IASLC/ITMIG Staging System and Lymph Node Map for Thymic Epithelial Neoplasms[1]

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Thymic epithelial neoplasms are rare malignancies that arise from the thymus and include thymoma, thymic carcinoma, and thymic neuroendocrine tumors. At least 15 different stage classifications have been proposed for thymic epithelial neoplasms and used to varying degrees in clinical practice, many of which have been constructed from small groups of patients. Traditionally, the Masaoka and Masaoka-Koga staging systems have been the schemes most commonly employed, and the latter has been recommended for use by the International Thymic Malignancy Interest Group (ITMIG). An official, consistent stage classification system has recently been recognized by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), which are responsible for defining stage classifications for neoplasms. To establish this stage classification system, the International Association for the Study of Lung Cancer (IASLC) and ITMIG amassed a large retrospective database and evaluated this group of cases to develop proposals for the eighth edition of the stage classification manuals. For this endeavor, IASLC provided funding and statistical analysis and ITMIG provided the involvement of the clinicians and researchers actively participating in the study of thymic epithelial neoplasms. To accomplish this, a Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) was established to formulate the rationale, methodology, and definitions of this tumor-node-metastasis (TNM) staging system, which is presented in this article.

Abbreviations: AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery, AJCC = American Joint Committee on Cancer, ASHNS = American Society for Head and Neck Surgery, IASLC = International Association for the Study of Lung Cancer, ITMIG = International Thymic Malignancy Interest Group, JART = Japanese Association for Research on the Thymus, SVC = superior vena cava, TD-SPFC = Thymic Domain of the Staging and Prognostic Factors Committee, TNM = tumor-node-metastasis, UICC = Union for International Cancer Control

RadioGraphics 2017; 37:758–776

Published online 10.1148/rg.2017160096

Content Codes: CH CT MR OI

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Discuss the epidemiology, clinical features, and classification of thymic epithelial neoplasms.
- Describe the tumor (T), node (N), and metastasis (M) descriptors and stage groupings for thymic epithelial neoplasms.
- Utilize the lymph node map for thymic epithelial neoplasms to localize and appropriately stage lymph node metastases.

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Introduction

Thymic epithelial neoplasms are rare malignancies of thymic origin and include thymoma, thymic carcinoma, and thymic neuroendocrine tumors. At least 15 different stage classification systems have been proposed and used to varying degrees clinically, most of which have been derived from data on small groups of patients (1). The most widely used staging classifications are the Masaoka and Masaoka-Koga staging systems, the latter of which has been recommended for use in staging of thymic epithelial neoplasms by the International Thymic Malignancy Interest Group (ITMIG); however, the Masa-

TEACHING POINTS

- Thymic epithelial neoplasms are rare malignant tumors that account for 0.2%–1.5% of all malignancies and affect 0.13 per 100 000 individuals in the United States but are the most common nonlymphomatous primary neoplasms of the anterior mediastinum. The epithelial neoplasms of the thymus include thymoma (the most common), thymic carcinoma, and thymic neuroendocrine tumors.
- At least 15 different staging systems have been proposed for thymic epithelial neoplasms. The Masaoka staging system or a variant of it, the Masaoka-Koga staging system, are the most commonly used systems for thymoma, and the latter is the one that has traditionally been recommended by ITMIG because of its correlation with patient survival.
- The goal of the TD-SPFC was to create a stage classification system that was TNM based and applicable to all thymic epithelial neoplasms. Specific thresholds between T, N, and M categories and overall stage groupings were based on prognostically distinct groups of patients, with specific endpoints including overall survival and recurrence.
- For the purposes of clinical staging, identification of pericardial involvement at multidetector CT is often imprecise or not possible; however, suspicion can be raised when a neoplasm abuts or surrounds a large portion of the pericardium.
- The lymph node map devised for thymic epithelial neoplasms defines anterior and deep regions based on boundaries that outline the peripheral extent of surgical dissection in all planes. This definition was selected because it reflects the technique used for thymic dissection, in which the specimen is removed en bloc. Anterior mediastinal lymph nodes have been described as the primary drainage pathway and other intrathoracic lymph nodes as the secondary drainage pathway.

oka classification originated from data on only 91 patients and the Koga modification was derived from data on only 76 patients (2,3). In clinical practice, it has been common for various institutions to interpret these staging systems differently, thus limiting the ability of clinicians from various specialties to communicate and collaborate effectively (4). An official stage classification system for thymic neoplasms has recently been adopted by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), the organizations responsible for defining stage classifications for neoplasms.

To establish this universal and consistent stage classification system, the International Association for the Study of Lung Cancer (IASLC) and ITMIG assembled a large retrospective database and evaluated this group of cases to develop proposals for the eighth edition of the stage classification manuals. For this partnership, IASLC provided funding and statistical analysis while ITMIG provided the involvement of the clinicians and researchers actively participating in the study of thymic epithelial neoplasms (5). To accomplish this, a Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) was established to formulate the rationale, methodology, and definitions of this tumor-node-metastasis (TNM) staging system.

In this article, we present the T, N, and M descriptors, lymph node map, and stage classifications for thymic epithelial neoplasms created by IASLC and ITMIG and recently included in the eighth edition of the AJCC staging manual.

Thymic Epithelial Neoplasms

Epidemiologic and Clinical Features

General Considerations.—Thymic epithelial neoplasms are rare malignant tumors that account for 0.2%–1.5% of all malignancies and affect 0.13 per 100 000 individuals in the United States but are the most common nonlymphomatous primary neoplasms of the anterior mediastinum (6). The epithelial neoplasms of the thymus include thymoma (the most common), thymic carcinoma, and thymic neuroendocrine tumors.

Thymoma.—Thymoma is the most common primary malignancy of the anterior mediastinum and the most common thymic epithelial neoplasm. The incidence of thymoma is one to five cases per 1 million individuals per year in the United States, but is higher in Asians and African Americans than in Hispanics and whites (6). Men and women are equally affected. The incidence of thymoma increases with advancing age, so that patients older than 40 years are most commonly affected, although the incidence starts decreasing after the age of 60 years. Thymomas are slow-growing neoplasms that may exhibit aggressive behavior such as invasion of adjacent structures and involvement of the pleura and pericardium, but distant metastases are rare (7).

The most common symptoms described at clinical presentation include those related to local effects of the malignancy, including compression and invasion of adjacent structures, which can produce dysphagia, diaphragmatic paralysis, or superior vena cava (SVC) syndrome. One-third of patients report chest pain, dyspnea, or cough (8).

Patients may present with systemic symptoms and paraneoplastic syndromes due to the release of hormones, antibodies, and cytokines by the neoplasm. Myasthenia gravis is the most common paraneoplastic syndrome associated with thymoma; 30%–50% of patients with thymoma display signs and symptoms of myasthenia gravis, whereas only 10%–15% of patients with myasthenia gravis have thymoma (9). Hypogammaglobulinemia and pure red cell aplasia are other significant paraneoplastic syndromes, which are present in 10% and 5% of cases, respectively (10). Finally, various autoimmune disorders may be associated

with thymoma, including systemic lupus erythematosus, polymyositis, and myocarditis (11).

Thymic Carcinoma.—Thymic carcinoma represents approximately 20% of thymic epithelial neoplasms but is uncommon in adults (12). The mean age of patients at presentation is 50 years (13). In contrast to thymoma, thymic carcinoma tends to demonstrate aggressive features such as local invasion, intrathoracic lymphadenopathy, and distant metastases; for example, 50%–65% of patients present with distant metastases at diagnosis (13).

The most common symptoms described at clinical presentation include those related to local effects of the neoplasm, principally compression and invasion of adjacent structures. In contrast to thymoma, paraneoplastic syndromes rarely accompany thymic carcinoma.

Thymic Neuroendocrine Neoplasms.—Of the thymic epithelial neoplasms, neuroendocrine tumors are the least common, representing 2%–5% of all such lesions (14). Most neuroendocrine tumors of thymic origin are carcinoids. Approximately 0.4% of all carcinoids arise from the thymus, and the annual incidence in the United States is 0.2 per 1 million (15). The largest series of reported cases revealed a median age at presentation of 57 years and a male-to-female ratio of 3:1 (15). Similar to thymic carcinoma, thymic neuroendocrine neoplasms may demonstrate aggressive behavior such as invasion of adjacent structures and mediastinal lymph node involvement, the latter of which is present in 50% of patients at diagnosis (16).

Approximately 25% of thymic neuroendocrine neoplasms develop in patients with multiple endocrine neoplasia (MEN) type 1, an autosomal dominant disorder that predisposes those with the genetic abnormality to developing endocrine and nonendocrine proliferations (17). Conversely, thymic neuroendocrine neoplasms develop in 3%–8% of patients with MEN 1. In published series, most patients with MEN 1–related thymic neuroendocrine neoplasms were heavy smokers, suggesting a possible link with tobacco.

Most patients are symptomatic at diagnosis with symptoms related to compression and invasion of adjacent structures, such as cough, dyspnea, and chest pain; SVC syndrome; and hoarseness due to involvement of the recurrent laryngeal nerve (18). Patients with neuroendocrine neoplasms of the thymus may present with paraneoplastic syndromes, the most common of which is Cushing syndrome, characterized by ectopic production of adrenocorticotropic hormone (ACTH). Other syndromes such as acromegaly and syndrome of inappropriate secretion of antidiuretic hormone are uncommon, and carcinoid syndrome is rare (19,20). However, approximately one-third of patients are asymptomatic, with neuroendocrine neoplasms incidentally discovered at imaging performed for other reasons or as part of surveillance for MEN 1 (14).

Histology and Classification

Thymoma and Thymic Carcinoma.—The histologic classification of thymoma and thymic carcinoma has been a source of controversy. The first classification system developed by the World Health Organization (WHO) Consensus Committee in 1999 classified thymomas into six separate subtypes (A, AB, B1, B2, B3, and C) based on morphologic features of the neoplastic epithelial cells and the lymphocyte–epithelial cell ratio. A revised scheme published in 2004 relocated type C (thymic carcinoma) to a separate category (21). Inherent limitations persist in these classification schemes, principally a result of the histologic heterogeneity of thymoma and thymic carcinoma, as many different subtypes may coexist within the same lesion (22). Additionally, the WHO histologic classification systems of 1999 and 2004 lacked intra- and interobserver reproducibility and clinical predictive value (23).

It is most important to identify thymic carcinoma as compared with thymoma, as the prognosis of thymic carcinoma is much worse compared with that of thymoma (24). Thymomas are composed of neoplastic cells with morphologic and immune-histochemical features characteristic of thymic epithelial cells, whereas thymic carcinomas exhibit neoplastic cells with overt atypia. Additionally, approximately two-thirds of thymomas are encapsulated, whereas thymic carcinomas typically lack a well-defined capsule.

Thymic Neuroendocrine Neoplasms.—The term *thymic carcinoid* was introduced in 1972 by Rosai and Higa (25), who reported eight cases of thymic neuroendocrine neoplasms. The 2004 WHO classification for thymic neuroendocrine neoplasms defines well-differentiated neuroendocrine tumors and poorly differentiated carcinomas, the former of which include typical carcinoid (low-grade) and atypical carcinoid (intermediate-grade) and the latter of which include small cell and large cell variants (26). Typical carcinoids demonstrate no necrosis and less than two mitoses per 2 mm^2, while atypical carcinoids show areas of necrosis and/or two to 10 mitoses per 2 mm^2. In contrast, large cell and small cell neuroendocrine carcinomas demonstrate average mitoses of 60–70 per 2 mm^2 (26).

Prior Staging Systems

At least 15 different staging systems have been proposed for thymic epithelial neoplasms. The Ma-

Table 1: Masaoka-Koga Staging System for Thymoma

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

saoka staging system or a variant of it, the Masaoka-Koga staging system (Table 1), are the most commonly used systems for thymoma, and the latter is the one that has traditionally been recommended by ITMIG because of its correlation with patient survival (27,28). In this system, thymomas are designated as stage I when completely encapsulated; as stage II in the setting of microscopic invasion through the capsule (IIa) or macroscopic invasion of the surrounding fat (IIb); as stage III when invasion of an adjacent structure such as the lung, pericardium, or great vessels is present; and as stage IV in the setting of pleural or pericardial spread (IVa) or lymphatic/hematogenous dissemination (IVb).

Role of Imaging

General Considerations

The role of imaging is to identify and accurately clinically stage thymic epithelial neoplasms, with emphasis on detection of advanced disease features such as local invasion, lymphadenopathy, and distant spread. Identification of patients with advanced disease is necessary, as preoperative neoadjuvant chemotherapy may be administered in hopes of bridging patients to surgical resection, as thymoma patients with completely resected recurrent disease have similar outcomes as those without recurrence (29,30).

Chest Radiography

At radiography, thymic epithelial neoplasms typically manifest as unilateral masses with smooth or lobular margins in the anterior mediastinum at any point from the thoracic inlet superiorly to the cardiophrenic angles inferiorly. These lesions may manifest as a nodular or mass-like opacity in the retrosternal region at lateral chest radiography, a mediastinal contour abnormality, or thickening of the anterior junction line at frontal chest radiography (31). Findings suggestive of advanced disease, including hemidiaphragm elevation due to phrenic nerve involvement, irregular margins with the adjacent lung parenchyma, and pleural thickening and/or nodularity, may be present.

Multidetector CT

Multidetector computed tomography (CT) is the imaging modality of choice for identifying, characterizing, and staging thymic epithelial neoplasms, as the extent of local tumor spread, lymphadenopathy, and spread of disease may be assessed. Intravenous contrast material should be administered unless significant contraindications are present, such as severe contrast agent allergy or renal failure, to adequately evaluate the vascular structures for evidence of invasion. Direct signs of vascular involvement include irregularity of the vessel lumen contour, encasement or obliteration of vessels, and endoluminal soft tissue, which can extend into cardiac chambers (32). Invasion of the adjacent lung parenchyma is rarely identified at multidetector CT and is typically detected at surgery. Compressive atelectasis caused by the adjacent malignancy is the most common pulmonary abnormality detected at multidetector CT but can be difficult to distinguish from intrapulmonary extension of tumor (33).

Identifying cardiac invasion is often challenging. Nevertheless, the pericardium and epicardial fat should be carefully evaluated for potential clues suggesting involvement. For instance, many neoplasms invading the pericardium result in an inflammatory reaction and associated pericardial effusion (34). Myocardial invasion may be suggested by obliteration of the epicardial fat, which adheres to the myocardium (34). However, cardiac magnetic resonance (MR) imaging is the imaging modality of choice for evaluating malignant cardiac disease.

Advanced thymomas may demonstrate pleural spread or "drop metastases," which manifest as single or multiple pleural nodules or masses typically ipsilateral to the primary malignancy. The presence of aggressive features such as local invasion, lymphadenopathy, pleural effusion, and distant metastases should prompt consideration of thymic epithelial neoplasms such as thymic carcinoma or thymic neuroendocrine tumor rather than thymoma.

Various studies have evaluated potential correlation between morphologic features of thymoma at multidetector CT and Masaoka staging (35–37). In several of these, the authors found that partial or complete obliteration of fat planes surrounding the lesion was not helpful in distinguishing stage I from advanced stages; however, lobulated or irregular contours, cystic or necrotic regions, and multifocal calcifications were suggestive of invasive thymoma using univariate analysis (36–38). In a larger study,

features of thymoma such as large size of the primary neoplasm, lobular contours, heterogeneity, calcifications, infiltration of adjacent fat, and tumor surrounding 50% or more of the circumference of a vascular structure were suggestive of advanced disease by univariate analysis (36). In the same study, features such as size greater than or equal to 7 cm, infiltration of adjacent fat, and lobular contours were associated with advanced disease by multivariate analysis (36).

MR Imaging

MR imaging is not routinely performed in staging of all patients with thymic epithelial neoplasms but has demonstrated efficacy in certain scenarios. In patients unable to undergo contrast-enhanced multidetector CT due to severe contrast material allergy and/or renal failure, MR imaging should be performed to evaluate for invasion of vascular structures.

Cardiac MR imaging is the optimal imaging modality for evaluating the presence and extent of myocardial involvement by malignancies, given its excellent soft-tissue contrast and ability to obtain images in multiple imaging planes. The myocardium can be evaluated with T1- or T2-weighted double inversion-recovery sequences, and tumor involvement can be identified as regions of abnormal signal intensity (34). Administration of intravenous gadolinium contrast material is also helpful, as atypical gadolinium enhancement has been reported in patients with myocardial invasion (39). Postcontrast sequences should be performed in the plane that best demonstrates the region of invasion. Internal regions of vascularity may be present on first-pass perfusion images. Finally, it has been suggested that cine MR imaging should be strongly considered when cardiac involvement is suspected (39).

Identification of phrenic nerve invasion is also important, as it indicates advanced disease necessitating preoperative neoadjuvant chemotherapy and affects plans for surgical resection. Multishot spiral sequences for real-time imaging of the diaphragm can be performed, as paradoxical movement and diaphragmatic movement can be evaluated (40).

Findings suggestive of chest wall invasion by a wide variety of thoracic malignancies, principally lung cancer but also mediastinal tumors such as thymic epithelial neoplasms, have been described. MR imaging is considered to be superior to multidetector CT in identifying chest wall invasion due to better soft-tissue contrast and spatial resolution (41). Specific findings include disruption of the extrapleural fat plane on T1-weighted images and high signal intensity of the parietal pleura and other structures on T2-weighted and short τ inversion-recovery (STIR) images (42,43). Administration of intravenous contrast material may be beneficial. Finally, cine MR imaging during breathing can demonstrate chest wall invasion, as attachment of the neoplasm to the chest wall suggests involvement (44).

One study assessed the ability of dynamic MR imaging to allow differentiation between early-stage (stages I and II) and advanced-stage (stage III) thymomas and showed that mean peak time was delayed in the latter compared with the former (45). In the same study, 92% of stage II, III, and IV thymomas displayed heterogenous signal intensity and 50% of these lesions showed lobular internal features due to the presence of fibrous septa. All stage I thymomas were heterogeneous in signal intensity, but none demonstrated lobulation (45).

Two studies have identified indirect signs of advanced disease at MR imaging, with thymic carcinoma more likely than thymoma to demonstrate irregular contours, cystic or necrotic components, heterogeneous enhancement, and lymphadenopathy. In contrast, thymoma was found to typically show a nearly complete capsule and homogeneous enhancement (46,47). One case report has described the superior ability of whole-body MR imaging to demonstrate metastatic disease relative to multidetector CT (48).

FDG PET/CT

The role of fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT in staging of thymic epithelial neoplasms remains controversial, and it is not routinely performed. In one study of both thymoma and thymic carcinoma, PET/CT did not show any benefit over multidetector CT for the patients with thymoma; however, in thymic carcinoma, two cases with lymph node metastases and one case with pleural metastasis were identified at PET/CT and not at multidetector CT (49). Other studies have shown no ability of maximum standardized uptake value (SUV) to allow differentiation between early- and late-stage disease, but suggested that neoplasms with high SUV have a higher likelihood of requiring chemotherapy and more rigorous histologic sampling and staging (50,51).

TNM Staging System

Methodology

General Considerations.—ITMIG organized a large retrospective database of 10 808 patients with cases collected from North and South American, European, and Korean institutions and the Chinese Alliance for Research of the Thymus (CART). Additional cases were provided by the Japanese Association for Research of the Thymus (JART) and the European Society of Thoracic Surgeons.

The goal of the TD-SPFC was to create a stage classification system that was TNM based and applicable to all thymic epithelial neoplasms (5). Specific thresholds between T, N, and M categories and overall stage groupings were based on prognostically distinct groups of patients, with specific endpoints including overall survival and recurrence. However, it is important to note that with regards to thymic neoplasms, these specific clinical outcomes are only partially connected; for instance, recurrence does not necessarily result in death and patient deaths are frequently not due to disease recurrence (52).

Patients who underwent surgical resection were classified into three groups: complete surgical resection, R0; microscopic residual tumor, R1; and macroscopic residual tumor, R2. Overall survival was assessed in the R0 cohort, as well as for patients with any R status. The cumulative incidence of recurrence, which accounts for the presence of the competing risk of death, was evaluated for the R0 patients and used to estimate recurrence. In determining overall survival and cumulative incidence of recurrence, outcome was calculated from the date of intervention, which was the baseline date included in the database information, and patients were censored at the date of last follow-up. Additional factors were considered in outlining specific T, N, and M descriptors and stage groups.

It is important to note that the TNM stage classification system presented here is intended only to describe the anatomic extent of disease. Subsequent endeavors will focus on development of a prognostic index (5,52).

Tumor (T) Component.—Of the 10 808 patients included in the retrospective database, 2663 (25%) were excluded due to missing endpoints, date errors, first treatment before 1990, and missing stage or diagnosis data in 422. Thus, 8145 patients remained for analysis, most of whom were treated between 2000 and 2010 and underwent surgical resection. Complete data on the pathologic stage were available for 8084 patients, on the clinical stage for 5232 patients, on survival for 8145 patients, and on recurrence for 4732 patients. Information regarding specific involved structures was available for 7197 patients, and resection status was reported in 7726 patients, the majority of whom (6621) were R0.

The TD-SPFC assessed the impact of invasion of various mediastinal structures to formulate the T component. Specific data points included the relationship of the primary malignancy to the mediastinum and whether primary malignancies were completely encapsulated, limited to the mediastinum, or involved structures such as the mediastinal pleura, pericardium, lung, SVC, brachiocephalic artery and vein, phrenic nerve, chest wall, pulmonary artery, aorta, and myocardium (53,54). Overall survival was considered in both R0 patients and all patients regardless of surgical resection status, whereas recurrence was considered in R0 resected patients.

N and M Components.—Specific information regarding the N or M status was available for only a small subset of patients in the retrospective database, most of which was included in the cases from JART. This limitation is likely due to several factors, including the fact that early-stage thymic neoplasms are more common than advanced-stage thymic tumors, that most of the data in the retrospective database was from patients undergoing surgical resection, and that information was collected according to stage classification systems that often did not discriminate among specific details of N and M disease (55).

Because of the limited amount of data regarding the N and M components, the analysis performed was based on a visual assessment that implied a difference, similarities between the N component and a consensus-based IASLC/ITMIG thymic lymph node map, similarities between the M component and the Masaoka and Masaoka-Koga stage classification systems, practical considerations regarding the surgical approach to thymic epithelial neoplasms, and a consensus opinion regarding significant points of distinction.

Lymph Node Map.—ITMIG initiated a collaborative process with the TD-SPFC to create a lymph node map for use with thymic epithelial neoplasms. This work group considered anatomic and surgical factors and existing lymph node maps for use with other neoplasms such as lung cancers and head and neck cancers, as well as schemes previously proposed for thymic malignancies. The lymph node map developed by this work group was similar to that created by the TD-SPFC through analysis of available cases in the retrospective database, and a consistent lymph node map and N classification scheme were constructed.

Tumor (T) Classification

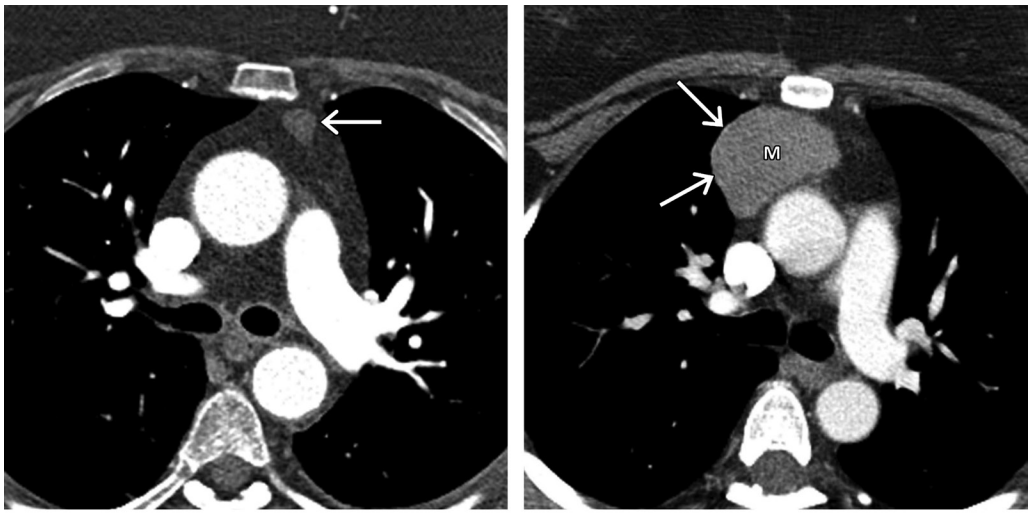
General Considerations

To determine the various T descriptors, the TD-SPFC selected an approach based on levels of involvement, as it allowed management of complex situations and was supported by outcomes data (survival and recurrence) that showed no significant difference for a particular level whether or not a lower-level structure was also involved. For instance, if a neoplasm involved one or more structures of

Table 2: Tumor (T) Descriptors

Category	Description
T1a	Encapsulated or unencapsulated tumor, with or without extension into mediastinal fat
T1b	Invasion of mediastinal pleura
T2	Invasion of pericardium
T3	Involvement of lung, chest wall, phrenic nerve, brachiocephalic vein, SVC, or hilar (extrapericardial) pulmonary vessels
T4	Invasion of thoracic aorta, arch vessels, main pulmonary artery, trachea, esophagus, or myocardium

Source.—Reference 52.



a. **b.**

Figure 1. T1 neoplasms. **(a)** T1a disease in a 49-year-old woman. Coned-down axial contrast-enhanced multidetector CT image at the level of the left pulmonary artery shows a thymoma (arrow) confined to the fat of the prevascular mediastinal compartment without involving the mediastinal pleura. These findings were confirmed at surgery as T1a disease. **(b)** T1b disease in a 41-year-old woman with thymoma. Coned-down axial contrast-enhanced multidetector CT image at the level of the left pulmonary artery shows the primary malignancy *(M)* in the right prevascular mediastinum, abutting and bulging into the mediastinal pleura (arrows), which was later proven to be involved. These findings are compatible with T1b disease.

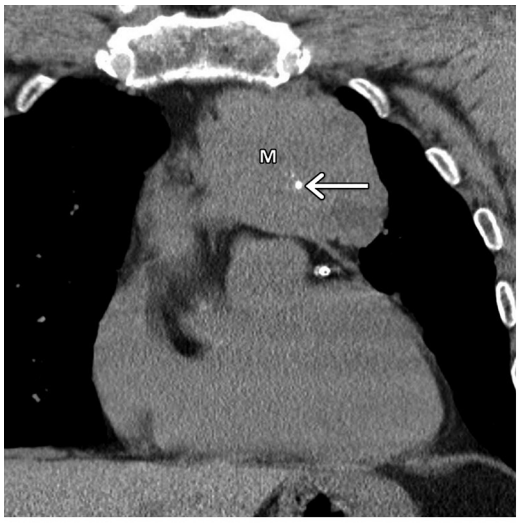
a specific level, with or without involvement of structures in a lower level, it would be assigned to the specific highest level of its involvement. Each level includes structures with similar outcomes. The specific T descriptors are listed in Table 2.

T1 Descriptor

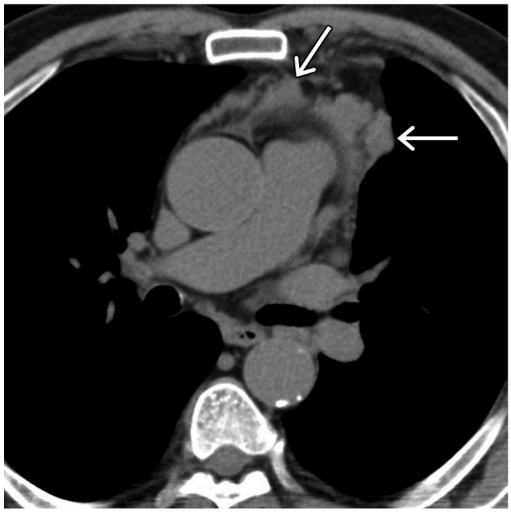
Encapsulated neoplasms and those that extend beyond the capsule into the anterior perithymic fat are classified as T1 disease (Fig 1). By this definition, the T1 descriptor includes thymic neoplasms classified as stage I or II (including IIa and IIb) in the Masaoka and Masaoka-Koga staging systems, as no consistent difference in survival or recurrence was identified among these groups or subgroups. In patients with disease limited to the thymus or perithymic fat, no significant difference in outcomes was identified whether the mediastinal pleura was involved or not, and the crude rate of recurrence or death with only mediastinal pleura involvement was similar to that of other T1 lesions. However, a slight difference in the cumulative incidence of recurrence was present in cases submitted from JART. Therefore, the TD-SPFC subdivided T1 disease into T1a (no mediastinal pleural involvement) and T1b (mediastinal pleural involvement) components.

T2 Descriptor

The T2 descriptor includes thymic neoplasms resulting in direct partial or full-thickness invasion of the pericardium, which is the only anatomic structure included in the T2 level (Fig 2). The pericardium is the most commonly involved mediastinal structure after the mediastinal pleura. Pathologic staging requires microscopic confirmation of pericardial involvement. For the purposes of clinical staging, identification of pericardial involvement at multidetector CT is often



a.



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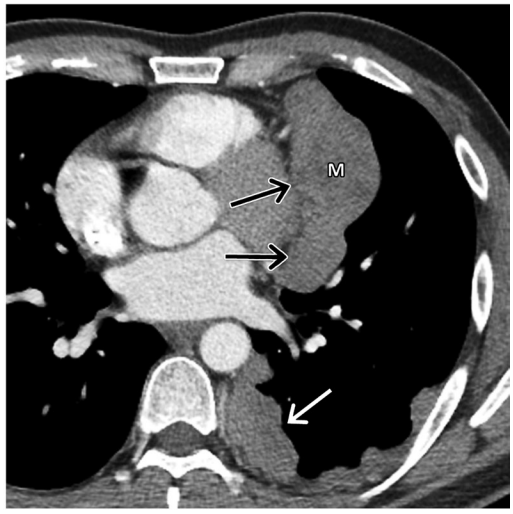


c.

Figure 2. T2 neoplasms. **(a, b)** Pericardial involvement in a 56-year-old man with thymic carcinoma. Coned-down coronal **(a)** and axial **(b)** nonenhanced multidetector CT images show a soft-tissue mass (*M* in **a**) with internal calcification (arrow in **a**), contiguous with multiple soft-tissue nodules (arrows in **b**) along the pericardium. These findings were suspicious for pericardial invasion but ultimately indeterminate; however, pericardial involvement was demonstrated at attempted surgical resection. **(c)** Pericardial invasion in a 58-year-old man with thymic carcinoma. Coned-down axial contrast-enhanced multidetector CT image at the level of the left atrium shows a heterogeneous left prevascular mediastinal mass *(M)* extending through the pericardium (black arrows), manifesting as slight obliteration of the epicardial fat. Pleural metastases (white arrow) are present in the left hemithorax.

imprecise or not possible; however, suspicion can be raised when a neoplasm abuts or surrounds a large portion of the pericardium (Fig 3).

Analysis of the database demonstrated worse survival and a higher rate of recurrence for patients with T2 disease compared with those with T1 involvement (either with or without mediastinal pleural involvement), but better survival and a lower rate of recurrence than patients with T3 disease.

T3 Descriptor

The T3 descriptor includes thymic neoplasms involving nonvascular structures such as the lung, phrenic nerve, or chest wall (Fig 4) and vascular structures such as the brachiocephalic vein, SVC, and extrapericardial pulmonary arteries or pulmonary veins (Fig 5).

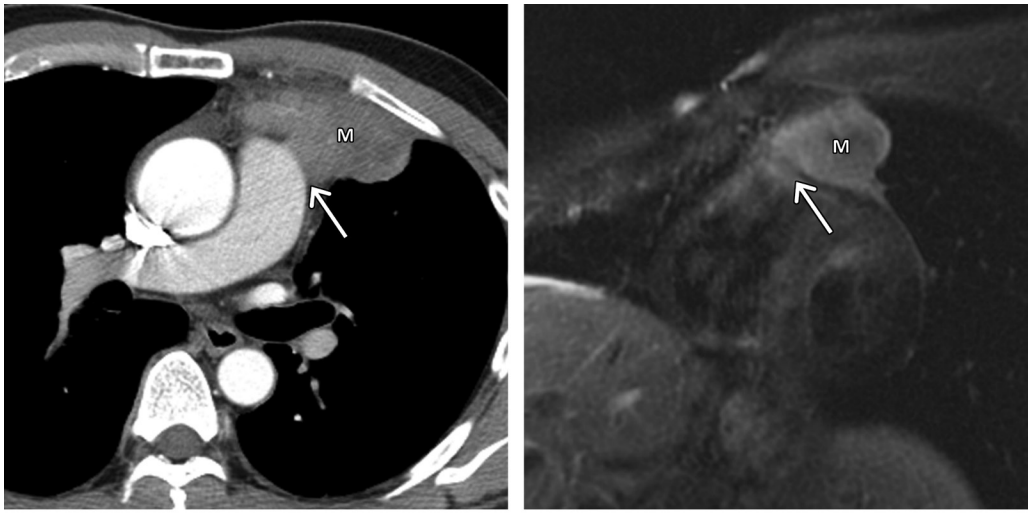
Comparison of individual structure involvement was performed, including the pericardial pleura and mediastinal pleura. Apart from mediastinal pleural involvement, which was associated with a few recurrences, no significant differences were identified.

Overall survival was similar for T2 and T3 disease; however, some differences regarding the recurrence rate for T3 structures were identified. For instance, the recurrence rate for a single level 3 structure was lower than that for involvement of multiple level 3 structures. In contrast, the recurrence rate for a single level 3 structure was higher than that for involvement of the pericardium (T2 disease). Regardless, the T3 component was judged to be clinically relevant, practically applicable, and consistent with outcomes data.

T4 Descriptor

Neoplasms involving the myocardium, intrapericardial pulmonary artery, thoracic aorta (ascending, arch, or descending), arch vessels (brachiocephalic, carotid, and subclavian arteries), trachea, and esophagus are classified as T4 disease (Fig 6). These structures are grouped together as level 4 structures.

Analysis of the retrospective database suggested an overall worse survival for patients with T4 disease than for those with T3 disease;



a. b.

Figure 3. Pericardial invasion in a 54-year-old man with thymic carcinoma. **(a)** Coned-down axial contrast-enhanced multidetector CT image at the level of the right pulmonary artery shows a heterogeneous mass *(M)* in the prevascular mediastinum and loss of the adjacent fat plane (arrow) between the lesion and the pulmonary trunk, suggestive of pericardial invasion. **(b)** Coned-down short-axis postcontrast T1-weighted MR image confirms invasion of the pericardium (arrow) by the mass *(M)*. In this case, MR imaging was superior to multidetector CT in identifying pericardial involvement.

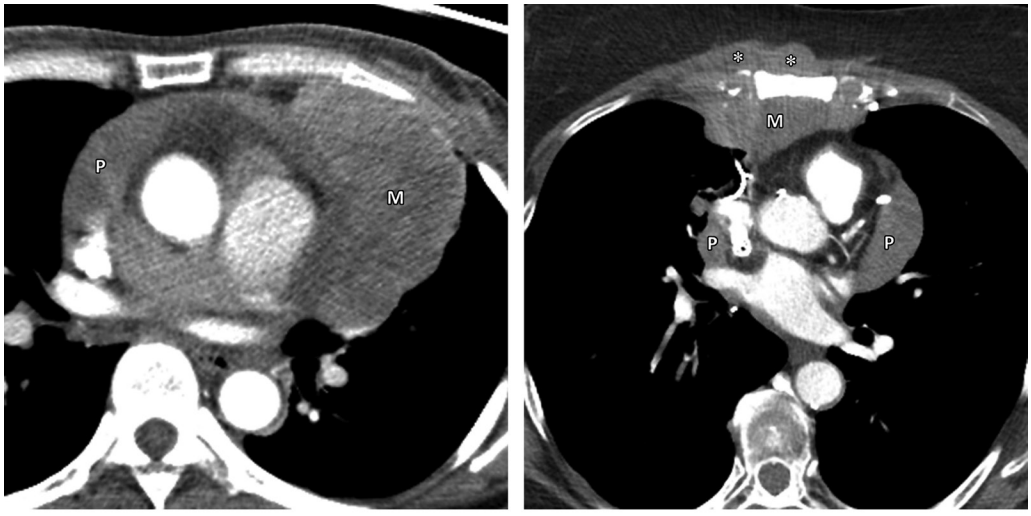


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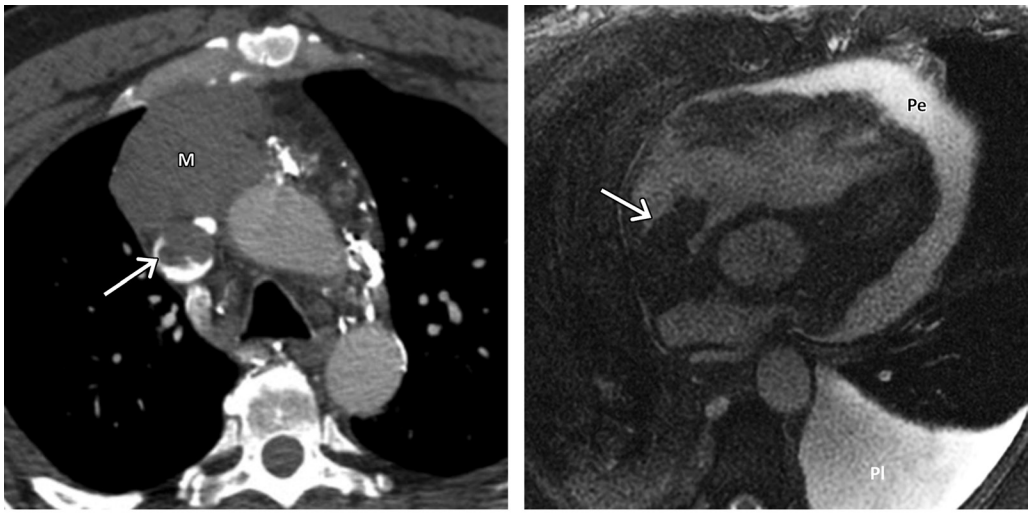
Figure 4. T3 neoplasms. **(a)** Pulmonary involvement in a 56-year-old woman with thymic carcinoma. Coned-down axial contrast-enhanced multidetector CT image at the level of the pulmonary trunk shows a heterogeneous mass *(M)* in the left prevascular mediastinum that was thought to involve the lung due to its extension into the lung, the lobular margins with respect to the lung, and its abutment to an adjacent pulmonary arterial branch. Pulmonary involvement was confirmed at attempted surgery, compatible with T3 disease. Note the pleural metastasis *(P)* along the right heart adjacent to the SVC. **(b)** Chest wall invasion in a 64-year-old woman with thymic carcinoma. Coned-down axial contrast-enhanced multidetector CT image at the level of the left atrium shows a soft-tissue mass *(M)* in the prevascular mediastinum that invades the sternum and anterior chest wall (*). Note the pleural metastases *(P)* along the heart. Neoplastic invasion of nonvascular structures such as the lung, phrenic nerve, or chest wall represents T3 disease.

however, only a limited number of cases were available. Cases were available of 31 patients with involvement of the aorta, 21 with involvement of the aortic arch vessels, 20 with involvement of the pulmonary artery, and one with involvement of the myocardium. In many cases, involvement of level 4 structures can be strongly suspected on the basis of findings at cross-sectional imaging with multidetector CT.

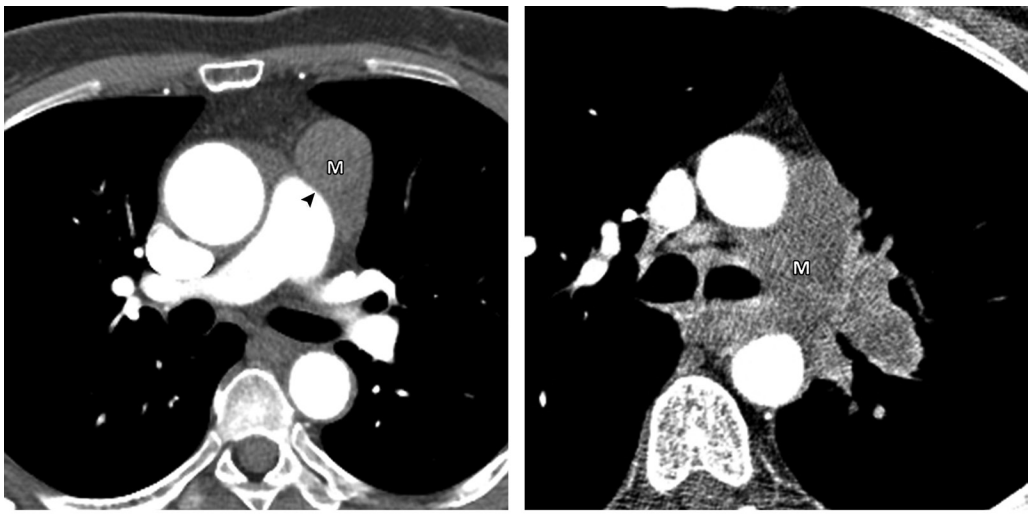
Other Tumor Features

Tumor Size.—The retrospective database included 5796 cases of thymic epithelial neoplasms with



a. b.

Figure 5. T3 neoplasms. **(a)** SVC involvement in a 67-year-old man with thymic carcinoma. Coned-down axial contrast-enhanced multidetector CT image below the level of the aortic arch shows a soft-tissue mass *(M)* in the right prevascular mediastinum with poorly defined margins that infiltrates the adjacent mediastinal fat, pericardium, and SVC (arrow). **(b)** SVC invasion in a 54-year-old man with an iodine allergy and thymoma. Coned-down oblique MR image from true fast imaging with steady-state precession (true FISP) shows extension of the tumor (arrow) into the right atrium through invasion of the SVC, which would not have been identifiable at nonenhanced multidetector CT. Note the pericardial *(Pe)* and left pleural *(Pl)* effusions. Thymic epithelial neoplasms resulting in invasion of vascular structures such as the brachiocephalic vein, SVC, and extrapericardial pulmonary arteries or pulmonary veins are consistent with T3 disease.



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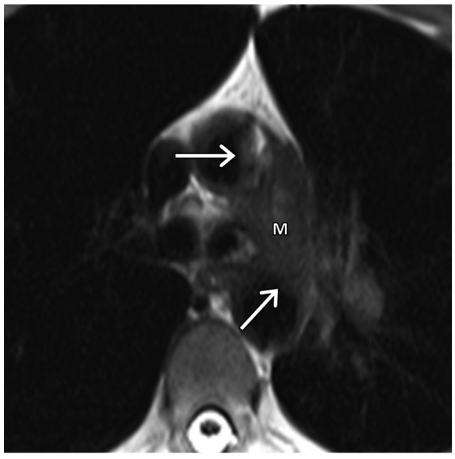


c.

Figure 6. T4 neoplasms. **(a)** Invasion of the pulmonary trunk in a 47-year-old woman with thymoma. Coned-down axial contrast-enhanced multidetector CT image at the level of the pulmonary arteries shows a soft-tissue mass *(M)* in the prevascular mediastinum that invades the pericardium (arrowhead) and results in eccentric thickening of the pulmonary trunk. This finding was suspicious for invasion of the pulmonary trunk and was better demonstrated at subsequent MR imaging (not shown). **(b, c)** Invasion of the aorta in a 47-year-old woman with thymoma. Coned-down axial contrast-enhanced multidetector CT **(b)** and T2-weighted MR **(c)** images below the carina show a soft-tissue mass *(M)* in the visceral mediastinal compartment, which represents inferior extension of the primary neoplasm. On the CT image, note the loss of distinct fat planes between the lesion and portions of the ascending and descending thoracic aorta, suspicious for invasion. The MR image shows clear invasion (arrows) of the aorta, compatible with T4 disease.

one-dimensional tumor measurements. A limited number of cases (231) were available with more than one measurement; however, a meaningful analysis of the latter was unable to be performed due to the small number. Statistical analysis of training and validation sets was performed to identify relevant thresholds for tumor size. In the R0 cohort, a size of 9.5 cm was the best threshold but was not significant. The only relevant cut point among the "any resection" cohort was 10 cm.

Although survival curves indicated a difference in the any R cohort, this was due to differences in outcomes of patients with incompletely resected lesions and no difference was present in the R0 patients. Additional investigation stratifying with the Masaoka and Masaoka-Koga stage classification systems showed that lesion size was predictive only in R1 and R2 patients with stage III and IV disease. Other analysis demonstrated that other tumor features were dominant to size in terms of separation for prognosis, and there was no evidence that it could be useful in terms of predicting the ability to perform a complete surgical resection. Because of the limited clinical utility of the tumor size marker, this was not considered further in the stage classification.

Histologic Type.—The outcomes for specific tumor descriptors followed a similar pattern for thymoma and thymic carinoma as compared with all diagnoses. No significant difference was present between T1a and T1b lesions. Involvement of the pericardium (T2 disease) was associated with a higher recurrence rate than T1 disease and a lower recurrence rate than T3 disease. The limited number of cases with data related to T4 disease prevented any assessment of outcomes of these groups within a specific histologic type of neoplasm. Additionally, the limited number of thymic neuroendocrine neoplasms prevented a separate analysis of T categories. It is important to note that neuroendocrine neoplasms were not included in the statistical analyses of thymic carcinoma but were considered in the analyses of all patients.

Lymph Node (N) Classification

The lymph node (N) descriptor is divided into three components based on the presence and location of lymph node involvement. N0 denotes absence of lymph node metastasis. N1 and N2 represent involved lymph nodes located in the anterior and deep compartments, respectively, as outlined in the specific lymph node map created for use with thymic epithelial neoplasms. The specific lymph node descriptors are listed in Table 3.

Analysis of the database revealed better survival among patients with any R status and N1 disease compared with N2 disease, with 5-year survival estimates of 69% and 47%, respectively. In this same cohort, the overall death rate of patients with N2 disease was worse than in patients with N1 disease. Evaluation of lymph node status in R0 resected patients was limited by small numbers of cases; however, survival appeared worse for N2 disease than for N1 disease with similar recurrence. However, it is important to note that the differences between N1 and N2 lymph nodes in these analyses were not statistically significant.

Table 3: Lymph Node (N) Descriptors

Category	Description
N0	No lymph node metastasis
N1	Involvement of anterior (perithymic) lymph nodes
N2	Involvement of deep intrathoracic or cervical lymph nodes

Source.—Reference 52.

This separation aligns with speculation that involvement of lymph nodes close to the thymus (N1) signifies less advanced or aggressive disease than involvement of deep (N2) lymph nodes, is similar to results of JART analyses, and corresponds to the ITMIG/IASLC consensus-based node map developed by a parallel process (56–58). The ability to distinguish between anterior and deep lymph node involvement is of interest to surgeons, as the former are typically included in an extended thymectomy, whereas the latter are not, and evaluation of lymph nodes in this region would require more extensive surgery.

Diagnosis of lymph node involvement is made by demonstration of microscopic disease. It is important to note that, similar to the IASLC/AJCC/UICC definition for lung cancer, spread to a lymph node and invasion of a lymph node are both treated as lymph node involvement. To ensure accurate staging of patients, ITMIG recommends that anterior mediastinal lymph nodes be routinely resected along with the thymus in cases of surgical resection.

For surgical resection of thymomas with invasion of mediastinal structures, systematic sampling of deep lymph nodes is encouraged (4). Systematic resection of both N1 and N2 lymph nodes is recommended during curative-intent resection for thymic carcinoma (4). In one study evaluating the role of lymph node dissection in thymic carcinoma, investigators suggested resection of anterior and paratracheal lymph nodes, especially in the setting of adjacent organ invasion; a minimum of 10 lymph nodes dissected appeared to correlate with better patient survival (59).

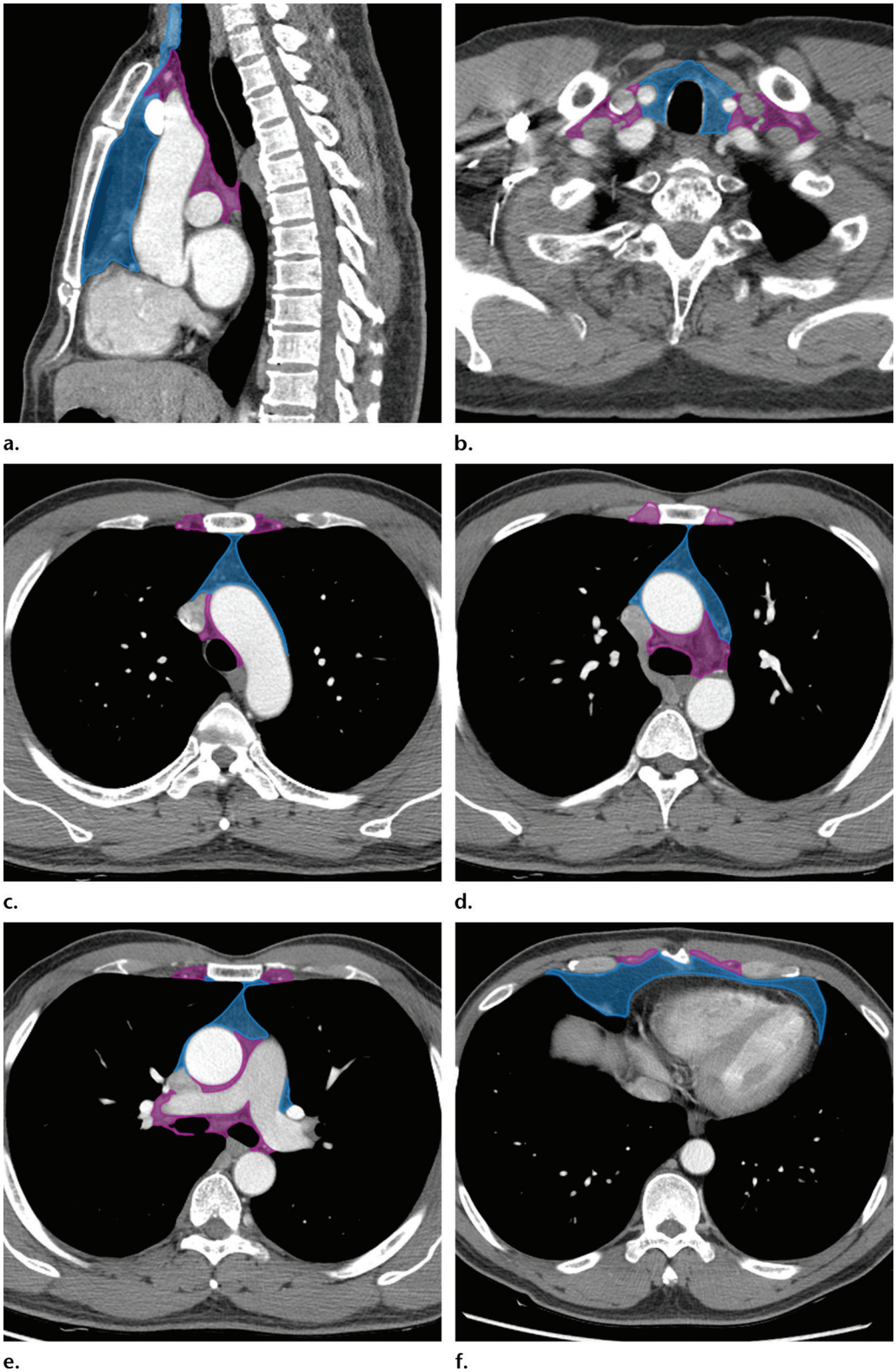


Figure 7. ITMIG/IASLC lymph node map. Sagittal contrast-enhanced multidetector CT image **(a)** and coned-down axial contrast-enhanced multidetector CT images at the level of the thoracic inlet **(b)**, aortic arch **(c)**, aortopulmonary window **(d)**, pulmonary arteries **(e)**, and base of the heart **(f)** show the anterior region (blue) and deep region (purple).

Lymph Node Map

The ITMIG/IASLC lymph node map (Fig 7) incorporates retrospective data, preexisting lymph node classifications in the IASLC and American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS)/American Society for Head

Table 4: Anterior Region (N1) (Anterior Mediastinal and Anterior Cervical Lymph Nodes)

Region or Lymph Node Group	Boundaries
Anterior region (N1)	Superior: hyoid bone Lateral (neck): medial border of carotid sheaths Lateral (chest): mediastinal pleura Anterior: sternum Posteromedial: great vessels and pericardium Posterolateral: phrenic nerve Inferior: xiphoid process and diaphragm
Low anterior cervical: pretracheal, paratracheal, perithyroid, precricoid/Delphian (AAO-HNS/ASHNS level 6, IASLC level 1)	Superior: inferior border of cricoid cartilage Lateral: common carotid arteries Inferior: superior border of manubrium
Perithymic	Proximity to thymus
Prevascular (IASLC level 3a)	Superior: apex of chest Anterior: posterior sternum Posterior: anterior SVC Inferior: carina
Para-aortic, ascending aorta, superior phrenic (IASLC level 6)	Superior: line tangential to superior border of aortic arch Inferior: inferior border of aortic arch
Supradiaphragmatic/inferior phrenic/pericardial (along inferior poles of thymus)	Superior: inferior border of aortic arch Anterior: posterior sternum Posterior: phrenic nerve (laterally) or pericardium (medially) Inferior: diaphragm

Source.—Reference 56.
Note.—Region and node group boundaries adapted directly from definitions established by the AAO-HNS, ASHNS, and IASLC.

and Neck Surgery (ASHNS) lymph node maps, and prominent lymph nodes defined by prior investigations (60–62). The lymph node map devised for thymic epithelial neoplasms defines anterior and deep regions based on boundaries that outline the peripheral extent of surgical dissection in all planes. This definition was selected because it reflects the technique used for thymic dissection, in which the specimen is removed en bloc. Anterior mediastinal lymph nodes have been described as the primary drainage pathway and other intrathoracic lymph nodes as the secondary drainage pathway (63–66). The lymph node map is outlined in Tables 4 and 5.

The anterior region contains N1 lymph nodes. The boundaries of the anterior region are as follows: superiorly, the hyoid bone; anteriorly, the sternum; laterally (in the neck), the medial border of the carotid sheaths; laterally (in the chest), the mediastinal pleura; posteromedially, the great vessels and pericardium; posterolaterally, the phrenic nerve; and inferiorly, the xiphoid process and diaphragm. These boundaries reflect the conventional dissection performed in extended thymectomy, which includes the thymus, contiguous left and right mediastinal pleura, mediastinal and pericardiophrenic fatty tissues, and para-aortic lymph nodes (67).

The anterior region encompasses anterior mediastinal lymph nodes, which include perithymic, prevascular, para-aortic, and supradiaphragmatic lymph node groups, and anterior cervical lymph nodes, which are defined by level 6 of the AAO-HNS/ASHNS classification. Perithymic lymph nodes indicate those located immediately adjacent to the thymus but not captured in one of the other lymph node categories. The posterior boundary of the region including the great vessels includes para-aortic lymph nodes (IASLC level 6) but not aortopulmonary window lymph nodes (IASLC level 5). It is important to note that the internal mammary lymph nodes are included in the deep region because they are rarely dissected in clinical practice and there is no current evidence supporting the significance of disease in this region in thymic epithelial neoplasms.

The deep region contains N2 lymph nodes. The boundaries of the deep region are as follows: superiorly, the lower border of the cricoid cartilage; anteromedially (in the neck), the lateral border of the sternohyoid muscle and medial border of the carotid sheath; anteriorly

Table 5: Deep Region (N2) (Middle Mediastinal and Deep Cervical Lymph Nodes)

Region or Lymph Node Group	Boundaries
Deep region (N2)	Superior: level of lower border of cricoid cartilage Anteromedial (neck): lateral border of sternohyoid muscle and medial border of carotid sheath Posterolateral (neck): anterior border of trapezius muscle Anterior (chest): aortic arch, aortopulmonary window–anterior border of SVC Posterior (chest): esophagus Lateral (chest): pulmonary hila Inferior: diaphragm
Lower jugular (AAO-HNS/ASHNS level 4)	Superior: level of lower border of cricoid cartilage Anteromedial: lateral border of sternohyoid muscle Posterolateral: lateral border of sternocleidomastoid muscle Inferior: clavicle
Supraclavicular/venous angle: confluence of internal jugular and subclavian veins (AAO-HNS/ASHNS level 5b)	Superior: level of lower border of cricoid cartilage Anteromedial: posterior border of sternocleidomastoid muscle Posterolateral: anterior border of trapezius muscle Inferior: clavicle
Internal mammary	Proximity to internal mammary arteries
Upper paratracheal (IASLC level 2)	Superior: superior border of manubrium, apices of lungs Inferior: intersection of lower border of innominate vein with trachea; superior border of aortic arch
Lower paratracheal (IASLC level 4)	Superior: intersection of lower border of innominate vein with trachea; superior border of aortic arch Inferior: lower border of azygos vein, superior border of left main pulmonary artery
Subaortic/aortopulmonary window (IASLC level 5)	Superior: inferior border of aortic arch Medial: ductus ligament Inferior: superior border of left main pulmonary artery
Subcarinal (IASLC level 7)	Superior: carina Inferior: upper border of lower lobe bronchus on left; lower border of bronchus intermedius on right
Hilar (IASLC level 10)	Superior: lower rim of azygos vein on right, upper rim of pulmonary artery on left Inferior: interlobar region bilaterally

Source.—Reference 56.
Note.—Region and node group boundaries adapted directly from definitions established by the AAO-HNS, ASHNS, and IASLC.

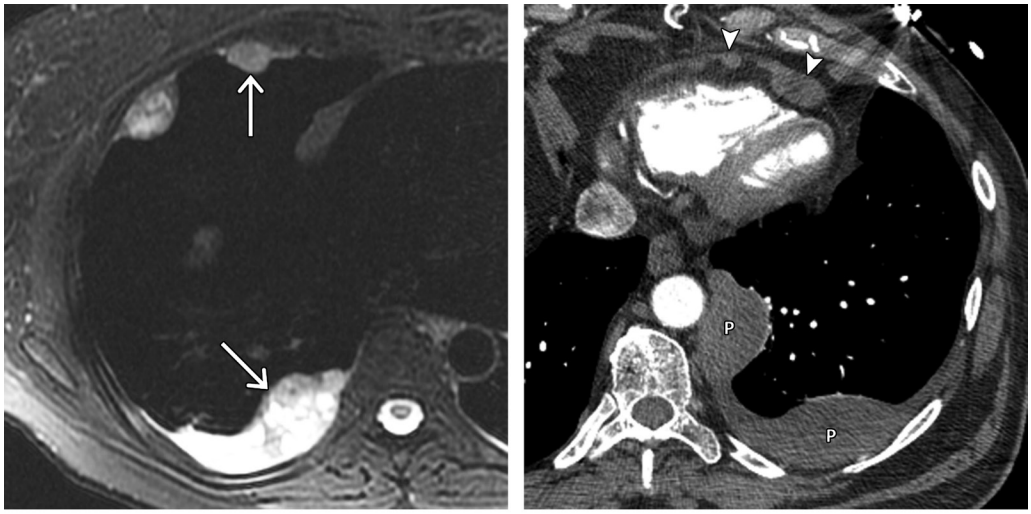
(in the chest), the aortic arch and aortopulmonary window–anterior border of the SVC; posterolaterally (in the neck), the anterior border of the trapezius muscle; posteriorly (in the chest), the esophagus; laterally (in the chest), the pulmonary hila; and inferiorly, the diaphragm. The deep region includes tracheobronchial and aortopulmonary window lymph nodes (as outlined in the IASLC lymph node map), internal mammary lymph nodes, deep cervical lymph nodes, and supraclavicular lymph nodes (as outlined by the AAO-HNS lymph node map). Aortopulmonary window lymph nodes are not always included at dissection, and there are no data regarding their prognostic significance.

All lymph nodes not included in the anterior and deep regions, such as axillary, retroperitoneal, and inguinal lymph node groups, are considered to represent extrathoracic metastases (M1b disease).

Metastasis (M) Classification

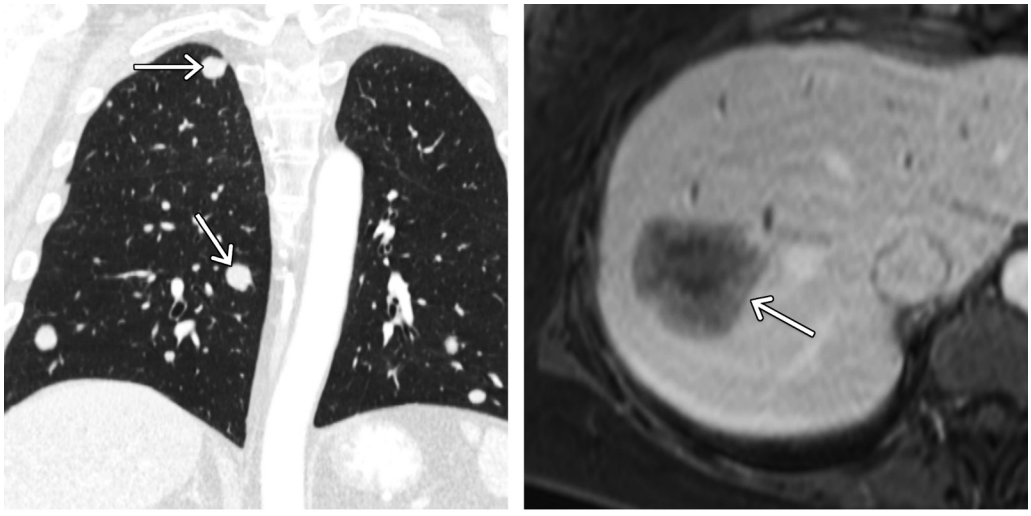
The M classification is divided into three components based on the presence and location of metastatic disease. M0 denotes absence of metastasis. M1 is subdivided into two components, M1a and M1b, based on the location of metastatic disease; M1a includes pleural and pericardial metastases (Fig 8), and M1b denotes pulmonary intraparenchymal tumor nodules and extrathoracic (or distant) metastatic disease (Fig 9). The metastasis descriptors are listed in Table 6.

The ability to investigate statistically significant differences in outcomes in different groups of patients was limited given the available data.



a. b.

Figure 8. M1a metastases. **(a)** Pleural metastases in a 38-year-old woman with thymoma. Coned-down axial T2-weighted MR image at the level of the left atrium shows multiple pleural metastases (arrows) in the right hemithorax. **(b)** Pleural and pericardial metastases in a 41-year-old man. Coned-down axial contrast-enhanced multidetector CT image near the base of the heart shows pleural metastases *(P)* in the left hemithorax and multiple pericardial nodules (arrowheads) compatible with metastases. Separate pleural or pericardial nodules are classified as M1a disease.



a. b.

Figure 9. M1b metastases. **(a)** Pulmonary metastases in a 52-year-old woman with thymoma. Coned-down coronal contrast-enhanced multidetector CT image at the level of the descending thoracic aorta shows numerous bilateral intraparenchymal pulmonary nodules (arrows) compatible with M1b metastases. **(b)** Hepatic metastasis in a 39-year-old woman with thymic carcinoma. Coned-down axial contrast-enhanced T1-weighted MR image of the upper abdomen shows a heterogeneously enhancing mass (arrow) in the right hepatic lobe. Ultrasonography (US)–guided core needle biopsy confirmed metastatic disease. Pulmonary intraparenchymal tumor nodules and extrathoracic (or distant) metastases are classified as M1b disease.

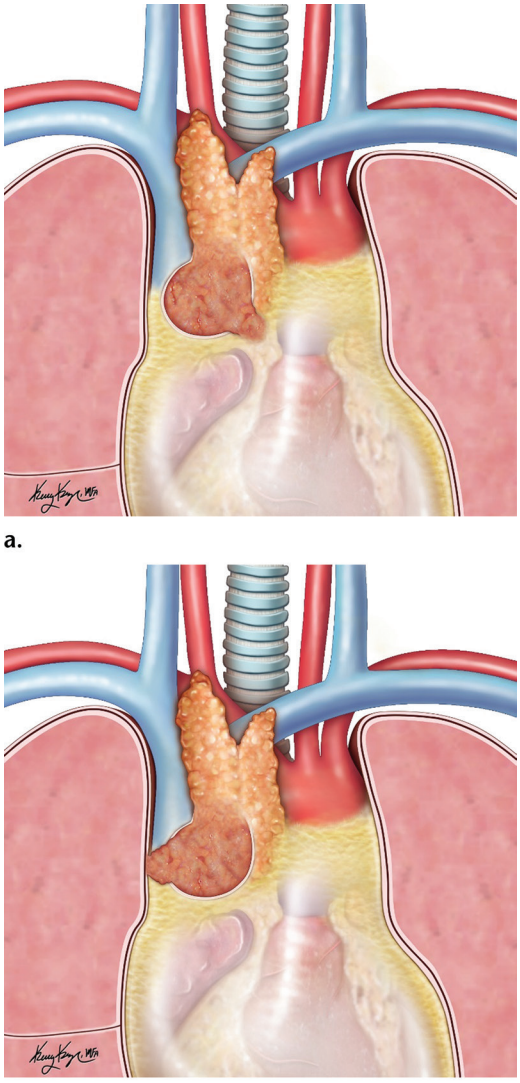
This was likely due to the fact that most cases in the retrospective database were composed primarily of surgically resected patients, and it was likely that instances of M1a and M1b disease were treated nonsurgically. Analysis of the retrospective database revealed better survival among N0 any R patients with M1a disease compared with M1b disease, with 5-year survival estimates of 71% and 56%, respectively; however, it is important to note that this difference was not statistically significant. Additionally, the overall death rate for patients with M1b disease was worse (45%) than for patients with M1a disease (31%).

Additional analyses performed by the TD-SPFC investigated whether significant differences in outcomes could be identified in patients with pleural nodules, pericardial nodules,

Table 6: Metastasis (M) Descriptors

Category	Description
M0	No metastasis
M1a	Pleural or pericardial metastatic nodule(s)
M1b	Pulmonary intraparenchymal metastatic nodule or distant-organ metastasis

Source.—Reference 52.



a.

b.

Figure 10. Stage I disease (T1N0M0). Drawings show thymic epithelial neoplasms that are predominantly encapsulated but extend into the surrounding mediastinal fat without (T1a) **(a)** or with (T1b) **(b)** direct involvement of the mediastinal pleura.

or intraparenchymal pulmonary nodules. There was no significant difference in the survival of patients with these features, although the number of cases with this information was limited.

Table 7: Stage Groups

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	T any	N1	M0
	T any	N0, N1	M1a
IVB	T any	N2	M0, M1a
	T any	N any	M1b

Source.—Reference 52.

Pleural and pericardial nodules have traditionally been grouped together, and this nomenclature is maintained, with both designated M1a. Although the database analysis suggested a slightly worse survival for patients with pericardial nodules, there was no clear difference and the number of patients was too few. However, it was decided that pulmonary parenchymal nodules should be designated as M1b disease based on the speculation regarding the mechanism of spread and consistency with the Masaoka and Masaoka-Koga stage classification systems (53).

Stage Groupings

The TNM descriptors are organized into specific stage groups as demonstrated in Table 7 and Figures 10–13. The definitions of stages I, II, IIIA, and IIIB are based predominantly on the T category in the absence of lymph node involvement (N0) and the absence of metastases (M0). In contrast, stages IVA and IVB are determined by the N or M categories. For instance, the presence of N1 or M1a disease denotes stage IVA and N2 or M1b disease represents stage IVB, regardless of the T category.

Conclusion

The TNM staging system for thymic epithelial malignancies is based on statistically sound data developed from a database containing over 10 000 patients as compared with older staging systems, which were based on less than 100 patients. Radiologists should be familiar with this system and indicate lesions that may upstage patients, particularly regions that are not routinely explored at thymectomy such as level N2 lymph nodes or distant metastases. By understanding this new TNM-based staging system, radiologists will assign more accurate clinical staging, guide the formulation of effective treatment strategies, and help optimize patient outcomes. IASLC and ITMIG hope that this staging system will

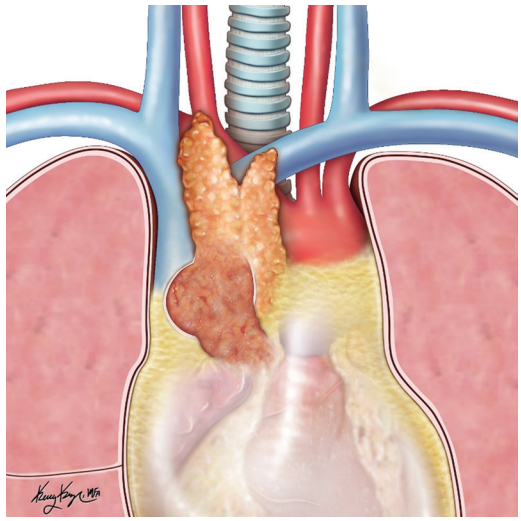
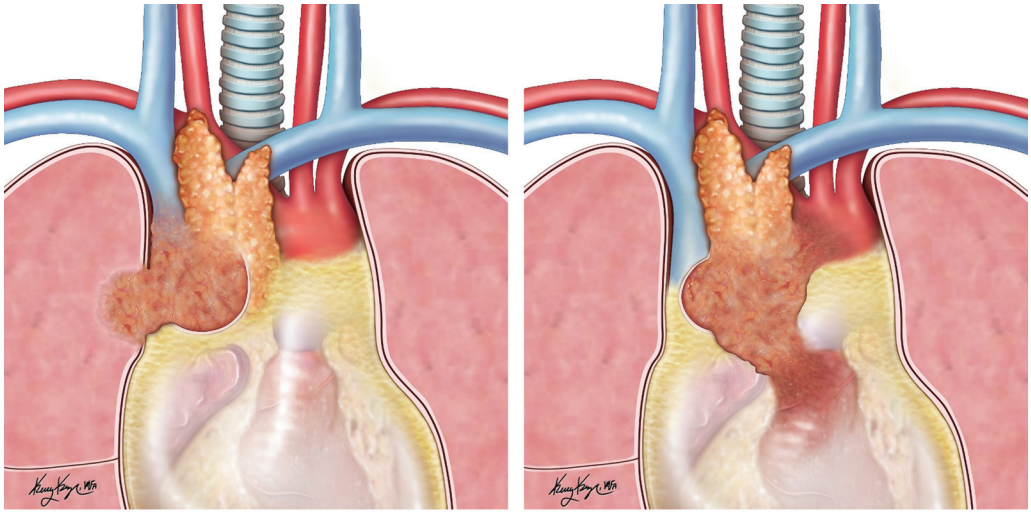


Figure 11. Stage II disease (T2N0M0). Drawing shows a thymic epithelial neoplasm invading the pericardium.



a. **b.**

Figure 12. Stage IIIa (T3N0M0) and IIIb (T4N0M0) disease. Drawings show thymic epithelial neoplasms invading the lung and SVC **(a)** and the myocardium **(b)**.

not only improve patient care but also encourage communication and collaboration between clinicians and researchers of all specialties dealing with this group of malignancies.

Acknowledgment.—The authors thank Kelly Kage for creating the drawings in Figures 10–13.

***Disclosures of Conflicts of Interest.*—M.L.R.d.C.** *Activities related to the present article:* disclosed no relevant relationships. *Activities not related to the present article:* book royalties from the American Registry of Pathology, Thieme Medical Publishers, and Amirsys Elsevier. *Other activities:* disclosed no relevant relationships.

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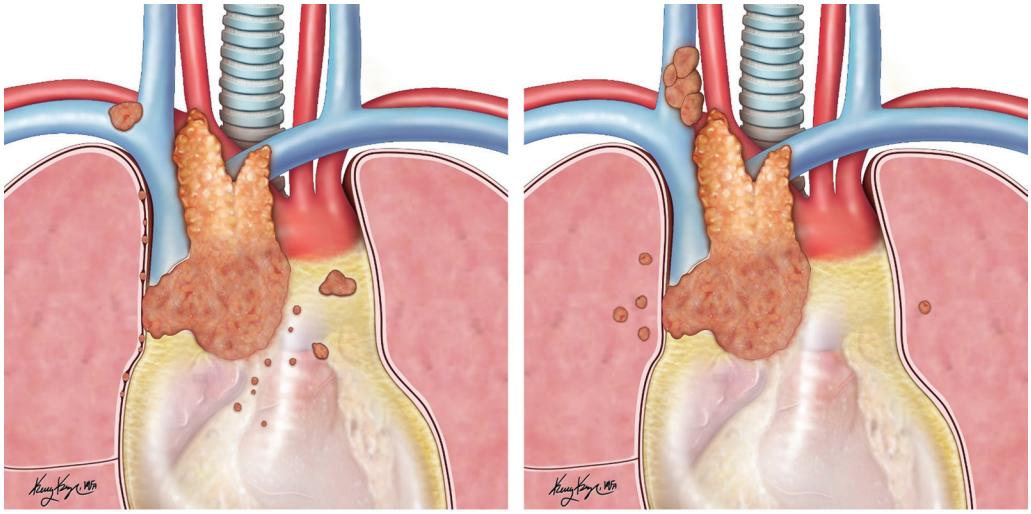

a. b.

Figure 13. Stage IVa and IVb disease. Drawings show thymic epithelial neoplasms resulting in involvement of anterior region lymph nodes (N1) and separate pleural and pericardial nodules (M1a) **(a)**, as well as involvement of deep region lymph nodes (N2) and intraparenchymal pulmonary nodules (M1b) **(b)**.

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