Thymic Epithelial Neoplasms
Tumor-Node-Metastasis Staging

Marcelo F.K. Benveniste, MD[a,*], Sonia L. Betancourt Cuellar, MD[a], Brett W. Carter, MD[b], Chad D. Strange, MD[a], Edith M. Marom, MD[c]

KEYWORDS

• Thymic epithelial neoplasms • Thymoma • Thymic carcinoma • Thymic neuroendocrine tumors • TNM • Staging

KEY POINTS

- Despite sharing a standardized staging system and many imaging characteristics, thymic epithelial neoplasms, including thymoma, thymic carcinoma, and thymic neuroendocrine tumors, differ from each other in several key clinical characteristics.
- The tumor-node-metastasis (TNM) staging system developed for thymic epithelial neoplasms correlates with patient survival and outcomes.
- The individual TNM descriptors are organized into specific stage groups.
- As part of the International Association for the study of Lung Cancer/International Thymic Malignancy Interest Group staging project, a lymph node map was developed that is similar to those developed for other neoplasms such as lung cancer.
- Although computed tomography (CT) is the imaging modality of choice for assessing the primary tumor and determining the T stage, MR imaging may be used to help assess for local invasion, and fluorodeoxyglucose PET/CT can be useful in identifying involved lymph nodes and metastases that may be overlooked on CT.

INTRODUCTION

Thymic epithelial neoplasms, a group of tumors including thymoma, thymic carcinoma, and thymic neuroendocrine cancers, are the most common primary malignancies of the prevascular mediastinum.[1] As surgical resection is the cornerstone of treatment, accurate staging is necessary to differentiate between patients who are operative candidates and those who are not.[2] Numerous staging systems have been developed over the years; however, their interpretation and implementation has been nonuniform. A partnership between the International Association for the study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) recently resulted in the creation of the first tumor-node-metastasis (TNM) staging system, which was adopted by the Union Internationale Contre le Cancer (UICC) and the American Joint Commission on Cancer (AJCC),[3–5] effectively replacing previous staging schemes in January 2017.[6] The objective of this article is to review the TNM staging system developed for thymic epithelial neoplasms and the role of imaging.

GENERAL CONSIDERATIONS

Despite sharing the same staging system and many imaging characteristics, thymoma, thymic carcinoma, and carcinoid tumors differ from each other in several key clinical characteristics.

[a] Division of Diagnostic Imaging, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1478, Houston, TX 77030, USA; [b] Department of Thoracic Imaging, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1478, Houston, TX 77030, USA; [c] Department of Diagnostic Radiology, The Chaim Sheba Medical Center, Affiliated with the Tel Aviv University, Tel Aviv, 2 Derech Sheba, Ramat Gan 5265601, Israel
* Corresponding author. Department of Thoracic Radiology, The University of Texas MD Anderson Cancer Center, Unit 1478, 1515 Holcombe Boulevard, Houston, TX 77030.
E-mail address: mfbenveniste@mdanderson.org

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Thymoma, the most common thymic epithelial neoplasm, typically occurs in patients older than 40 years, peaking in the seventh decade, and affects men and women equally.[1,7] Most thymomas are solid neoplasms that are localized to the thymus but may exhibit aggressive behavior such as invasion of adjacent structures. Although involvement of the pleura and pericardium may occur, distant metastases are rare. With the widespread availability and increased use of computed tomography (CT), a greater number of thymomas are incidentally discovered while patients are asymptomatic. When patients present with clinical symptoms, such as dysphagia, diaphragm paralysis, or superior vena cava syndrome, these are usually related to local effects from compression or invasion of adjacent structures.[8] Other patients may present with paraneoplastic syndromes, the most common of which is myasthenia gravis. Between 30% and 50% of patients with thymoma have myasthenia gravis, whereas only 10% to 15% of patients with myasthenia gravis have a thymoma.[9] Additional paraneoplastic syndromes such as hypogammaglobulinemia and pure red cell aplasia are seen in 10% and 5% of patients with thymoma, respectively.[10] Thymoma has also been associated with autoimmune disorders such as systemic lupus erythematosus, polymyositis, and myocarditis.[11]

Thymic carcinoma comprises 20% of thymic epithelial neoplasms, with a mean age of 50 years at presentation.[12,13] It is more aggressive than thymoma and is more likely to result in local invasion and intrathoracic lymphadenopathy. At presentation, 50% to 65% of patients have distant metastases.[14,15] Symptoms usually relate to the intrathoracic 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 comprise only 2% to 5% of thymic epithelial neoplasms, most of which are carcinoid tumors.[16] Thymic neuroendocrine tumors are more frequent in men, typically occurring in the fourth and fifth decades of life.[17] Clinical symptoms reported by patients and imaging findings on cross-sectional imaging are similar to those encountered in thymic carcinoma.[18] One-third of patients are asymptomatic, and the tumor may be discovered when imaging is performed as routine surveillance of patients with multiple endocrine neoplasia type 1, as they are predisposed to develop thymic carcinoids.[16] Acromegaly, syndrome of inappropriate secretion of antidiuretic hormone, and carcinoid syndrome, although rare, are paraneoplastic syndromes associated with thymic neuroendocrine tumors.[19,20]

PROGNOSTICATION

Multiple key pieces of information related to thymic epithelial neoplasms affect patient prognosis, including anatomic spread of disease, histologic classification, age, and functional status. The histologic classification of thymic epithelial neoplasms was most recently updated by the World Health Organization (WHO) Consensus Committee in 2015.[21] Thymomas are classified into 5 separate histologic subtypes—A, AB, B1, B2, B3—based on the morphology of the neoplastic epithelial cells together with the lymphocyte. Thymic carcinomas are divided into multiple histologic subtypes including adenocarcinoma, squamous, basaloid, mucoepidermoid, lymphoepithelioma-like, clear cell, and sarcomatoid carcinomas. Thymic neuroendocrine tumors are divided into carcinoid, large cell carcinomas, and small cell carcinomas. Although thymic carcinoma and thymic neuroendocrine neoplasms are associated with a poorer prognosis compared with thymoma, the different subtypes of thymoma have little practical clinical use. The WHO histologic classification lacks inter- and intraobserver reproducibility and clinical predictive value.[22,23] In addition, multiple WHO subtypes are often present in the same tumor, which makes classification more challenging especially in needle biopsy specimen where the predominant tumor subtype may not be sampled.[23] Management decisions rest primarily on the stage of disease and the completeness of resection, both of which were repeatedly found to correlate with prognosis.[24–26]

Multiple anatomic staging schemes have been used over the years, all based on small series from single institutions.[27] Before 2017, the most widely used staging systems included the Masaoka system, proposed in 1981, based on 91 patients,[28] or and its variant, the Masaoka-Koga system, proposed in 1994, based on 79 patients.[29] The Masaoka-Koga staging is based on the gross and microscopic properties of the tumor. Stage I tumors are characterized by complete encapsulation; stage II by microscopic invasion through the capsule (IIa) or macroscopic invasion into surrounding fat (IIb); stage III by invasion into any neighboring organs such as the pericardium, great vessels, trachea, esophagus, or lung; and stage IV by pleural or pericardial metastases (IVa) or hematogenous or lymphatic metastases (IVb).

Several limitations of the Masaoka-based staging systems have been described. The reliance on a capsule for staging was difficult, as not all thymomas have a complete capsule. Masaoka stage III included involvement of many organs; however, the staging was based on such a small number of

patients that there was insufficient statistical power to address the nuances of the stage. The TNM staging system developed by the IASLC and ITMIG used a retrospective database of 10,808 cases gathered from 105 institutions worldwide, which correlates with overall survival.[30]

TUMOR-NECROSIS-METASTASIS DESCRIPTORS

Primary Tumor

The tumor (T) descriptor is determined by the presence and extent of local tumor invasion[5] (**Table 1**). T1 describes encapsulated or unencapsulated tumors with or without extension into the adjacent prevascular (perithymic) mediastinal fat. The T1 category is further divided into T1a with no mediastinal pleural involvement or T1b with direct invasion of the mediastinal pleura (**Fig. 1**). T2 describes lesions with direct invasion of the pericardium (**Fig. 2**). T3 is characterized by tumor involvement of the lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins (**Fig. 3**). Finally, T4 tumors include those that invade the aorta (ascending, arch, or descending), aortic arch vessels (brachiocephalic, carotid, and subclavian arteries), intrapericardial pulmonary artery, myocardium, trachea, or the esophagus (**Fig. 4**).

Regional Lymph Nodes

The lymph node (N) descriptor is determined by the presence or absence of intrathoracic lymph node involvement. *The N stage defines lymph node regions as defined by the IASLC/ITMIG project*[31] *(KP)*. N0 describes the absence of lymph node metastasis. N1 and N2 represent involved lymph nodes located in the prevascular and deep spaces of the mediastinum, respectively, as outlined in the specific lymph node map created for use with thymic epithelial neoplasms (**Fig. 5**). N1 node includes prevascular mediastinal and perithymic lymph nodes, and N2 disease describes deep intrathoracic and cervical lymph nodes, including tracheobronchial and aortopulmonary window, internal mammary, deep cervical, and supraclavicular lymph nodes (see **Table 1**).

Distant Metastases

The metastasis (M) descriptor is divided into 3 categories based on the presence and location of metastatic disease (see **Table 1**). M0 indicates the absence of metastasis. The M1 descriptor is subdivided into 2 components—M1a and M1b—and reflects whether pleural and pericardial nodules (M1a) (**Fig. 6**) or distant organ metastases (M1b), including pulmonary intraparenchymal metastatic nodules and extrathoracic (distant) metastases, are present (**Fig. 7**).

Stage Groups

The individual TNM descriptors are organized into specific stage groups (KP) (**Fig. 8**). The definitions of stages I, II, IIIA, and IIIB are based on the T category in the absence of lymph node involvement (N0) and the absence of metastases (M0). In addition, the M stage separates pleural or pericardial

Table 1
Tumor staging

T	T1a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
	T1b	Extension into mediastinal pleura
	T2	Involvement of pericardium
	T3	Involvement of lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
	T4	Involvement of aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus
N	N0	No lymph node metastasis
	N1	Involvement of anterior (perithymic) lymph nodes
	N2	Involvement of deep intrathoracic or cervical lymph nodes
M	M0	No metastasis
	M1a	Pleural or pericardial metastatic nodules
	M1b	Pulmonary intraparenchymal metastatic nodule or distant organ metastasis

From Detterbeck, F.C., et al., The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol, 2014. 9(9 Suppl 2): p. S65-72; with permission.

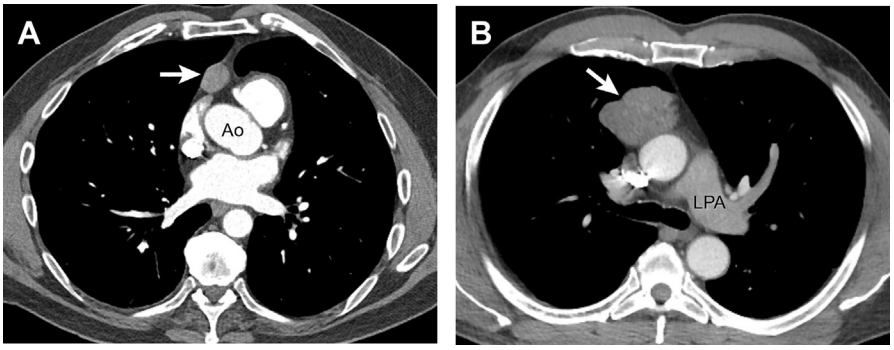

Fig. 1. T1 tumors. (*A*) Contrast-enhanced axial CT of the chest at the level of the ascending aorta (Ao) shows a 3-cm oval mass in the right prevascular mediastinum (*arrow*) surrounded by fat. A thymoma with no capsular invasion was diagnosed at surgery, representing T1a disease. (*B*) Contrast-enhanced axial CT of the chest at the level of the left pulmonary artery (LPA) shows a 6-cm thymoma abutting the ascending aorta with a lobular contour with the lung (*arrow*). At surgery there was tumor invasion into perithymic adipose tissue and pleura only. Abutment of structures, such as the aorta or lung, does not necessarily translate to invasion.

nodules (M1a) from pulmonary nodules or distant metastases (M1b). In contrast, stages IVA and IVB are determined by the N or M categories, regardless of the T descriptor (see **Fig. 8**).

LIMITATIONS OF THE TUMOR-NECROSIS-METASTASIS STAGING SYSTEM

Although the newly developed TNM staging system for thymic epithelial neoplasms described herein enables more detailed prognostication based on anatomic tumor spread, a few notable limitations have been described. Because most of the collected data were based on surgical cases, advanced disease is underrepresented when compared with earlier stage thymic epithelial neoplasms.[3] Tumor size, a quantitative parameter that can be easily be assessed, is used in staging other intrathoracic malignancies and is not part of the TNM staging system, as it did not correlate with advanced disease or overall survival and did not predict the ability to perform complete tumor resection.[5,32] Despite the size of the dataset used to develop the TNM staging system, a limited number of cases with T4 disease prevented a detailed assessment of behavior based on involvement of different organs within a specific histologic type of neoplasm. In addition, the small number of thymic neuroendocrine neoplasms limited a separate analysis of T categories in this tumor type.[3]

TREATMENT

Treatment of thymic epithelial neoplasms is based on staging, although there are no standardized guidelines concerning optimal management.[33] The main role of clinical staging is to distinguish between early disease (stage I) and advanced disease (stages II–IV), identifying candidates that may benefit from preoperative neoadjuvant therapy. A multidisciplinary approach should be developed before treatment decisions are made, including involvement of thoracic surgeons, medical oncologists, radiation oncologists, and diagnostic radiologists. Surgical resection is the cornerstone of treatment of thymic epithelial neoplasms.[2] The goal is complete resection, even in advanced stages when neighboring organs are involved, as it improves survival and has been shown to be the most important predictor of outcomes.[2,34,35] There is general agreement that early stage disease is treated with surgical resection. With incomplete surgical resection confirmed by microscopic disease at the surgical site, multimodality therapy, including chemotherapy and postoperative radiotherapy, is recommended to

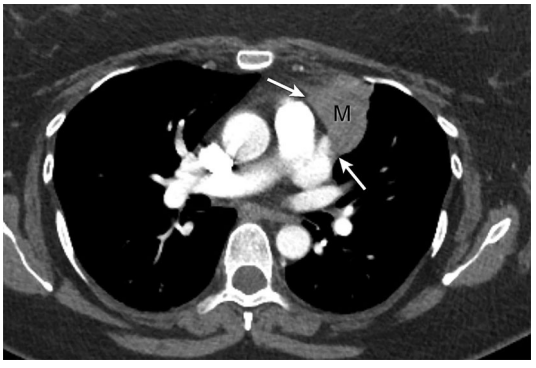

Fig. 2. T2 tumor. Contrast-enhanced axial CT of the chest demonstrates a 4-cm mass (M) abutting the pericardium (*arrows*). At surgery, a thymic carcinoma involving the perithymic adipose tissue and pericardium was detected, consistent with a T2 tumor.

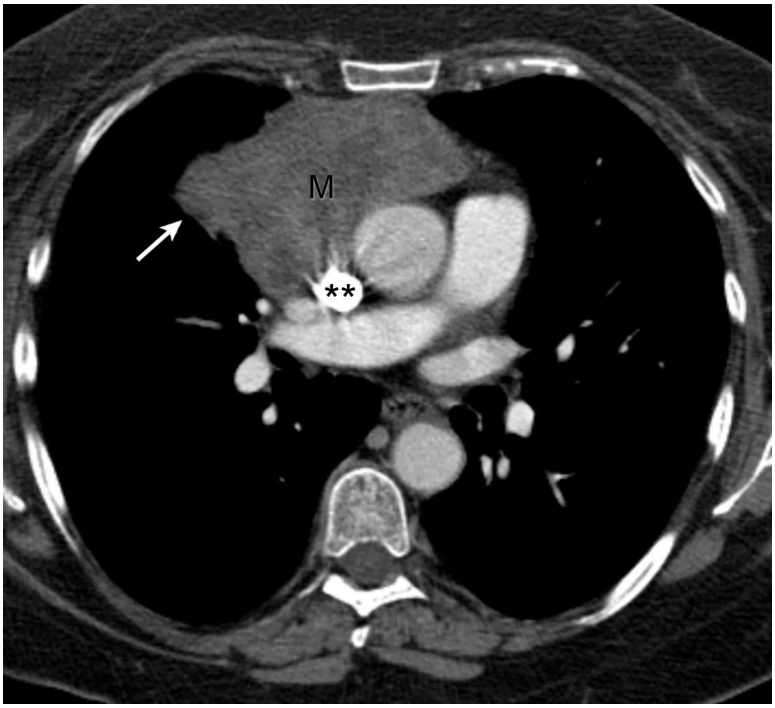

Fig. 3. T3 tumor. Contrast-enhanced axial CT of the chest demonstrates a prevascular mediastinal mass (M), which forms a lobular border with the lung (*arrow*) and surrounds a portion of the superior vena cava (*double asterisk*). At surgery, a thymoma was diagnosed and involvement of the lung and superior vena cava was confirmed, the findings of which are consistent with T3 disease.

achieve complete disease eradication.[33,36,37] Neoadjuvant chemotherapy is recommended for potentially resectable locally advanced thymic malignancies.[38,39] Following surgical resection, postoperative radiation therapy is recommended, as these patients are at higher risk of recurrence.[40] Solitary metastasis and ipsilateral pleural metastatic disease are managed surgically combined with chemoradiotherapy. Patients with extrathoracic metastases are treated with chemotherapy with palliative intent.

THE ROLE OF IMAGING AND ITS LIMITATIONS

Although staging is determined by histologic examination of the resected tumor, initial treatment decisions are imaging based, determining those patients that receive upfront surgery, neoadjuvant therapy followed by surgery, and those who are not surgical candidates. Thus, the role of the radiologist is to identify local tumor invasion and spread of tumor to mediastinal lymph nodes, pleura, pericardium, and distant organs.

Chest Radiography

The role of chest radiography in clinical staging is limited, although findings that suggest locally advanced disease, including irregular borders of the mediastinal mass and elevation of the hemidiaphragm related to phrenic nerve involvement, may be ascertained.

Computed Tomography

CT is the imaging modality of choice for staging thymic epithelial neoplasms, as it provides excellent spatial resolution for identifying local invasion. The use of intravenous iodinated contrast material

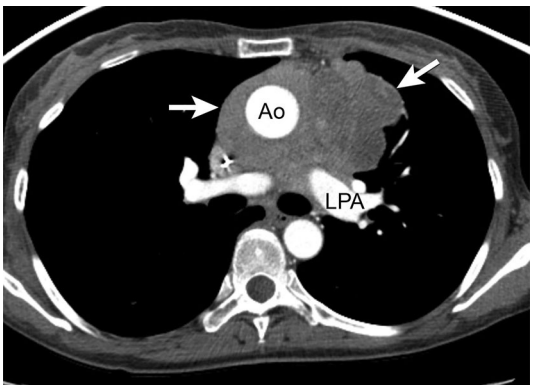

Fig. 4. T4 tumor. Contrast-enhanced axial CT of the chest shows a large prevascular mediastinal mass (*arrows*) encircling the ascending aorta (Ao) and left pulmonary artery (LPA). At surgery, this thymoma involved the mediastinal pleura, lung parenchyma, pericardium, aorta, and left pulmonary artery, consistent with a T4 tumor.

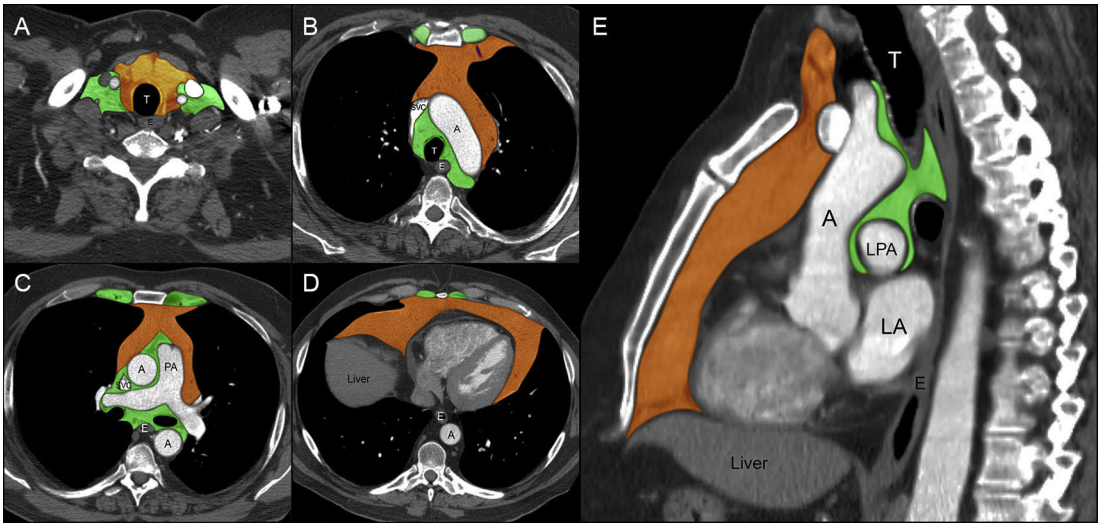

Fig. 5. The lymph node map developed by IASLC and ITMIG. (*A*) Axial CT images (*A–D*) at the level of the thoracic inlet (*A*), transverse aorta (*B*), pulmonary artery (*C*), and base of the heart (*D*) show N1 lymph nodes (*orange*), including anterior cervical and prevascular mediastinal lymph nodes, and N2 disease (*green*), including deep cervical and visceral mediastinal lymph nodes. Sagittal CT images (*E*) demonstrate N1 lymph nodes (*orange*) and N2 lymph nodes (*green*). T, trachea; E, esophagus; A, aorta; SVC, superior vena cava; PA, pulmonary artery; LPA, left pulmonary artery; ITMIG, International Thymic Malignancy Interest Group; IASCL, International Association for the Study of Lung Cancer. (*From* Bhora, Y.F., et al., The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification of Malignant Tumors. Journal of Thoracic Oncology, 2014. 9(9 Suppl 2): p. S88-S96; with permission.)

is indicated for this purpose. Direct signs of invasion include endoluminal soft tissue, irregularity of the vessel lumen, and vascular encasement or obliteration. Although the assessment of tumor extension into the lung by CT is limited, findings such as a lobular lung-tumor border are suggestive. However, confirmation of this extent of invasion is usually delineated at surgery. The role of CT in differentiating tumor abutment from involvement of adjacent structures is also limited. Prior studies have demonstrated that detection of tumor abutting greater than or equal to 50% of a vessel circumference correlates with advanced disease (Masaoka-Koga stage III–IV) and is a potential predictor of an incomplete tumor surgical resection.[41,42] *When assessing the N and M descriptors, CT has a high sensitivity for detecting lesions suspicious for metastatic disease (KP).* Involvement of cardiac structures such as the epicardial fat and pericardium may be identifiable on CT (**Fig. 9**). Pericardial effusion may suggest cardiac metastasis although tumors invading the pericardium may cause an inflammatory reaction with consequent effusion as well.[43]

MR Imaging

MR imaging is typically used as a problem-solving tool for staging questions arising from CT imaging or is reserved for assessing patients with a contraindication to intravenous iodinated contrast material.[32] MR imaging is characterized by superior contrast resolution related to CT and may be used to better define local invasion but also has the ability to image in motion for the assessment of adherence/invasion and functionality of the phrenic nerve when there is concern for invasion. Fat-suppression techniques may be useful in differentiating tumor involvement from

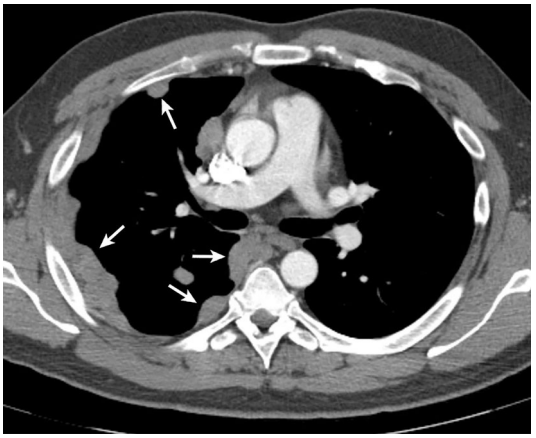

Fig. 6. M1a disease. Contrast-enhanced axial CT of the chest shows multiple right pleural metastases (*arrows*) from a thymoma (not shown).

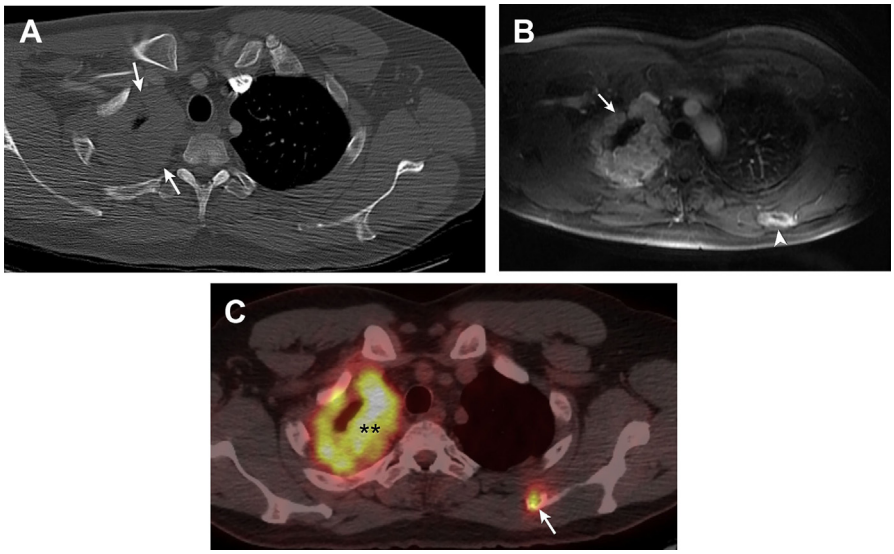

Fig. 7. M1b disease. (*A*) Contrast-enhanced axial CT of the chest demonstrates concentric right pleural nodular thickening (*arrows*) consistent with pleural metastatic disease from thymic carcinoma (not shown). (*B*) Axial T1-weighted fast spin echo with fat saturation MR image after the administration of paramagnetic intravenous contrast, performed 3 days following the CT, shows the right circumferential pleural metastatic disease (*arrow*) and an enhancing left scapular metastasis (*arrow head*). With its superior contrast resolution, MR imaging is a valuable tool in the assessment of the chest wall and soft tissues and in identifying distant metastatic disease that may be overlooked on CT. (*C*) Fused axial FDG PET/CT shows marked FDG uptake in the metastases to the pleura (*double asterisk*) and scapula (*arrow*), typical of thymic carcinoma.

surrounding fat. Cardiac MR imaging is the optimal imaging modality for evaluating suspected or known involvement of the heart and/or pericardium (see **Fig. 9**). In addition, MR imaging is considered superior to CT in identifying chest wall invasion and may result in improved visualization of soft tissue metastases previously undetected on CT (see **Fig. 7**B).[44] A study comparing tumor stage according to IASCL/ITMIG classification in 64 patients with thymic epithelial neoplasms showed that the staging capabilities of MR imaging were superior compared with CT.[45] There is controversy regarding the ability of apparent diffusion coefficient (ADC) values to

		PRIMARY TUMOR (T)					
		T1	T2	T3	T4		
LYMPH NODES (N)	N0	I	II	IIIA	IIIB	M0	METASTASIS (M)
	N1	IVA					
	N0, N1	IVA				M1a	
	N2	IVB				M0, M1a	
	Any N	IVB				M1b	

Fig. 8. Tumor stage groups.

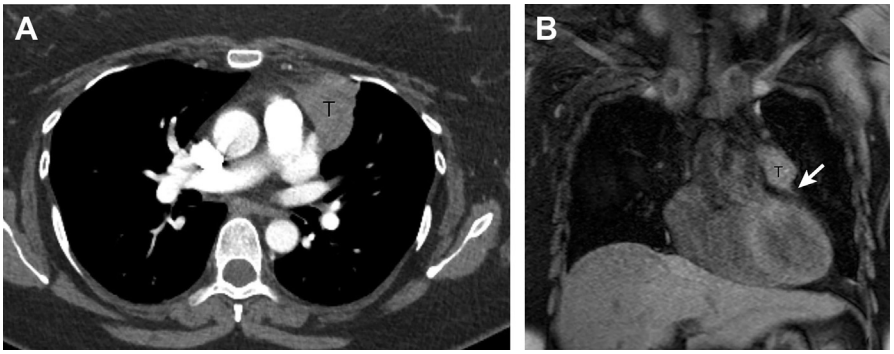

Fig. 9. Pericardial Involvement. (*A*) Contrast-enhanced chest CT scan demonstrates 4 cm anterior mediastinal tumor (T) abutting the pericardium with no obvious pericardial involvement. (*B*) Coronal axial T1-weighted fast spin echo with fat saturation shows the tumor (T) with extends into the adjacent pericardium (*arrow*). At surgery a thymic carcinoma involving the pericardium was detected. MRI of the chest is beneficial in challenging cases for assessment of pericardial and cardiac involvement.

predict tumor stage. A study of 30 patients with thymic epithelial neoplasms demonstrated a statistically significant difference in ADC values for early stage versus advanced stage disease,[46] although a different analysis of 41 patients evaluated with MR imaging showed that ADC values could not discriminate early from advanced disease.[47]

Nuclear Medicine

In general, fluorodeoxyglucose (FDG) PET/CT does not have a routine role in staging of thymoma. In a study assessing 51 patients with thymic epithelial neoplasms, there was no association between higher FDG uptake and advanced disease.[48]

FDG PET/CT has no role in T-staging due to its poor spatial resolution. However, as with other malignancies, FDG PET/CT is particularly useful for determining the N and M descriptors and sometimes identifying findings overlooked by CT (see **Fig. 7**C). Unfortunately, there are thymomas that are not FDG-avid, and thus, for them, FDG PET/CT is not useful. However, because thymic carcinoma has high FDG uptake and has a tendency to present at advanced stage, FDG PET/CT may play an important role for the assessment of these tumors. For example, a study assessing FDG PET/CT in 33 patients with thymic carcinoma demonstrated benefit by enabling detection of lymph node and distant metastases originally overlooked by CT.[49]

^{68}Ga-labeled somatostatin analogues, including ^{68}Ga-DOTATATE or ^{68}Ga-DOTA-try-octreotide (DOTATOC), have replaced imaging with Indium^{111} Octreotide. As PET radiotracers, they provide improved spatial resolution for disease detection as compared with Indium^{111} Octreotide.[50] Preoperative ^{68}Ga-DOTA-somatostatin analogue-PET/CT has shown increased detection rates of neuroendocrine tumors and may serve as an additional tool for assessment of disease spread in thymic epithelial neoplasms.[51,52] However, imaging with somatostatin analogues is usually reserved for selection of candidates for second-line chemotherapy with somatostatin analogues.

SUMMARY

The TNM staging system for thymic epithelial neoplasms is inconclusive of all malignant tumors classified as such, is universally accepted, and correlates with survival. Imaging enables accurate staging of patients and determination of effective treatment strategies. Thus, radiologists should be familiar with this system to correctly differentiate between patients who may benefit from upfront surgery and those who require neoadjuvant therapy.

CLINICS CARE POINTS

- To understand different staging systems for thymic malignancies and implications in prognosis and treatment.
- To identify role of imaging modalities and its limitations in the TNM staging of thymic malignancies.

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