Overall, it is estimated that 30% of patients diagnosed with thymic epithelial tumor present with locally advanced disease at time of diagnosis [12, 13]. The thin thymic own capsule is the only fence between thymic neoplasm and its progression to mediastinal fat where no anatomic boundary protects mediastinal compartments from local invasion. Several schemes were proposed to facilitate surgical planning of mediastinal masses [14].

Thymomas growing within prevascular compartment may be asymptomatic and incidentally discovered in about one-third of cases [15]. However, the majority of thymic tumors progressively enlarge until compression on adjacent structures and subsequent clinical manifestations.

Table 6.4a TNM staging

Stage		Descriptor
T1	T1a	Encapsulated or unencapsulated, with or without extension into the mediastinal fat
	T1b	Extension into the mediastinal pleura
T2		Direct invasion of the pericardium
T3		Direct invasion of the lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerveand/or hilar (extra pericardial) pulmonary vessels
T4		Direct invasion of the aorta, arch vessels, main pulmonary artery, myocardium, trachea or oesophagus
Node		
N0		No nodal involvement
N1		Anterior (peri-thymic) nodes (IASLC levels 1, 3a, 6 and/or supradiaphragmatic/inferior phrenic/pericardial)
N2		Deep intrathoracic or cervical nodes (IASLC levels 2, 4, 5, 7, 10 and/or internal mammary nodes)
Metastasis		
M0		No metastatic pleural, pericardial or distant sites
M1	M1a	Separate pleural or pericardial nodule(s)
	M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

In case of predominantly posterior growth, the trachea and oesophagus can be compressed causing pain, cough, dyspnoea and dysphagia. Other clinical manifestations may be related to superior vena cava syndrome (arm or facial swelling) (Fig. 6.3) and to superior laryngeal (hoarseness) or phrenic (diaphragmatic palsy) nerve damage (Table 6.5) [16].

Tumor size is not included as a predictor of survival for thymic epithelial tumors [17], unlike many solid malignancies (e.g. breast, lung, renal

Table 6.4b TNM staging and corresponding Masaoka-Koga stage

Stage grouping	T	N	M	Corresponding Masaoka-Koga stage	Descriptors
I	T1	N0	M0	I	Grossly and microscopically completely encapsulated tumor
				IIA	Microscopic transcapsular invasion
				IIB	Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to, but not breaking through, the mediastinal pleura or pericardium
II	T2	N0	M0	III	Macroscopic invasion into neighbouring organ (i.e. pericardium, great vessel or lung)
IIIA	T3	N0	M0		
IIIB	T4	N0	M0		
IVA	T any	N1	M0	IVA	Pleural or pericardial metastasis
	T any	N0, N1	M1a	IVB	Lymphatic or hematogenous metastasis
IVB	T any	N2	M0, M1a		
	T any	N any	M1b		

and pancreatic cancers). Nonetheless, a size greater than 40 mm represented an independent negative prognostic factor for recurrence-free survival in IASLC-ITMIG stage I disease ($T_1N_0M_0$) [18].

Malignant mediastinal tumors may directly extend in all directions, notably through the pleura and pericardium, or other mediastinal structures. A well-defined fat interface usually indicates absence of extensive local invasion; still, minimal invasion may be undetectable at imaging. On the other hand, infiltration of fat planes, irregular interfaces and encasement of mediastinal structures are highly suggestive of invasion.

Thickening, nodularity and effusion of either the pleura or pericardium are signs of infiltration and spread through the serous cavity [19].

Thymic lesions displaying lobulated or irregular contours, cystic or necrotic regions and multifocal calcifications are consistent with an underlying invasive thymoma, which can also associate with signs of fat infiltration, progression to lung parenchyma and great vessel invasion or encasement [20–23]. Endobronchial spread of thymic tumors has been occasionally reported as mass trespassing bronchial walls and further growth within the bronchial lumen [24].

6.2.3 Metastatic Dissemination

Independently from their histological grade, all thymic epithelial tumors may involve distant structures by *transcoelomic* (towards pleura and pericardium), *lymphatic* (towards thoracic and extra-thoracic lymph node) and *hematogenous* spread (towards any organ).

- The *transcoelomic* pathway is the most common modality of dissemination in thymic malignancies. It occurs when a locally aggressive neoplasm grows across the thymic capsule, invading the lungs, heart or great mediastinal vessels.

Subsequently, seeding phenomenon can take place in the pleural or pericardial cavity (Fig. 6.4) [25].

- The *lymphatic* pathway of dissemination is the second most common modality. It occurs when neoplastic cells are transported through lymphatics to regional lymph nodes. Of note, the thymus features only efferent lymphatics, which drain towards anterior mediastinal or parasternal lymph nodes [26].

Lymphatic involvement is seldom in early stage and low-grade thymic tumors as compared with

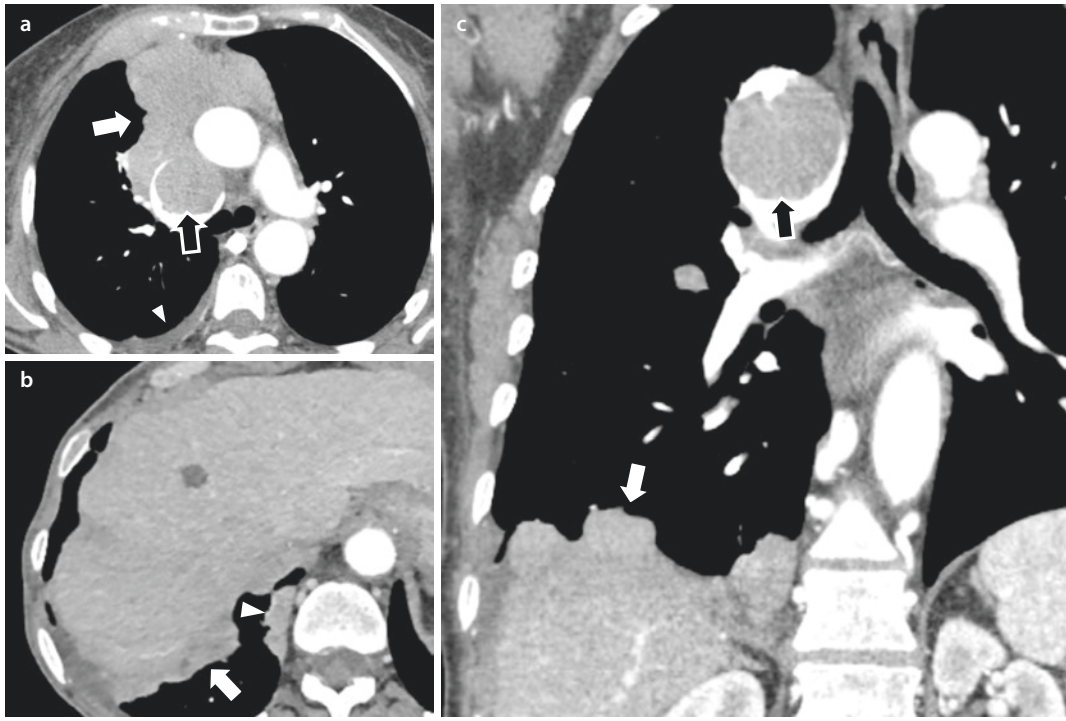

Fig. 6.3 **a** Axial CT image after intravenous administration of iodinated contrast media showing a large, lobulated and homogeneously enhancing mass (white arrow) located in the prevascular compartment. The superior vena cava is enlarged, and a soft-tissue lesion grows into its lumen (black arrow). A small right pleural effusion can be detected (white arrowhead). **b** Same patient of **a**, at a caudal level. Pleural nodules with homogeneous contrast enhancement involve paravertebral space (white arrowhead) and diaphragmatic surface (white arrow), without an adipose fat plane with the hepatic parenchyma. The coronal reformatted image **c** shows both pleural nodules (white arrow) and the vascular invasion of the superior vena cava (black arrow). The patient was diagnosed with high-grade thymoma

Table 6.5 Local growth-related symptoms

Mediastinal structure	Related symptoms
Superior vena cava	Superior vena cava syndrome
Laryngeal recurrent nerve	Cough, dysphonia
Phrenic nerve	Diaphragm paralysis
Trachea	Dyspnoea, cough, haemoptysis
Oesophagus	Cough, dysphagia
Sympathetic cervical system	Claude-Bernard-Horner syndrome (ptosis, miosis, enophthalmos)

locally invasive and high-grade lesions such as thymic carcinoma where lymphatic involvement is reported in about 27% of cases [27, 61].

- *Hematogenous* spread occurs more frequently in high-grade thymoma, thymic carcinoma and thymic carcinoid [8]. Cancer cells access systemic circulation by trespassing into venous capillaries or indirectly via lymphatics [28]. The lung is the most common site of hematogenous metastatization, where metastases are displayed by solid and well-defined round nodules/masses randomly distributed [29]. Extra-thoracic organs are far less commonly involved, including the abdominopelvic organs (liver, pancreas, adrenal, spleen, kidney, small bowel and ovary), distant bone and brain. On *CT*, liver metastases are described as heterogeneous formations with central hypodense areas and peripheral enhancement (Fig. 6.5). On *magnetic resonance imaging (MRI),* they appear as expansive well-defined heterogeneous formations showing T1 hypointensity, T2 hyperintensity and restricted diffusion on

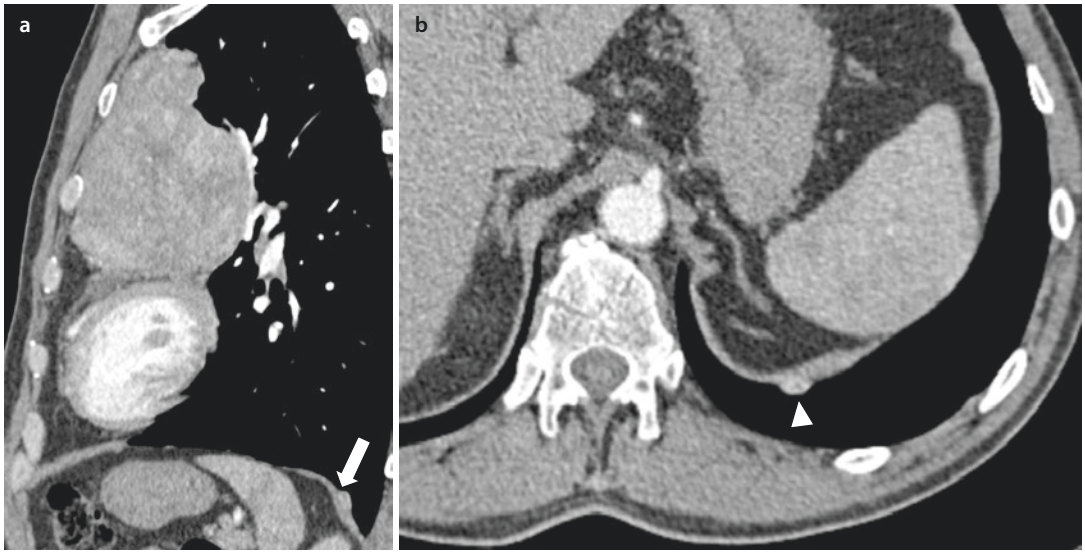

Fig. 6.4 **a** Magnification of a CT image (sagittal view) of a male patient suffering from chronic cough undergoing CT evaluation after chest radiograph detection of a mediastinal mass displaying a large and heterogeneously enhancing anterior mediastinal mass. A nodule showing contrast enhancement can be detected located at the diaphragmatic surface of the left lung (white arrow). **b** Same patient of image **a** magnification of the enhancing pleural nodule (white arrowhead) showing intense contrast enhancement. The finding represents a drop metastasis in a patient with thymic carcinoma

diffusion-weighted image sequences [30]. Bone localizations can be lithic, sclerosing and mixed [31]. Spine metastases are rare, causing various neurological symptoms based on location (hoarseness, dysphagia, paraesthesia, sensory change, weakness, numbness, paraparesis/paralysis). Spine metastases might cause spinal instability in case of vertebral collapse [32]. Bone marrow metastases from thymic carcinoma are usually detected in late-stage diseases [33]. Brain metastases are very rare, being either solid or cystic, mostly located within the brain parenchyma (intra-axial location), although extradural extension invading the skull and mimicking meningiomas (extra-axial location) has been reported. Complications may include haemorrhage or extracranial extension. Notably, patients with brain metastases from thymic neoplasm show better prognosis compared to patients with brain metastases from other solid tumors [34].

6.2.4 Follow-Up

Median time to metastasis or recurrence happens to be longer than 5 years even after surgical removal of high-risk thymomas, thus setting the role for long-term follow-up [8]. Intensity of surveillance procedures has been debated, as various approaches are possible, ranging from CT every 6 months for the first three years, followed by annual CT for 5 years and further 5 years of follow-up by alternating CXR and CT, to life-long annual CT (Table 6.6) [35].

6.3 Thymoma

6.3.1 Epidemiology

Thymoma is a rare malignancy (overall incidence: 0.13/100.000 person-years), involving more frequently middle-aged patients (peak in the seventh decade of life) with unknown aetiology. Thymoma patients may be at risk for development of other malignancies, such as soft-tissue sarcomas or B-cell non-Hodgkin lymphoma (NHL). The relationship between the latter and thymoma may be due to immune disturbance arising from thymoma itself or follow-up therapeutic treatment [36].

Most cases of thymoma develop from anterosuperior mediastinum, whilst only a small number involves either posterior mediastinum, cervical

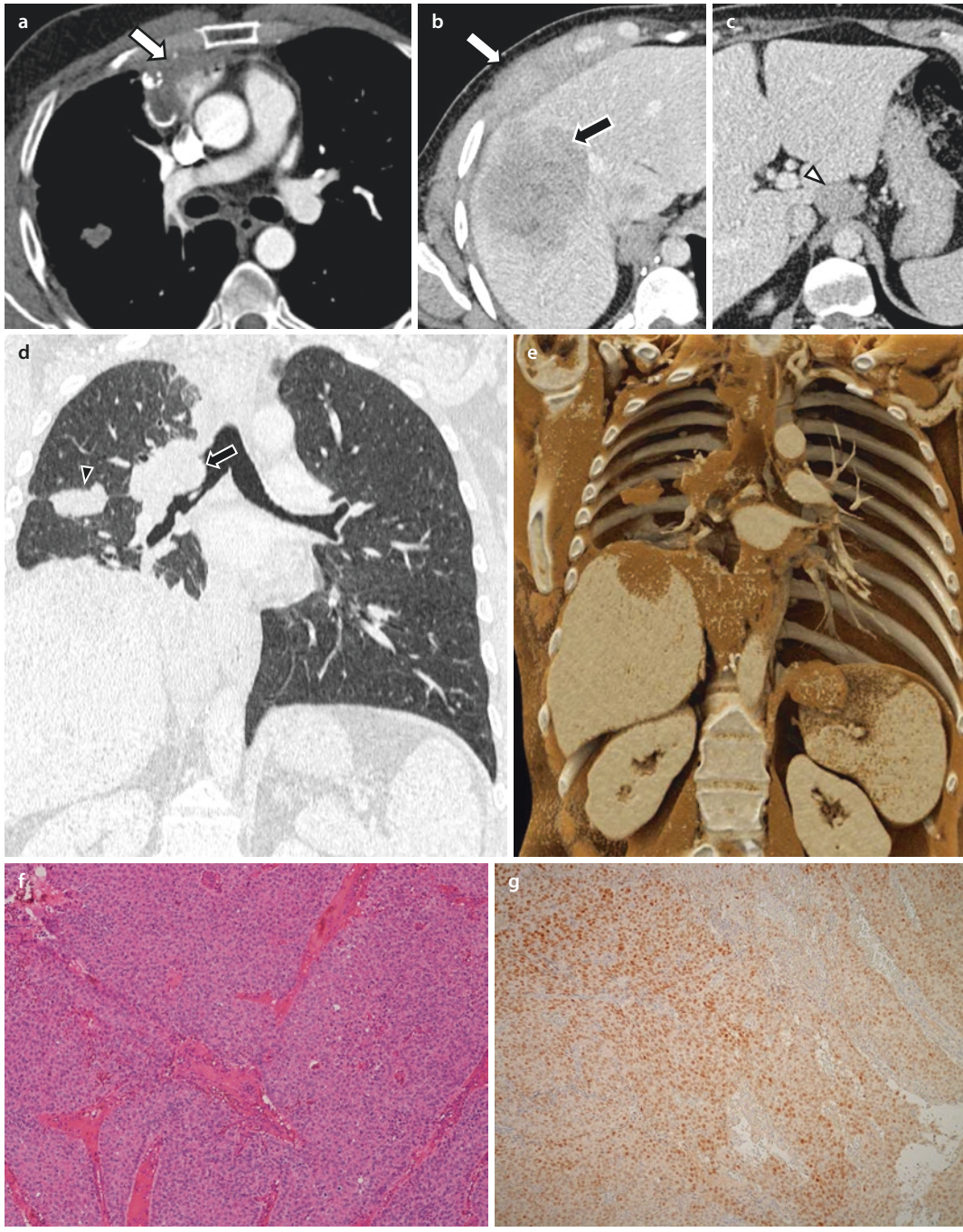

Fig. 6.5 **a** Follow-up CT scan of a 40-year-old male patients with previous resection of a B3 thymoma. Heterogeneous partly calcified mass within prevascular compartment that does not display an adipose fat plane with adjacent structures. Various localizations were detected, including a heterogeneous liver lesion in the right lobe (black arrow in **b**) and a diffuse thickening of anterior thoracic wall (white arrow in **b**), an enlarged coeliac lymph node (white arrowhead in **c**). The patient suffered from respiratory symptoms caused by bronchial invasion (black arrow in **d**, multiplanar reformatted image). A large fissural nodule can be detected (black arrowhead). **e** Cinematic para-coronal reformatted image highlighting the different sites of metastization. **f** EE (20×) specimen derived from sampling obtained during bronchoscopy performed for bronchial disobstruction showing a solid neoplasm with thymic origin as demonstrated by positivity for PAX-8 **g**. PAX-8 20x. (The authors thank Letizia Gnetti, MD (Section of Pathology, Unit of Surgical Sciences, Diagnostic Department, University Hospital of Parma, Parma, Italy), for providing iconographic materials)

Table 6.6 Recommended follow-up protocols by ITMIG

After R0 surgical resection	Annual CT for 5 years
	Then annual CXR alternating with CT for 5 years
After curative intent treatment stage III, IVa	CT every 6 month for 3 years
	Then CT with contrast for 5 years
	Then CXR alternating with CT for 5 years

regions or other locations, following the presence of ectopic thymic tissue. Noteworthy, thymoma may involve various structures, including the trachea, thyroid, parathyroid, pericardium, heart, pleura and lung. Primary intrapulmonary thymomas are very rare and slow-growing lesions either located below the visceral pleura or entirely circumscribed by lung parenchyma. Beside the hypothesis of ectopic intrapulmonary tissue, another option postulated the presence of germinative cells capable of differentiating along a variety of cellular lines, including thymocytes [37]. Usually, they do not cause symptoms; however, local growth can develop into compression and invasion with chest pain, as well as bronchial obstruction or haemoptysis. Notably, intrapulmonary thymoma can be associated with paraneoplastic syndromes and late local recurrence [38, 39].

6.3.2 Symptoms

Because of the wide spectrum of appearance of thymoma, clinical manifestations might vary widely. Up to one-third of cases are asymptomatic thymomas incidentally detected on chest radiograph. In case of locally disseminated thymomas, patients may report symptoms related to airways, nerves or oesophageal involvement (i.e. cough, dyspnoea, respiratory infections, hoarseness, chest pain or dysphagia), whilst invasion of vascular or cardiac (e.g. right atrium) structures causes superior vena cava syndrome or sudden cardiac death, respectively [40].

Systemic symptoms (e.g. weight loss, fever and night sweats) are reported in about 30% of cases, and here, the differential diagnosis with lymphoma is challenging. Furthermore, thymoma can be associated with autoimmune and paraneoplastic phenomena, including myasthenia gravis, pure red cell aplasia, hypogammaglobulinaemia, thymoma-associated multiorgan autoimmunity (TAMA) [41] and endocrine, cutaneous or connective tissue disorders [35, 36, 39, 40, 42, 43].

6.3.3 Imaging

Between 45% and 80% of thymomas are visible in chest radiograph (Fig. 6.6). In about one-third of cases, they appear as ovoid or lobulated soft-tissue masses located in the anterior mediastinum (median size ranging from 5 to 10 cm and extremely large ones over 30 cm) [40, 44, 45]. In such cases, lateral view usually depicts a soft-tissue mass in the retrosternal clear space. Thymomas more frequently are asymmetrical, although bilateral protrusion has been reported. CT can show also small thymoma few millimetres in diameter and a variety of locations such as the junction of the great vessels and the pericardium, the cardiophrenic angle, or the neck [38, 40].

CXR signs of local invasion are of difficult detection and evaluation. Irregular interface with pulmonary parenchyma may suggest intrapulmonary dissemination [40]. Pleural dissemination displays unilateral predominance, yet findings (pleural thickening/masses or diffuse/circumferential nodular thickening encasing pulmonary parenchyma) are usually non-specific, and differentiating thymoma from malignant mesothelioma or metastatic adenocarcinoma is utopian on CXR [40].

Individuals with strong clinical suspicion without detectable radiographic abnormalities are referred to CT for further investigation, which may confirm presence of anterior mediastinal masses and provide an overview on relationships with adjacent structures as well as signs of distant dissemination. On CT, thymomas are generally homogeneous, well-defined oval/rounded lobulated soft-tissue masses. Usually, thymoma shows homogeneous contrast enhancement, although hypodense areas reflecting cystic changes or haemorrhage and necrosis can be detected as well as punctuate, course, curvilinear calcifications. In up to 40% of cases, CT depicts large cystic lesions harbouring nodules on their inner wall; this is

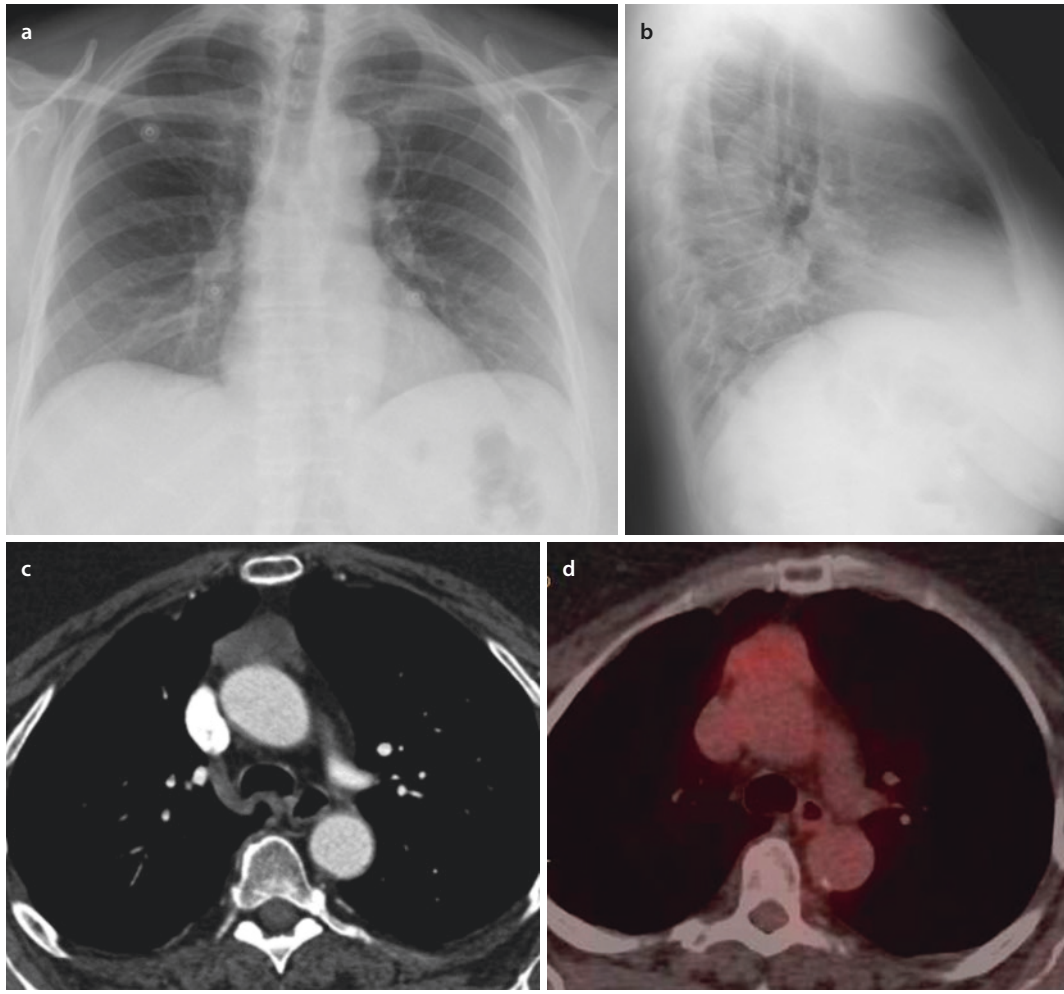

Fig. 6.6 **a** PA and **b** LL view of a chest radiograph in a female patient suffering from myasthenia gravis. The PA view appears regular, whilst on the LL view, an enlargement of the anterior mediastinal compartment can be detected. **c** The patient underwent contrast-enhanced CT, showing a soft-tissue density mass, in the prevascular compartment. The lesion does not display a significant contrast enhancement. **d** A PET-CT scan was obtained, reporting an uptake of the radiotracer (SUVmax 3.6). The patient underwent surgery with a final diagnosis of thymoma

more frequently seen in larger lesions [46]. Thymomas can be partially or completely outlined by adipose tissue: local invasion may be reflected by absent fat planes between the lesion and mediastinal structures, yet this finding shows variable sensitivity. A mass showing irregular borders with pulmonary parenchyma is highly consistent for thymoma invading the lungs. CT allows detection of signs of local invasion and of encasement of vascular structures, for which intravenous administration of iodinated contrast media is demanded. Detecting areas of contrast enhancement within a mediastinal lesion as well as features consistent with local invasion and pleural or pericardial implants allow for the differentiation between thymic lymphoid hyperplasia (TLH) and thymoma [40]. CT depicts pleural parietal dissemination ("drop metastases"), frequently found in posterior basilar pleural spaces and the diaphragm [35, 45].

MRI may be helpful to differentiate between thymoma and thymic cysts. Thymomas show signal intensity (SI) similar to muscular or normal thymic tissue on T1-weighted images and heterogeneous intensity on T2-weighted images. As previously mentioned, thymoma may show cystic, necrotic or haemorrhagic changes, and fibrous septa and nodules. These findings can be detailed on T2-weighted

Table 6.7 CT and MR findings of low-risk thymomas, high-risk thymomas and thymic carcinomas [94–97]

	Low risk (type A, AB, B1)	High-risk (type B2, B3)	Thymic carcinoma
CT – irregular margin	7%	22%	75%
CT – necrotic or cystic component	13%	28%	58%
CT – heterogeneous enhancement	33%	44%	92%
MR – complete or almost complete capsule[a]	27%	17%	0%
MR – partial capsule[a]	/	/	42%
MR – septum[a]	57%	44%	8%
MR – heterogeneous signal intensity	33%	56%	100%
MR – CT lymphadenopathy	3%	6%	58%
Surgical detection of great vessel invasion	0%	6%	42%
MR – smooth contours	A 100%	B2 64%	31%
	AB 64%	B3 33%	
	B1 42%		
MR – heterogeneous signal intensity T2W	A 20%	B2 64%	94%
	AB 45%		
	B1 58%		
MR – mean ADC value	1.82 ± 0.40 ($x10^{-3}$ mm^2/s)	1.11 ± 0.40 ($x10^{-3}$ mm^2/s)	1.11 ± 0.40 ($x10^{-3}$ mm^2/s)
MR – intratumor low-signal foci T2W[b]	A 0%	B2 27%	56%
	AB 7%	B3 17%	
	B1 12%		
Calcification	B1 44%	B2 61%	6%
		B3 75%	

Gender, age and size have no statistical significance
[a]MR is superior to CT in the depiction of capsule, septum and haemorrhage within the tumor
[b]Probably due to abundant collagenous tissue

images, and post-contrast sequences may allow detection of solid components within cystic lesions, thus suggesting the presence of an underlying cystic thymoma [15, 17, 18].

PET with fluorine-18 (F-18) fluorodeoxyglucose (FDG-PET) helps in differentiating thymic carcinoma from other thymic neoplasms, as well as from thymic hyperplasia or normal physiological uptake. Notably, standardized uptake value (SUV) is expected to be greater in thymic carcinoma than either invasive or non-invasive thymomas [1, 35].

Imaging findings and their incidence are summarized in Table 6.7.

6.3.4 Local Spread and Metastatic Dissemination

Local spread of thymoma shows preferential mediastinal/pleural involvement, whilst distant metastases of thymoma most frequently occur within pulmonary parenchyma [20, 47]. Extrathoracic metastases are extremely rare (3–6% of

cases), and they are mainly reported in association with B subtypes of thymoma [21, 48].

Local spread beyond capsular invasion can happen with two prototypical pathways: infiltration of mediastinal and visceral pleural layers and eventually pulmonary parenchyma and progressive involvement of mediastinal adipose tissue until mediastinal structures such as the pericardium, heart and vessels [47, 48]. Endobronchial spread was reported as a rare pattern of presentation with few cases in the literature [49–51] (Figs. 6.5, 6.7, and 6.8).

Pleural dissemination is particularly frequent, and it may be present at time of diagnosis or it might occur even after tumor resection in up to 20% of cases. Prognosis is worse in case of many of pleural nodules (>11 nodules). Complete macroscopic resection of pleural lesions improves survival and reduces recurrence rate; nonetheless, life-long follow-up after surgical resection is recommended to promptly detect extra-thoracic recurrence [52, 53]. Pleural metastases from thymoma are seen as enhancing pleura-based nodules/masses, also called "drop metastasis", they are variably associated with pleural effusion [19].

Distant metastases may involve pulmonary parenchyma and extra-thoracic organs, mainly the kidney, liver, brain and bones [40].

Liver metastases are the most frequent extra-thoracic localization, and indeed, exclusive liver involvement was reported in up to 40% of extra-thoracic metastatic thymoma [53]. Furthermore, liver metastases were found to occur also with a delay of more than 10 years after surgical resection of the thymoma [30].

Pancreatic and gastrointestinal metastases are particularly rare, and they were described in retroperitoneal space, stomach, transverse colon and mesentery [53, 54]. Cases of thymoma dissemination to ovary were described in autopsy series [55].

Hematogenous spread to bone may follow invasion of the superior vena cava [31]. Rarely, thymoma may metastasize to the spine. Likewise other dissemination target of thymoma, also spine involvement may be diagnosed ever lately after initial diagnosis. Symptoms include spinal cord/cauda equina compression [32].

6.4 Thymic Carcinoma

6.4.1 Epidemiology

Thymic carcinoma displays high malignant potential and aggressive behaviour related to its epithelial origin, resulting in poor prognosis. It represents about 1% of thymic malignancies, featuring male predominance and a mean age at diagnosis ranging from 47 to 60 years [26]. Interestingly, thymic carcinoma may arise de novo or follow transformation from pre-existing thymomas.

According to differences in cell morphology, the most common entity is squamous cell carcinoma, which can present as well-differentiated (keratinizing) squamous cell carcinoma, moderately differentiated squamous cell carcinoma and poorly differentiated (nonkeratinizing) squamous cell carcinoma, the latter also known as lymphoepithelioma-like carcinoma. Further subtypes are described that are extremely rare: basal cell, mucoepidermoid, sarcomatoid, adenosquamous, clear cell and undifferentiated carcinomas [56].

6.4.2 Symptoms

Thymic carcinoma may be either asymptomatic or cause various symptoms because of local invasiveness and/or metastatization. Cough, chest tightness and substernal pain, phrenic nerve palsy and superior vena cava syndrome can be associated with systemic and unspecific findings (e.g. fever, fatigue, anaemia, night sweats, weight loss and anorexia) [26]. Paraneoplastic syndromes (e.g. myasthenia gravis, pure red cell aplasia, hypercalcaemia) are reported with lower frequency compared with thymoma, and they are usually associated with thymic carcinoma arising from pre-existing thymomas [33].

6.4.3 Imaging

CXR may depict anterior mediastinal/hilar masses or subtle abnormalities including small mediastinal widening or paratracheal bulging. For such imaging manifestations, the differential

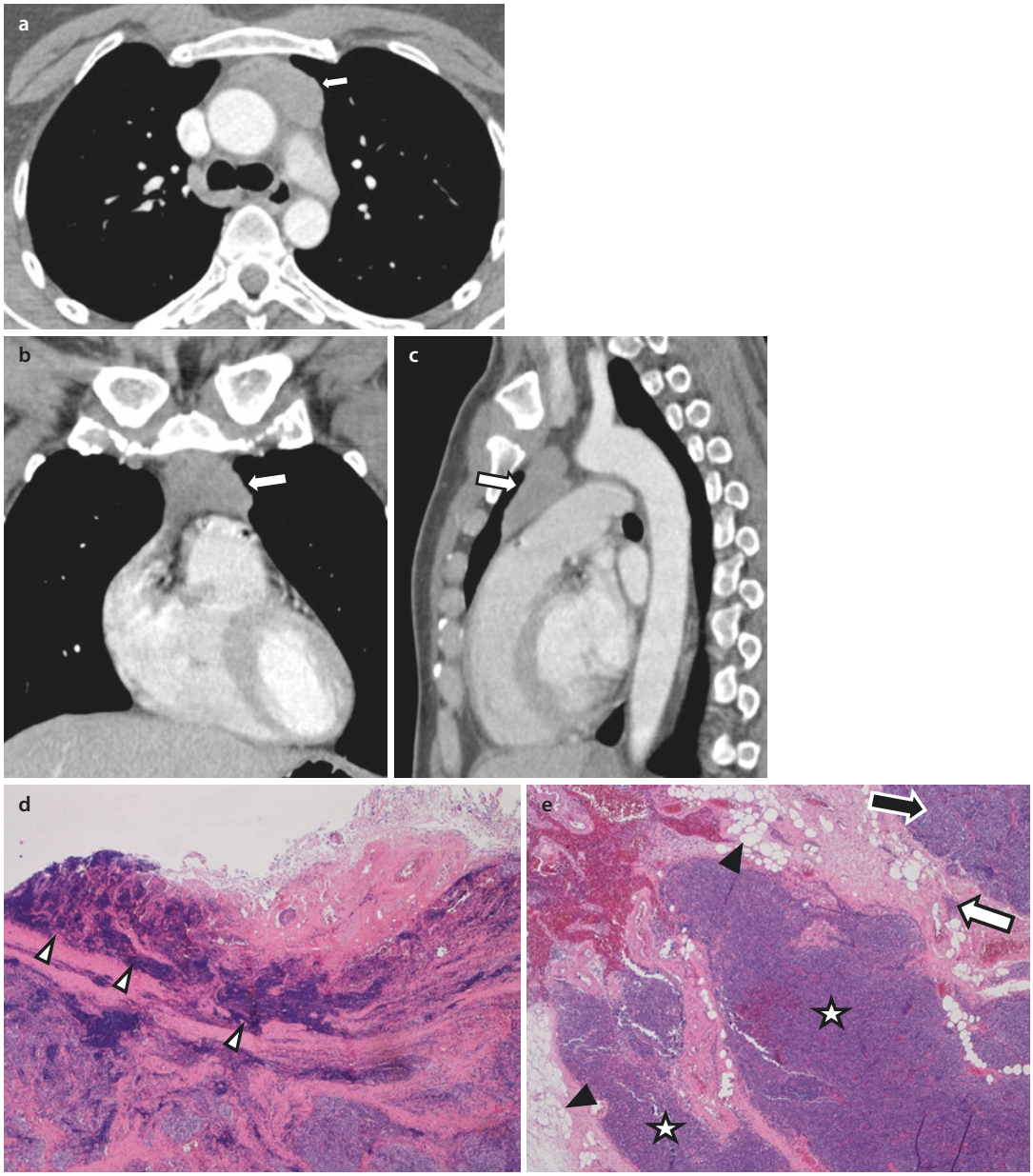

Fig. 6.7 CT scan (**a**, axial image; **b**, coronal reformatted image; **c**, sagittal reformatted image) of a 48-year-old female patient suffering from myasthenia gravis revealing a solid lesion in the prevascular compartment. The lesion shows smooth margins and homogeneous contrast enhancement. No clear signs of adjacent structures' invasion were reported. On histological evaluation performed after surgery, the lesion showed capsular invasion with growth mediastinal adipose tissue: (**d**, EE 10×) numerous neoplastic nodules (white arrowheads) intermingled with fibrous tissue. At higher magnification (**e**, EE 20×), the nodule of greatest dimensions (black arrow) invades thymic fibrous capsule (white arrow) resulting in mediastinal adipose tissue (black arrowheads) infiltration from solid nodules (white stars) stemmed from the main nodule (black arrow). (The authors thank Letizia Gnetti, MD (Section of Pathology, Unit of Surgical Sciences, Diagnostic Department, University Hospital of Parma, Parma, Italy), for providing iconographic materials)

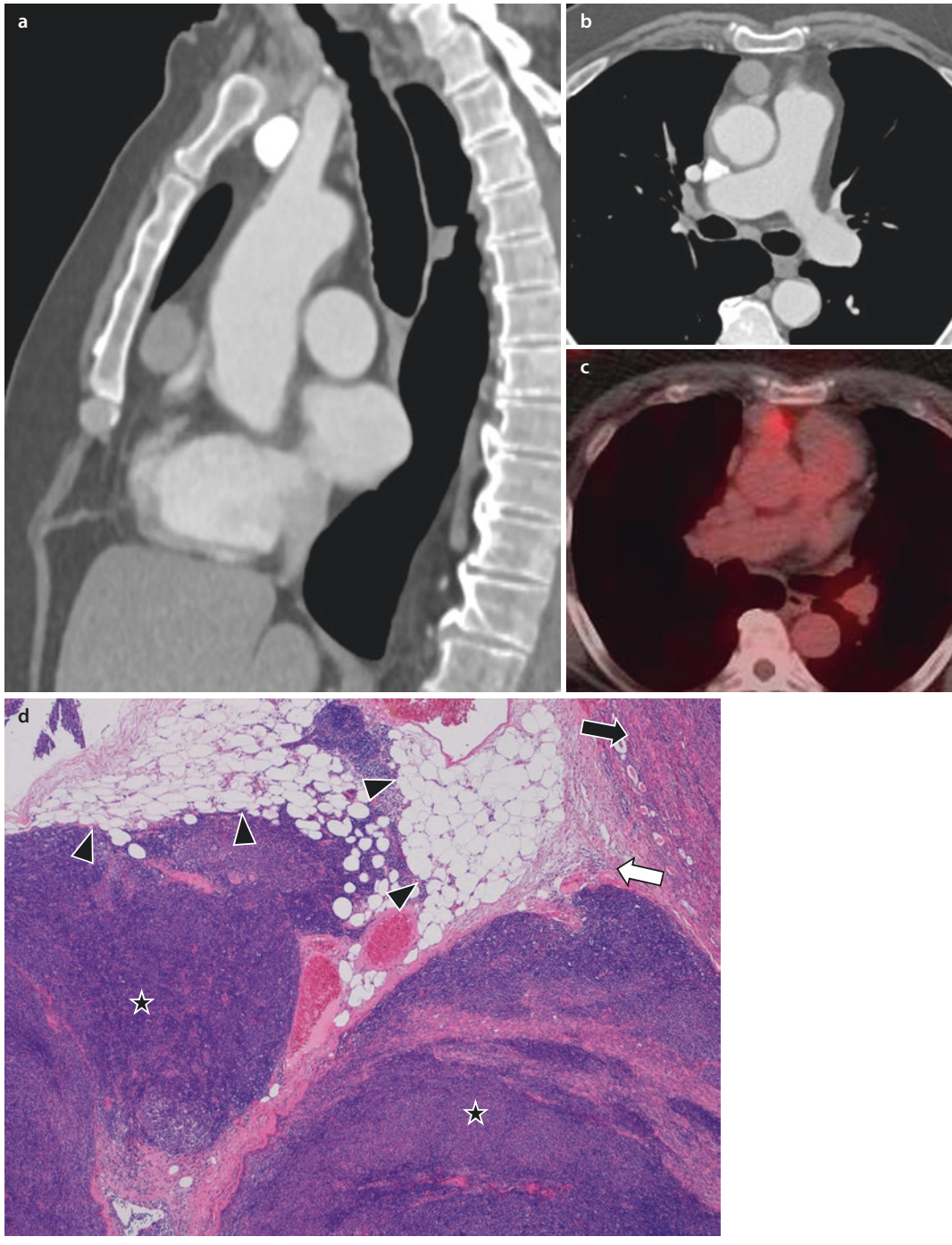

Fig. 6.8 Seventy-year-old male patient with a solid homogeneously enhancing nodule located in the prevascular compartment incidentally detected at a follow-up CT for melanoma. CT image (**a**, sagittal reformatted image; **b**, axial view) showing a soft-tissue density nodule with smooth margins located in the prevascular compartment. **c** FDG-PET scan showed uptake of the radiotracer. After surgery, histological evaluation (**d**, EE 20×) depicted the neoplastic nodule (black arrow, AB thymoma) intermingled with fibrous tissue showing invasion of the thymic fibrous capsule (white arrow), resulting in mediastinal adipose tissue (black arrowhead) infiltration from solid nodules (black stars) stemming from the main nodule. (The authors thank Letizia Gnetti, MD - Section of Pathology, Unit of Surgical Sciences, Diagnostic Department, University Hospital of Parma, Parma, Italy, for providing iconographic materials)

diagnosis is wide; hence, further imaging evaluation is mandatory. On CT, thymic carcinomas appear as large masses with irregular margins and hypodense areas related to necrotic, haemorrhagic or cystic degenerations. The diagnosis of thymic carcinoma is also associated with heterogeneous contrast enhancement, lymphadenopathies and great vessel invasion assessed on CT (or MRI) [57].

CT after intravenous administration of contrast media is paramount for preoperative staging because it allows description of signs of local invasion, pleural seeding and metastatic disease. However, CT is hampered by various limitations, ranging from difficulty in differentiating between lymphoid/rebound hyperplasia and malignancy. Furthermore, detection of early local invasion or small pleural implants might be challenging by CT.

MRI is rarely performed, and nonetheless, it can provide valuable evaluation of fat planes between tumor and adjacent organs. It also allows mass characterization by description of necrotic, haemorrhagic or cystic degenerations [58–60].

6.4.4 Local Spread and Metastatic Dissemination

Thymic carcinoma invades adjacent mediastinal structures in up to 80% of cases at time of diagnosis. The most common sites of local invasion include brachiocephalic vein, pleura, lung, lymph nodes (supraclavicular, paraesophageal, retrocrural, pericardial and axillary nodes) and pericardium [8, 26, 61, 62]. Endobronchial dissemination is particularly rare, represented by polypoid lesions either mono- or bilateral (one case reported in the literature) [63, 64]. Intralesional calcifications, pleural nodules and adipose tissue infiltration were associated with increased risk of metastasis or recurrence [8]. Similarly, lymphatic involvement shows a positive correlation with tumor invasiveness [27]. Systematic surgical resection of lymph nodes is proposed in high-risk patients because thymic carcinoma shows high rates of recurrence (Table 6.8): 21% at 3 years, 27% at 5 years and 32% at 10 years [27, 48, 61, 65–67].

Table 6.8 Type of recurrence of thymic carcinoma

Recurrence	Regrowth after complete resection or radiographic complete response to curative intent therapy
Local recurrence	At site of original tumor or in thymic bed including adjacent nodes
Regional recurrence	Intrathoracic, but not contiguous with original tumor or thymus
Distant recurrence	Outside of the thorax or intraparenchymal nodules

Extra-thoracic metastases may involve multiple organs, including the bone, liver, adrenal gland, bone marrow, brain, ovary, spleen, pancreas, skin, breast and extra-thoracic lymph nodes [26, 48, 54, 68–72].

Bone marrow metastases are usually detected in late-stage diseases, although a case of a patient with bone marrow metastasis as first manifestation of otherwise occult thymic carcinoma has been reported [33].

Brain metastases are rare yet severely affecting prognosis. They can be located within frontal, parietal, cerebellar, temporal and occipital lobes, either being silent and incidentally discovered or causing headache and neurological manifestations including vision and mental status change, memory loss, speech difficulty and seizures. Lesions may appear solid or cystic and cause haemorrhage and extracranial extension [34, 73].

Spine metastases are rare, with neurological symptoms depending on location, such as hoarseness and dysphagia (C3–C4 location), paraesthesia, sensory change, weakness, numbness and paraparesis/paralysis. Furthermore, metastases may cause spinal instability because of vertebral collapse, as well as spinal cord compression [32].

Gastrointestinal tract invasion is extremely uncommon, with preferential involvement of small bowel tracts [54]. Similarly, splenic metastases are particularly rare [74].

Breast metastases are extremely rare, and they may develop by lymphatic (through intercostal lymphatics to parasternal lymph nodes) or hematogenous (intercostal perforators from internal thoracic artery) spread [72].

6.5 Carcinoid

6.5.1 Epidemiology

Thymic neuroendocrine tumors (NETs) are rare neoplasms composed of neuroendocrine cells (2–5% of epithelial tumors) with poor prognosis related to local invasion, recurrence or distant metastases [57]. Thymic carcinoids may arise at various ages (median age at presentation is 43 years) and usually show male predominance [1]. Thymic NETs are classified according to histopathological findings into typical carcinoid, atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell neuroendocrine carcinoma (SCC) (Table 6.9). In the 2015 update of WHO classification of NETs, the term "well-differentiated neuroendocrine carcinoma" (referring to carcinoids) and "poorly differentiated neuroendocrine carcinoma" (referring to LCNEC and SCC) of the previous (third) edition were abandoned, because LCNECs and even SCC may be highly differentiated in terms of neuroendocrine features. Indeed, the fourth edition separates typical and atypical carcinoids as low-grade and intermediate-grade neuroendocrine tumors, respectively, from high-grade neuroendocrine carcinoma that comprise LCNEC and SCC [43].

Table 6.9 Thymic neuroendocrine tumor classification

Typical carcinoid	< 2 mitoses/2mm^2; no necrosis
Atypical carcinoid	< 2 mitoses/2mm^2; with necrosis; or 2–10 mitoses/2mm^2; + or − necrosis
LCNEC	> 10 mitoses/2mm^2; no small-cell features
Combined LCNEC	LCNEC combined with any thymoma(s) or thymic carcinoma(s)
SCC	Typical SCC histology
Combined SCC	SCC combined with any thymoma(s) or thymic carcinoma(s)

6.5.2 Symptoms

Thymic carcinoids are often hormonally active and endocrine manifestations are mostly represented by Cushing's syndrome (ectopic ACTH production), whilst non-active lesions may be associated with parathyroid adenoma, islet cell tumor of the pancreas and pituitary adenoma as component of multiple endocrine neoplasia (MEN) type I syndrome [26, 57, 75]. Furthermore, symptoms may follow compression or invasion of adjacent structures, such as the trachea, pleura, pulmonary parenchyma or blood vessels [57].

6.5.3 Imaging

Most typical carcinoid tumors are not encapsulated and can be grossly invasive, their size ranging from 2 to 20 cm. Of note, carcinoids causing Cushing's syndrome tend to be smaller due to earlier detection. Calcifications are more frequently encountered in thymic than extra-thymic NETs, possibly because ACs are associated with necrosis and subsequent development of calcifications are more frequently encountered in the thymus [76].

CXR may be normal or equivocal in cases of small lesions and carcinoids may be more easily detected on CT [75]. Thymic carcinoids most frequently appear as large, lobulated and heterogeneous anterior mediastinal mass. Heterogeneity is due to intralesional calcifications and necrotic or cystic changes (as previously mentioned, more frequently appearing in ACs). Generally, thymic carcinoids display moderate-to-strong enhancement after intravenous administration of contrast media. CT scan can also highlight infiltration of surrounding structures and metastases [1, 77].

On MRI, thymic carcinoids manifest as T1-weighted hypointense and T2-weighted heterogeneous hyperintense masses with irregular contours and heterogeneous enhancement. ADC values in thymic carcinoids may be misleading because of cystic or necrotic changes that might interfere with ADC values [57, 60, 78].

6.5.4 Local Spread and Metastatic Dissemination

Thymic carcinoids display a more aggressive biological behaviour and have a higher propen-

sity to metastasize to distant sites as compared with other thymic epithelial tumors. Local invasion is reported in 50% of cases, notably involving the pericardium, mediastinal adipose tissue, blood vessels and lungs. Distant hematogenous metastatization is reported in 20–30% of cases [79–82] (metastatic spread ranges from 20% in carcinoids up to 80% in SCCs) [26, 83–85], most frequently reported in the bones, lungs, spleen, liver, brain and adrenal glands. Notably, local recurrence or distant metastases (usually abdominal lymph nodes and skeletal involvement) can occur after several years from diagnosis, despite surgical resection and perioperative chemotherapy [49].

Prognostic factors affecting long-term outcome include histological grade, mitotic activity, capsular invasion, incomplete resection, lymph node status and presence of metastasis at the time of diagnosis [80, 86]. In particular, prognosis of typical carcinoids (5-year survival rate ranges from 50% to 100%, median survival of about 10 years) is slightly better as compared to ACs and LCNEC (5-year survival rate ranges from 30% to 66%) [87]. About 75% of LCNEC infiltrates adjacent organs or shows distant metastases, usually to the spine and liver [87]. Most SCCs are diagnosed at advanced stage with signs of local invasion (to lung or pericardium) or with distant metastases to the lung, liver, bone or brain; commonly, prognosis is poor (5-year survival rate, 0%; median survival about 1 year) [76].

6.6 Thymoliposarcoma

Primary liposarcomas of the mediastinum are extremely rare lesions (<1% of mediastinal tumors, with about 150 cases reported), usually affecting adult individuals [88]. Malignant liposarcomas develop more commonly in the posterior mediastinum; still, thymoliposarcoma is the most common sarcoma of the anterior mediastinum. Noteworthy, a minority of cases of anterior mediastinum liposarcoma may exhibit extensive thymic tissue within the lesion, thus being considered as thymoliposarcomas [89].

Thymoliposarcomas grow mostly with an expansible pattern. No histologically proven metastases were reported except for local recurrence, similarly to biological behaviour of well-differentiated liposarcoma [89]. Signs and symptoms are related to size and direct invasion of adjacent structures such as the pericardium or superior vena cava (i.e. dyspnoea, chest pain and tachypnoea), although incidental asymptomatic lesions have also been reported [88].

The predominant finding of mediastinal liposarcoma on CXR is a widened mediastinum. On CT, the appearance of mediastinal liposarcomas varies from a predominantly fat-containing mass to a solid mass. Low attenuation values between −50 and −150 Hounsfield unit are consistent with adipose tissue. Higher HU values are related to necrotic or soft-tissue intralesional components. MR is particularly useful: T1-weighted images show adipose tissue with a high SI, whereas SI diminishes in T2-weighted image [88].

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