Advances in Thymoma Imaging

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Abstract: Thymoma is the most common primary neoplasm of the anterior mediastinum, but it accounts for <1% of all adult malignancies. It is the most common of the thymic epithelial neoplasms, which, in addition to thymoma, include thymic carcinoma and thymic carcinoid. Because of the rarity of thymoma, it has not been studied thoroughly. Over the last half decade, there has been increased interest in this disease, with greater international collaboration and dedicated thymic malignancy work groups; this has culminated in the formation of the International Thymic Malignancy Interest Group, instituted to provide a scientific infrastructure for the study of these lesions and foster collaborative research. Imaging plays a major role in the identification and staging of thymoma, as well as in the follow-up monitoring for its recurrence. Currently, imaging is predominantly carried out with computed tomography (CT). In selected cases, there is a role for magnetic resonance imaging and ^{18}F-fluorodeoxyglucose positron emission tomography in the investigation of an anterior mediastinal mass suspected to be thymoma. Because patients with advanced thymoma receive neoadjuvant chemotherapy, radiologists should be familiar with the staging system of thymoma and the imaging features of advanced-stage thymoma to identify such patients before surgery. This review serves as an update of the recent imaging studies on thymoma, which may help in tailoring the approach to the patient with a biopsy-proven or suspected thymoma.

Key Words: thymoma, staging, positron emission tomography, computed tomography, magnetic resonance imaging

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LEARNING OBJECTIVES

After participating in this activity, the physician should be able to:

1. Identify the epidemiology of thymic epithelial neoplasms.
2. Compare the relative advantages and disadvantages of CT, MRI, and FDG-PET for the evaluation of thymic epithelial neoplasms.
3. Accurately apply the 2004 WHO classification and clinical Masaoka-Koga staging system.

Thymoma is the most common primary neoplasm of the anterior mediastinum, but it accounts for <1% of all adult malignancies.[1] It is the most common of the thymic epithelial neoplasms, which, in addition to thymoma, include thymic carcinoma and thymic carcinoid. Because of the rarity of thymoma, it has not been studied thoroughly. The few imaging studies assessing thymoma were single-institution studies that spanned multiple decades. Over the last half decade, there has been increased interest in this disease, with greater international collaboration and dedicated thymic malignancy work groups; this has culminated in the formation of the International Thymic Malignancy Interest Group (ITMIG), instituted to provide a scientific infrastructure for the study of these lesions and foster collaborative research. This review serves as an update of the recent imaging studies on thymoma, which may help in tailoring the approach to the patient with a biopsy-proven or suspected thymoma.

EPIDEMIOLOGY

The incidence of thymoma in the United States is 1 to 5 cases per million people per year; it is higher in African Americans and Asians than in other ethnic groups, whereas men and women are affected equally.[2,3] It is rare in children, although the tumor affects relatively young patients; it rises in incidence with age, as expected with other malignancies, but declines after the age of 60 years.[2,3]

CLINICAL FEATURES

Historically, about a third of the patients with newly diagnosed thymoma presented with chest pain, dyspnea, or cough due to local tumor effects such as compression or invasion of adjacent mediastinal structures; about a third to a half presented with systemic complaints and paraneoplastic syndromes due to secretion of hormones, antibodies, or cytokines by the tumor. Myasthenia gravis is the most common of these paraneoplastic syndromes, occurring in 30% to 50% of patients with thymoma, more frequently in women.[4] Less common paraneoplastic syndromes are hypogammaglobulinemia and pure red cell aplasia, which occur in 10% and 5% of thymoma patients, respectively.[5] Thymomas are also associated with various autoimmune disorders, such as systemic lupus erythematosus, polymyositis, and myocarditis.[6] With the increased use of computed tomography (CT) for evaluation and follow-up monitoring of diverse oncological and benign diseases, and, more recently, the use of CT for screening for lung cancer, an increasing number of thymomas are diagnosed in asymptomatic patients.[7]

PATHOLOGY

On gross pathologic examination, thymoma presents as a solid neoplasm that is encapsulated and localized to the thymus. Approximately one third exhibit necrosis, hemorrhage, or cystic components, and approximately one third invade the tumor capsule and the surrounding structures. They are typically slow growing and late to metastasize. More aggressive features include invasion of adjacent structures, such as the pericardium, superior vena cava, or brachiocephalic vein, and spread to the pleura, but distant metastases are rare.[8] In general, thymoma cannot be differentiated grossly from the less common thymic epithelial malignancies, thymic carcinoma and thymic carcinoid, but both thymic carcinoma and carcinoid are more aggressive and typically present with local and/or metastatic spread.[9]

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The histologic classification of thymoma has changed continuously over the years and is currently being revised. The original classification of thymoma published by the World Health Organization (WHO) Consensus Committee in 1999 included thymic carcinoma in this classification, calling it type C. In the 2004 revised WHO classification of thymoma,[3] the much more aggressive type C was relegated to a separate category. Under the 2004 WHO classification, thymomas are classified on the combined basis of the morphology of the neoplastic epithelial cells and the lymphocyte to epithelial cell ratio, with 5 separate histologic subtypes: types A, AB, B1, B2, and B3. There are inherent problems with this classification.[10] Interobserver and intraobserver reproducibility for pathologists interpreting thymoma specimens is poor.[11] Thymomas typically have morphologic heterogeneity, with several WHO subtypes often coexisting in the same tumor.[12] Thus, assigning them to a single tumor classification is difficult, in particular when basing this on a needle biopsy, which may not sample the predominant tumor subtype.[10] Moreover, the WHO classification system cannot be used to predict clinical outcome,[11–14] although type B3 classification has been shown to have a worse outcome than the other types combined.[10,15]

TREATMENT APPROACH

Because of the complexities of the current classification system and insufficient correlation with patient outcome, treatment of patients with thymoma is based on disease stage and completeness of resection. These 2 factors have been found consistently to correlate with the duration of progression-free and overall survival.[16–19] No official stage classification for staging of thymic malignancies has been defined by the Union Internationale Contre le Cancer or the American Joint Commission on Cancer. Although several different staging systems are reported in the literature,[17–21] they are similar and usually variants of the Masaoka staging system first described in 1981.[18] To facilitate collaborative research efforts and formation of a uniform thymoma database, ITMIG has adopted the Masaoka-Koga staging system (Table 1) as the official staging system for thymoma, and it is the most widely used system today.[22] This staging system is based on gross operative findings with microscopic confirmation of the invasive properties of the tumor. Stage I is assigned when the tumor is completely encapsulated; stage II when the tumor manifests either microscopic invasion into the capsule (IIa) or invasion into surrounding fat (IIb); stage III when there is invasion into a neighboring organ such as the pericardium, great vessels, or lung; and stage IV when there is pleural or pericardial dissemination (IVa) or lymphatic/hematogenous metastasis (IVb).

The treatment of Masaoka-Koga stage I or II thymoma is surgery alone. This is supported by the fact that there is no statistically significant difference in survival between completely resected stages I and II,[19] with 5-year survival rates as high as 100%.[19,23] If a stage II tumor is incompletely resected, postoperative radiation therapy is recommended to try to eradicate the residual disease.[23,24] In treating more advanced disease, in particular locoregional spread into neighboring mediastinal organs (stage III disease), the goal is to achieve complete resection, which prolongs survival.[25,26] This is the rationale for providing patients who have locally advanced disease with

TABLE 1. Masaoka-Koga Staging System for Thymoma

Stage I	Tumor completely encapsulated
Stage IIa	Microscopic tumor invasion into capsule
Stage IIb	Tumor invasion into surrounding fat
Stage III	Tumor invasion into a neighboring organ such as the pericardium, great vessel, or lung
Stage IVa	Pleural or pericardial dissemination
Stage IVb	Lymphatic or hematogenous metastasis

Adapted with permission from Koga et al[17]

neoadjuvant chemotherapy.[16,25] There have been reports suggesting that neoadjuvant therapy provides a survival advantage compared with adjuvant therapy for patients with stage III thymoma.[26–28] Postoperative radiotherapy is recommended in cases of incompletely resected stage III thymoma, and postoperative chemotherapy is considered.[23,24] Treatment for stage IVa thymoma is similar to that of stage III lesions. Stage IVb should be treated with chemotherapy with palliative intent.

Although this treatment scheme may seem straightforward, the Masaoka-Koga staging system on which it is based is a postsurgical staging system that relies on microscopic identification of disease spread. If patients with advanced disease, that is, stages III and IV, are to receive neoadjuvant chemotherapy, this advanced stage must be identified preoperatively by imaging.

IMAGING

Imaging plays a role in thymoma identification and staging and in follow-up monitoring for recurrence. Initial investigation of thymoma starts with a chest radiograph, which is followed by a chest CT scan for further characterization and staging. CT scan is not only more user friendly, with better spatial resolution compared with magnetic resonance imaging (MRI), but in a study assessing 127 patients with an anterior mediastinal mass, CT was shown to be equal or superior to MRI in the diagnosis of all such tumors, except for thymic cysts.[29] In the future, MRI and positron emission tomography (PET)/CT may play a greater role in the investigation of suspected thymomas and in staging of the disease.

Chest Radiograph

Historically, as many as 80% of thymomas were identified by chest radiography.[30] When large, they usually appear as an ovoid, well-marginated, smooth unilateral mass, which may be found anywhere from the thoracic inlet to the cardiophrenic angle. When smaller, they may present as thickening of the anterior junction line. Occasionally, advanced disease may be detected on the chest radiograph, manifesting as an irregular border with the lung, signifying direct lung invasion; as an elevation of the ipsilateral hemidiaphragm, signifying phrenic nerve involvement; or as pleural nodules, signifying metastases (Fig. 1).

CT

Typically, thymomas present on the CT scan as a spherical or ovoid, smooth, 5- to 10-cm anterior mediastinal mass, although they have been described as ranging from a few millimeters to 34 cm in diameter (Fig. 2).[30] They are usually closely related to the superior pericardium, although they may present anywhere from the thoracic inlet to the cardiophrenic border. The tumor enhances
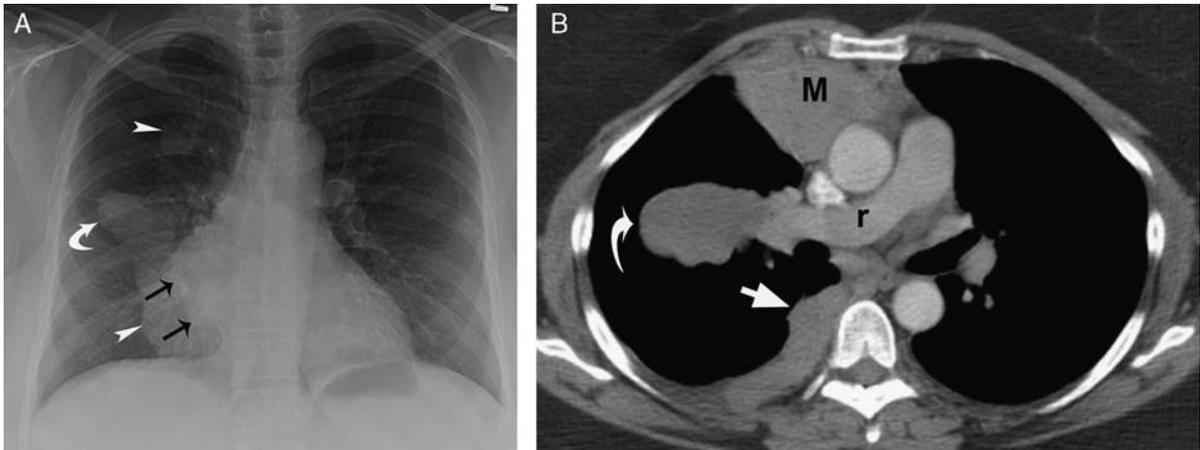
FIGURE 1. A 59-year-old woman with stage IVa thymoma. A, The frontal chest radiograph obtained because of complaints of increasing chest pain over a period of 18 months demonstrates an anterior mediastinal mass (black arrows) with pleural metastases at the periphery (arrowheads) and within the major fissure (curved arrow). B, Contrast-enhanced chest CT at the level of the right pulmonary artery (r) confirms the primary tumor as an anterior mediastinal mass (M) and pleural metastases involving the periphery (straight arrow) and within the major fissure (curved arrow).
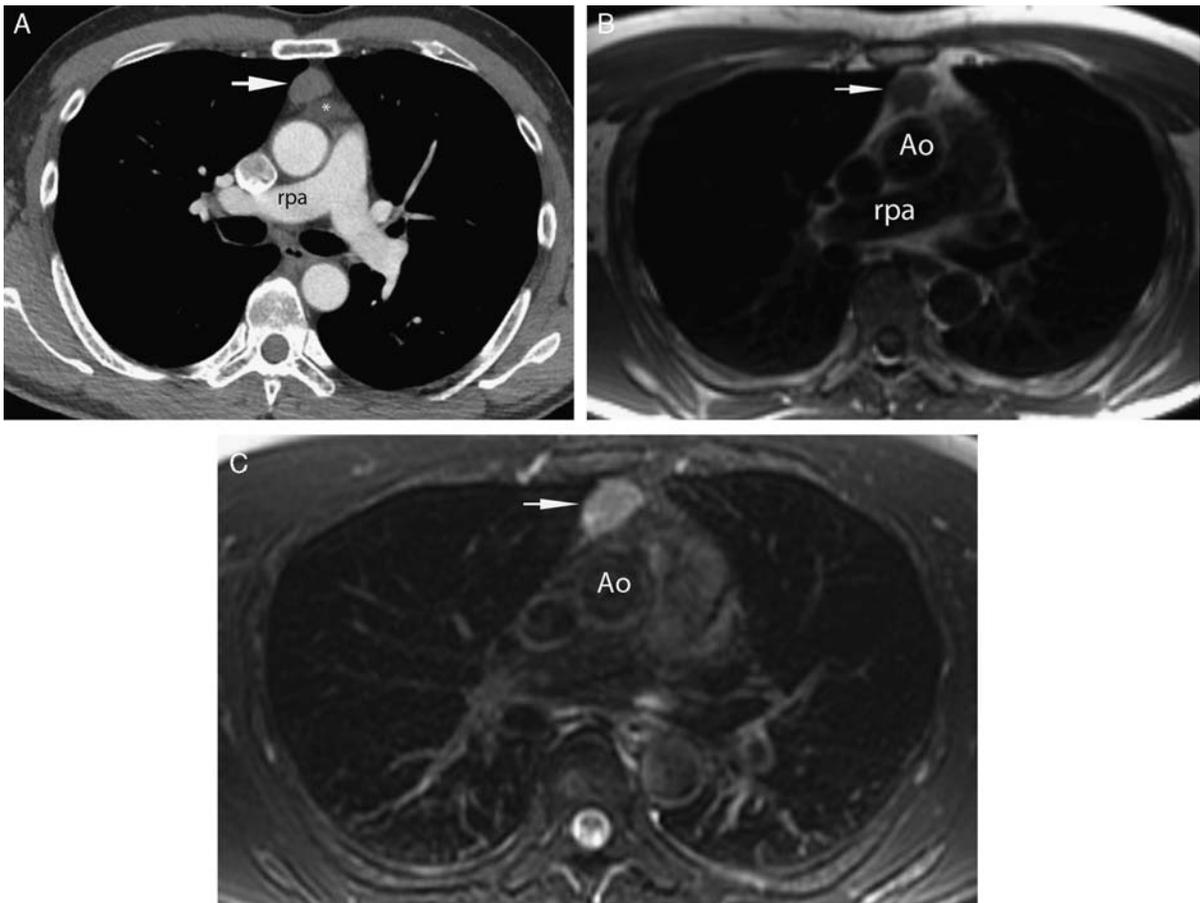
FIGURE 2. A 55-year-old man incidentally discovered to have a 2 cm anterior mediastinal mass. A, Staging contrast-enhanced chest CT at the level of the right pulmonary artery (rpa) demonstrates a smooth 2 cm homogenous anterior mediastinal nodule (arrow) adjacent to the pericardium, surrounded by a rim of fat separating it from the pericardium. *Fluid in the pericardium. B, Axial T1-weighted MRI at the level of the right pulmonary artery (rpa) shows that the mass (arrow) is of low intensity, similar to the muscle intensity. C, A fast spin echo T2-weighted image at the same level shows that the mass (arrow) is of high signal intensity. At surgery the mass was found to invade the mediastinal fat, Masaoka-Koga stage IIb. Ao indicates Ascending aorta.
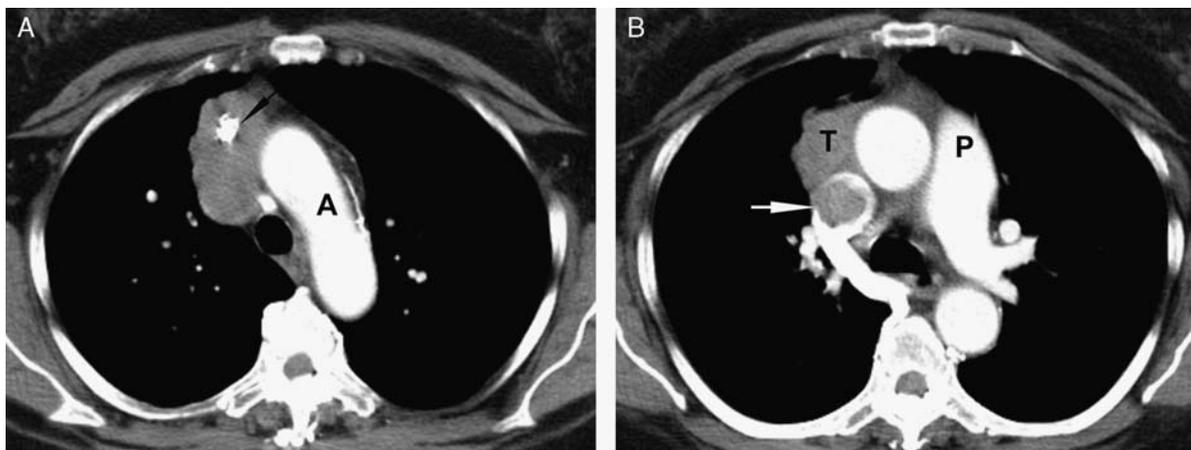
FIGURE 3. A 63-year-old woman with stage III thymoma. A, Contrast-enhanced chest CT at the level of the transverse aorta (A) shows a lobulated mass with course calcification (arrow). B, At the level of the main pulmonary artery (P), the tumor (T) invades the superior vena cava (arrow).

homogenously. It may present with lobulated borders or may be heterogenous or even cystic because of areas of hemorrhage and necrosis. The tumor can be partially or completely outlined by fat and may contain punctuate, coarse, or curvilinear calcifications (Fig. 3).[30,31]

Intravenous contrast is not needed for identification of a thymic mass, but it is necessary for staging of thymoma. Typical CT findings for stage III disease with vascular involvement include an irregular vessel lumen contour, endoluminal soft tissue (Fig. 3), and vascular encasement. Ipsilateral pleural nodules are suggestive of stage IVa disease (Fig. 1). Unfortunately, the majority of stage III thymomas present without an effect on the vessel lumen and with no direct CT sign. It is because of this that CT was thought for years to have a limited role in thymoma staging,[32] even though very few systematic studies have compared CT findings and thymoma invasiveness. Studies assessing the thymus often included patients with thymic hyperplasia or thymic carcinoma and did not provide statistical analysis for the thymoma patients alone; they usually compared these tumors by the WHO classification system rather than by the Masaoka-Koga staging system used in the clinical setting.[33–38]

To improve our preoperative staging of thymoma, there have been attempts to study the morphology of the primary tumor as it compares with Masaoka staging.[39–41] In 2 retrospective studies assessing 50 and 58 patients with thymoma,[40,41] the authors tried to distinguish stage I thymoma from more advanced disease (stages II to IV) and found that partial or complete obliteration of fat planes around the tumor was not helpful in distinguishing stage I from higher stages. However, using univariable analysis alone, they found that lobulated or irregular contours, cystic or necrotic regions within the tumor, and multifocal calcifications were more suggestive of invasive thymoma. Similar correlations were found in a study assessing 129 patients.[42] Because the more crucial question facing the clinician and radiologist trying to stage thymoma is the distinction between early disease (stages I and II) and more advanced disease (stages III and IV) requiring neoadjuvant chemotherapy, a study comparing the CT appearance of 99 thymomas tried to differentiate stages I and II from stages III and IV.[39] This study found that some morphologic

features of the primary tumor were predictive of advanced disease. Although several CT findings were suggestive of advanced disease by univariable analysis, including large tumor size, lobulated contours, heterogenous tumor, presence of calcifications, infiltration of surrounding mediastinal fat, and tumor abutting 50% or more of the circumference of a mediastinal vessel, multivariable analysis showed that only tumor diameter ≥ 7 cm, infiltration of the fat surrounding the tumor, and lobulated contours were associated with advanced disease (Fig. 4) (stages III and IV). The tumor size criterion in this study was established using a regression tree model constructed to predict stage III/IV disease. Size is particularly useful when extreme. For example, only 4% to 29% of tumors < 5 cm in diameter were advanced-stage disease,[39,42] and only 20% of tumors > 12 cm were early-stage disease. A nomogram constructed from these 3 variables showed that, when all 3 were present, the likelihood of advanced-stage disease was 75% (Fig. 5), and the nomogram was predictive of progression-free survival duration.[39]

Studies comparing CT imaging variables with the WHO histologic classification of thymoma have yielded conflicting results. This may be because of the limitations of the classification system. One of these studies found that thymomas with lobulated contours were usually type B2 and B3 tumors,[33] whereas another study found that CT is of limited value in differentiating thymoma WHO types A, AB, and B1 from types B2 and B3.[39] Tomiyama et al[36] found that type A thymomas were more likely to have smooth contours, but CT was of limited value in differentiating types AB, B1, B2, and B3. Marom et al[39] found that the only feature that could be connected with the WHO system was tumor size; tumors ≥ 7 cm in diameter were significantly more likely to be B3 disease.

MRI

MRI has been insufficiently studied in the staging of thymoma and follow-up monitoring of patients with the disease, despite the relative youth of the thymoma patient population and the necessity for repeated imaging for follow-up surveillance. However, MRI does play a major role in the investigation of the anterior mediastinal mass and in the staging of thymoma in patients with iodine allergy or
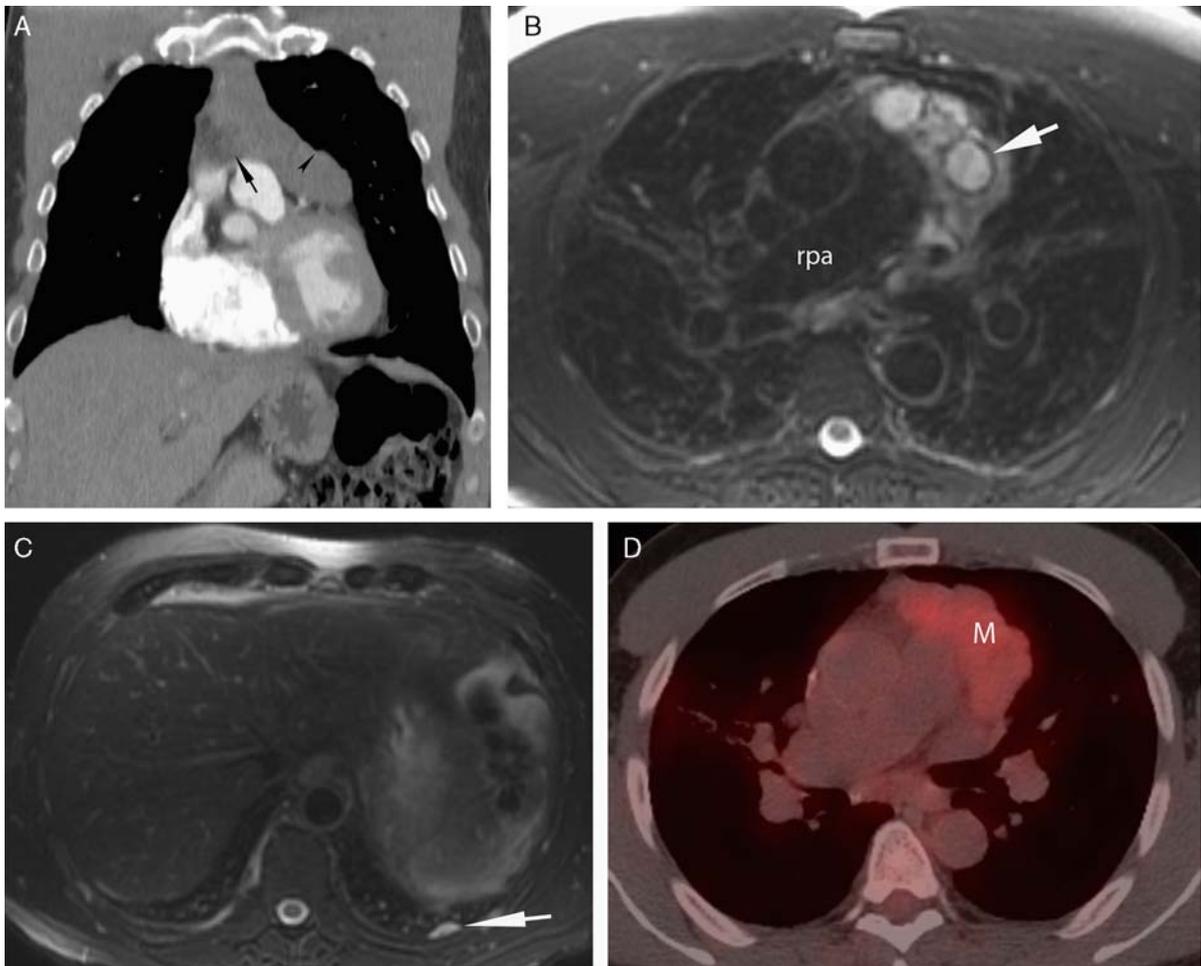
FIGURE 4. A 56-year-old man with newly developed wheezing and shortness of breath. A, Coronal reconstruction from a contrast-enhanced chest CT shows a 10 cm anterior mediastinal mass with lobulations (arrowhead) and infiltration of the anterior mediastinal fat (arrow). B, A fast spin echo T2-weighted axial MRI through the right pulmonary artery (rpa) demonstrates the mass to be of high intensity. Septa surrounding tumor lobulations are appreciated within it (arrow). C, A fast spin echo T2-weighted axial MRI through the costophrenic recess demonstrates a pleural nodule (arrow). D, Fused FDG PET-CT at the same level shows FDG uptake within the mass (M) as being higher than mediastinal background activity. At surgery the primary tumor involved the anterior mediastinal fat and mediastinal pleura, and separate pleural implants were confirmed as metastatic. Histology of the tumor was predominantly of type B2 pattern with focal regions displaying features of types B1 and B3. full color online

with renal failure, as evaluation of the mediastinal vessels is crucial for this staging (Fig. 6).

Thymoma manifests with low to intermediate signal intensity on T1-weighted images and with high signal intensity on T2-weighted images (Fig. 2).[30,43] Signal intensity is heterogenous in tumors with necrosis, hemorrhage, or cystic change. The better contrast resolution of MRI as compared with CT is advantageous in the patient with a cystic anterior mediastinal mass when distinction between a congenital cyst and cystic thymoma should be made. Fibrous septa and/or mural nodules are typically present in cystic thymoma but absent from a congenital cyst. These septa and nodules are often not appreciated on CT but are seen readily on T2-weighted MRI images (Fig. 4). Similarly, with the good contrast resolution of MRI, septa and the tumor capsule are sometimes appreciated within solid tumors as well. Their visualization was shown to be associated with a less aggressive histologic classification.[37] In this same study, predominance of a necrotic or cystic component and heterogenous enhancement were signs of aggressiveness and were much more common with thymic cancer than with thymoma.[37] Hemorrhage within the tumor may vary in its MRI appearance with the age of the hemorrhage; hemosiderin deposition may appear as low signal intensity on T1-weighted and T2-weighted images. MRI is inferior to CT in demonstrating calcification within thymomas.

Only 1 study has assessed the ability of MRI to distinguish advanced-stage disease (stage III) from earlier-stage disease (stages I and II). By using dynamic MRI, Sakai et al were able to demonstrate in a study on 31 thymoma patients that mean peak time was delayed in advanced-stage thymomas (stage III) as compared with tumors of earlier stages.[44] Another study assessing 5 patients with stage I thymoma and 12 patients with stages II to IV thymoma found that 92% of stages II to IV tumors had heterogenous signal intensity and 50% of stages II to IV tumors had a lobulated internal architecture caused by fibrous septa. None of the stage I tumors had lobulation
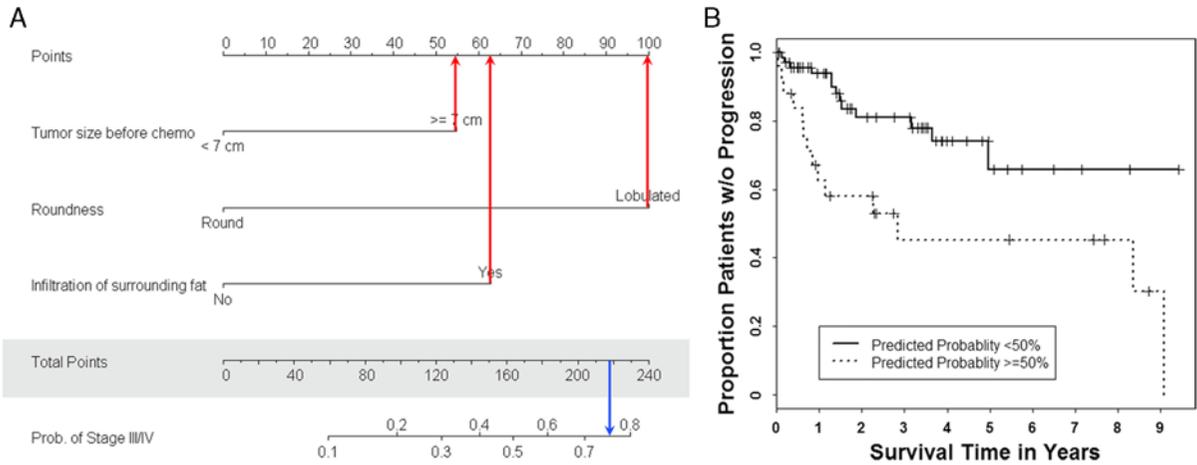
FIGURE 5. A, A nomogram to predict stage III/IV thymoma using CT findings at presentation. The nomogram consists of 6 rows. Row 1 (points row) is the point assignment for each variable. Rows 2 to 4 correspond to the variables included in the model. For an individual patient, each variable in rows 2 to 4 is assigned a point value, which is determined by drawing a vertical line from the appropriate position on the variable row to the points row (red arrows). The assigned points for all 3 variables are added (blue arrow), and the total is marked on row 5 (shaded row called: total points). Thereafter, the probability of having stage III/IV disease is calculated by drawing a vertical line from the appropriate position on the total points row to row 6, which shows the probability of stage III or IV disease. Thus, for the case shown in Figure 4, that is, a >7 cm lobulated tumor that infiltrates the surrounding fat, the points added would be 100, 55, and 63, respectively, which adds to 218 total points or a 75% probability of having stage III/IV disease. B, Kaplan-Meier estimate of progression-free survival according to the nomogram in this study predicted probability of having stage III/IV disease ($P = 0.005$). Reprinted with permission from Marom et al.[39] full color online

but all were heterogenous.[45] Although the heterogeneity of stage I tumors may seem surprising, as CT studies have shown that heterogeneity is associated with more advanced disease,[39–42] it may be because of the improved contrast resolution of MRI, such that tumors that appear homogenous on CT show some heterogeneity when imaged by MRI (Fig. 4).

Although whole-body MRI was shown in a case report to identify more foci of metastatic disease in thymic cancer compared with chest CT scan,[46] its utility with thymoma is limited as thymoma rarely presents with distant metastasis.

It is unknown whether MRI will replace CT scan in the follow-up monitoring of patients for recurrence of disease following treatment. Because of concerns about the cumulative radiation effects of repeated CT scans over multiyear patient follow-up, ITMIG in a consensus statement suggested replacing some follow-up CT imaging with MRI, but this was not based on a comparison study.[22]
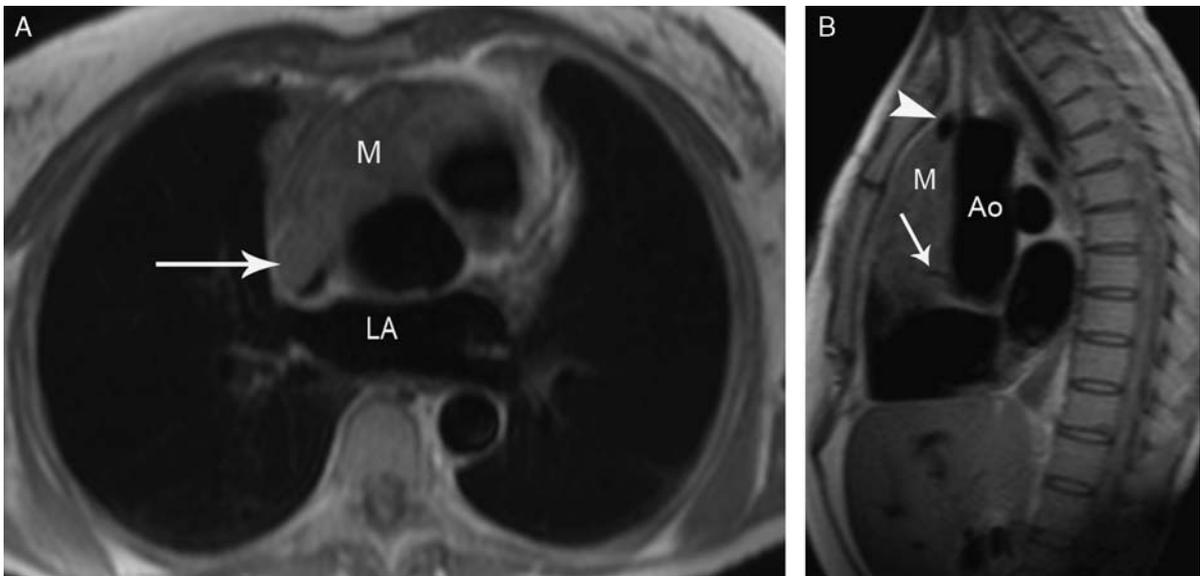
FIGURE 6. A 53-year-old woman with an iodine allergy and stage III thymoma. A, Axial MRI, inversion recovery single shot fast spin echo black blood sequence at the level of the left atrium (LA) shows an anterior mediastinal mass (M) invading the superior vena cava (arrow). B, Sagittal image demonstrates the large anterior mediastinal mass (M) encasing the right coronary artery (arrow), abutting and inseparable from the left brachiocephalic vein (arrowhead). Ao indicates Ascending aorta.
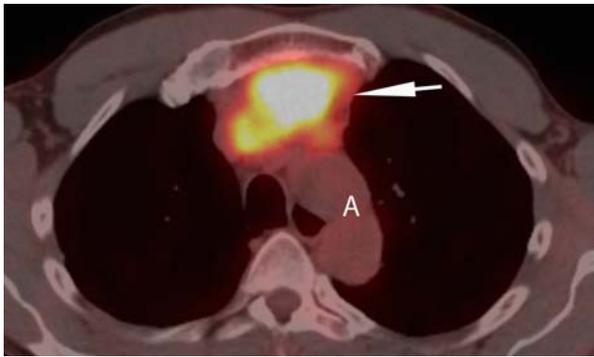
FIGURE 7. Fused FDG PET-CT of a 54-year-old man with newly diagnosed thymic cancer shows a markedly FDG-avid primary tumor (arrow), which measured SUV_{max} 14.1. A indicates transverse aorta.

NUCLEAR MEDICINE

Currently, nuclear medicine does not play an important role in the routine evaluation of thymoma, nor of the anterior mediastinal mass. This is predominantly because of its lack of sufficient specificity and its lower spatial resolution, which limits its use for staging. Two types of radiopharmaceuticals can be used to detect thymic masses: receptor-mediated radiopharmaceuticals and nonspecific tracers. Indium-111 octreotide, a receptor-mediated radionuclide that specifically binds with high affinity to somatostatin receptor subtype 2, which is expressed in the normal thymus[44] but is also present in a wide variety of tumors, has been used primarily to image neuroendocrine tumors.[47] Indium-111 octreotide uptake may be seen in thymic hyperplasia.[48] Although thought to have good specificity for identifying thymoma deposits >15 mm in size,[49] indium-111 octreotide uptake was detected in only 27% of 29 patients being assessed for recurrence of thymoma.[50] Thus, diagnosis and staging is based on morphologic imaging (ie, CT or MRI). Indium-111 octreotide is now used to identify patients whose tumor may respond to treatment with octreotide, a second-line or third-line therapy sometimes given when conventional chemotherapy fails.[51]

To overcome the lower sensitivity of indium-111 octreotide scintigraphy, there have been attempts to create a somatostatin receptor radionuclide suitable for PET imaging,

as the sensitivity of PET imaging as compared with single-photon emission CT is about 100:1 to 1000:1. An example of these agents is DOTA (1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetra-acetic acid)-TOC (D-Phe1-Tyr3-octreotide).[52] Although DOTA has been shown to be superior to octreotide single-photon emission CT imaging in the detection of neuroendocrine tumor metastases, only 1 thymoma has been documented in the literature so far as being imaged with this agent, and the uptake within this thymoma was low (SUV_{max} 2.5).[53] It is to be hoped that, with new imaging agents being continuously introduced, a more useful one for the management of thymoma patients will be found.

Of the nonspecific tracers, gallium-67 citrate, which in the past was commonly used to image lymphoma, also concentrates in thymic hyperplasia and thymic tumors.[54] Thallium-201 chloride, a cationic radioisotope used to image myocardial perfusion, shows uptake in thymic tumors and thymic hyperplasia.[54] Neither gallium-67 citrate nor thallium-201 chloride is used today for evaluation of thymic malignancies. Of the nonspecific tracers, ^{18}F-fluorodeoxyglucose (FDG), a glucose analog, is the tracer most widely used for oncological PET imaging. Its precise role in the management of thymic epithelial malignancies, especially thymoma, has yet to be defined. Studies assessing the use of FDG-PET in thymic epithelial malignancies have been small, reviewing from 10 to 51 patients.[55] Early results consistently showed that FDG uptake is much higher in thymic carcinoma than in thymoma,[56–63] which correlates with the more aggressive nature of thymic carcinoma (Figs. 4, 7, 8).

The FDG uptake of thymoma is variable. The most aggressive classification, type B3, does have increased FDG avidity compared with more indolent histologic types, A through B2 (Figs. 4, 8, 9).[63] Thymoma at times may have very low FDG avidity, similar to or even lower than the mediastinal blood pool activity (Fig. 8). Thus the absence or presence of FDG activity in a thymic mass cannot differentiate a benign from a malignant process.

There was hope that FDG-PET/CT would improve identification of advanced disease and help overcome the limitations of CT identification of stage III disease. Unfortunately, the FDG uptake as measured by SUV_{max} has not yet proven useful in differentiating early thymoma (stages I and II) from more advanced disease (stages III and IV).[60,63,64] Lately, there has been debate as to whether the
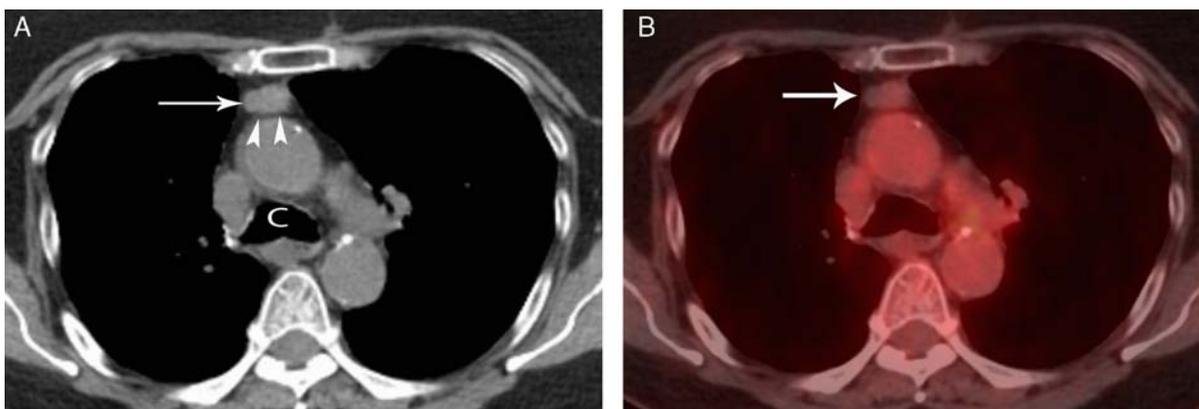
FIGURE 8. A 66-year-old woman discovered to have an anterior mediastinal nodule at staging PET-CT for newly diagnosed stage I lung cancer. A, Axial unenhanced chest CT at the level of the carina (C) shows a 2 cm anterior mediastinal nodule (arrow) abutting the pericardial reflection (arrowheads). B, Fused FDG PET-CT demonstrates FDG uptake lower than the mediastinal blood pool activity (arrow) with SUV_{max} of 1.5. At surgery, a type B2 thymoma was resected, stage IIB.
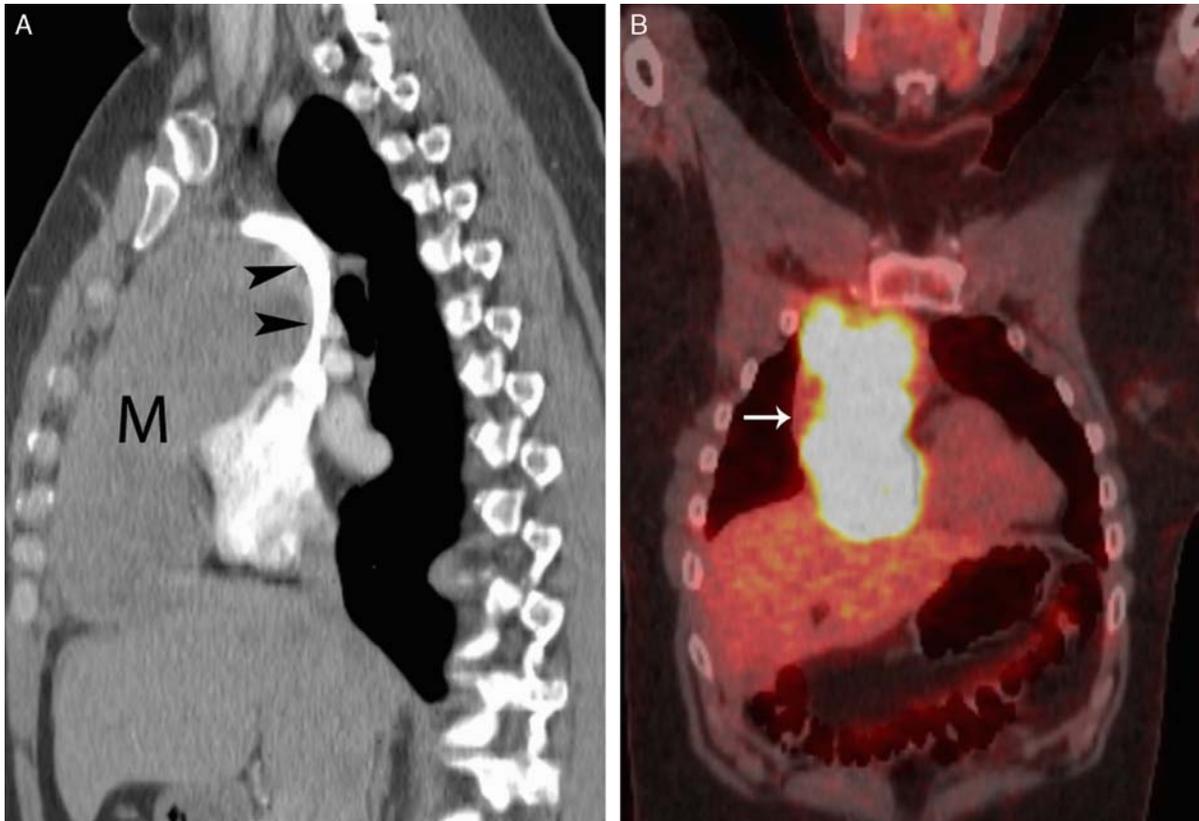
FIGURE 9. A 29-year-old man with a 1-year history of chest pain. A, Sagittal contrast-enhanced chest CT through the superior vena cava shows a large anterior mediastinal mass (M) displacing the superior vena cava posteriorly (arrowheads). B, Coronal FDG PET-CT shows intense FDG uptake by the primary mass (arrow) with an SUV_{max} of 15.5. At resection this type B3 thymoma directly involved the superior vena cava and pericardium, and there was a diaphragmatic pleura drop metastasis. full color online

measurement of SUV_{max}, based on a single voxel value, is the most appropriate one for measuring FDG uptake. However, in one study, SUV_{peak}, which assesses a volume of approximately $1 cm^3$ around the area of maximal FDG uptake,[65] was not predictive of advanced disease either.[63] The strength of FDG-PET lies in its ability to often demonstrate unexpected hematogenous disease spread. As thymoma rarely presents with disseminated disease, FDG-PET imaging has been disappointing in this respect as well, failing to show unexpected disease sites that would alter management. This is unlike thymic carcinoma, which often presents with metastatic disease and in which FDG has been shown to accumulate in unexpected foci when compared with CT.[61]

Other PET tracers have been studied. Carbon-11 methionine, a PET tracer used to measure amino acid metabolism in vivo, was assessed in 28 patients: 14 with thymic cancer and 14 with thymoma. Carbon-11 methionine uptake was similar among thymic cancer and invasive and stage I thymomas and thus was not recommended for the evaluation of thymic malignancies.[59] Another PET tracer, carbon-11 acetate, used to measure lipid and cholesterol synthesis, is known to be useful for non–FDG-avid tumors such as prostate cancer. In a study comparing the uptake of FDG with that of carbon-11 acetate in 37 patients with thymoma and in 3 patients with thymic cancer, neither FDG nor carbon-11 acetate could predict

Masaoka stage.[60] Thymic epithelial tumors have been recently shown to express high levels of insulin-like growth factor-1 receptor,[66] which may open a new frontier for imaging and treatment by molecular targeting.

FOLLOW-UP MONITORING

Response to chemotherapy and/or radiation therapy is monitored in patients with nonresectable disease, in those with recurrence, and in those undergoing neoadjuvant therapy before surgery. Response is measured according to a modification of the RECIST criteria version 1.1.[22,67] The RECIST criteria prohibit the use of the pleura as a target organ; however, because thymoma metastasis has a predilection for the pleura, for the purposes of measuring tumor response the pleura is considered as an organ, and the Byrne criteria are used.[22,68]

The follow-up monitoring of patients with resected thymoma is lengthy, as the average time to recurrence of a completely resected thymoma has been reported to be between 3 and 7 years.[22] Patients with higher stage and/or incompletely resected thymoma should be assessed more often, as recurrence occurs earlier in these groups.[69] It is important to detect tumor recurrence early, as early detection affords outcomes similar to those of patients without tumor recurrence after initial resection, with 5-year survival rates ranging from 65% to 80%.[70,71]

ITMIG follow-up recommendations suggest that, at a minimum, yearly chest CT should be performed for 5 years after surgical resection and then alternating annually with chest radiography until year 11, followed by annual chest radiography alone,[22] as late recurrences are not uncommon. A chest CT scan every 6 months for 3 years is recommended for patients with advanced-stage disease (stage III or IVa) or for those who had incomplete tumor resection. ITMIG also suggests alternating these scans with MRI to reduce the cumulative radiation dose from this repeated imaging, although there has been no study comparing the accuracy of CT with that of MRI for identification of tumor recurrence.

DIFFERENTIAL DIAGNOSIS

With the presentation of an anterior mediastinal mass, the differential diagnosis includes, besides thymoma, other primary thymic malignancies, such as thymic carcinoma and thymic carcinoid, and nonthymic tumors, such as lymphoma, germ cell tumor, small cell lung cancer, and mediastinal metastasis. CT is by far the most common imaging modality used to assess an anterior mediastinal mass. In a study assessing the diagnostic accuracy of CT versus MRI in 127 patients with an anterior mediastinal tumor, which comprised thymoma, thymic carcinoma, thymic cyst, mature teratoma, malignant germ cell tumor, and lymphoma, the correct first choice diagnosis was made by CT in 61% of patients, by MRI in 56%, and by a combination of CT and MRI in 86%.[31] CT was equal or superior to MRI in the diagnosis of all anterior mediastinal tumors, except for thymic cysts.

Patient age and gender and the presence of myasthenia gravis, as well as tissue composition as assessed by CT scan, ancillary CT findings, and evidence of tumor invasiveness, are helpful in the differential diagnosis of anterior mediastinal masses and usually suffice for management decisions. For example, thymoma rarely presents with lymphadenopathy, pleural effusion, or extrathoracic metastases. Any of these suggest a diagnosis other than thymoma. Some anterior mediastinal masses have a typical appearance. For example, a cystic anterior mediastinal mass with intrinsic fat attenuation is typically a mature teratoma. Malignant germ cell neoplasms almost exclusively affect men and are more common in patients younger than 40 years.

There are certain scenarios in which the addition of MRI or PET/CT may prove beneficial in the management of patients with an anterior mediastinal mass. Occasionally, MRI may be needed to differentiate thymic hyperplasia from thymoma, both of which are common in patients with myasthenia gravis. Usually, the two can be differentiated by their CT appearance: thymic hyperplasia appears as diffuse enlargement of the thymus while maintaining its arrowhead morphology, whereas thymoma presents as an eccentric mass. However, thymic hyperplasia does present rarely as a mass-like enlargement. The use of chemical shift MRI sequences (in-phase and out-of-phase gradient echo sequences) can be helpful in distinguishing thymoma from thymic hyperplasia in such cases.[72,73] This technique identifies the normal fatty infiltration of the normal or hyperplastic thymus, which manifests as homogenous signal
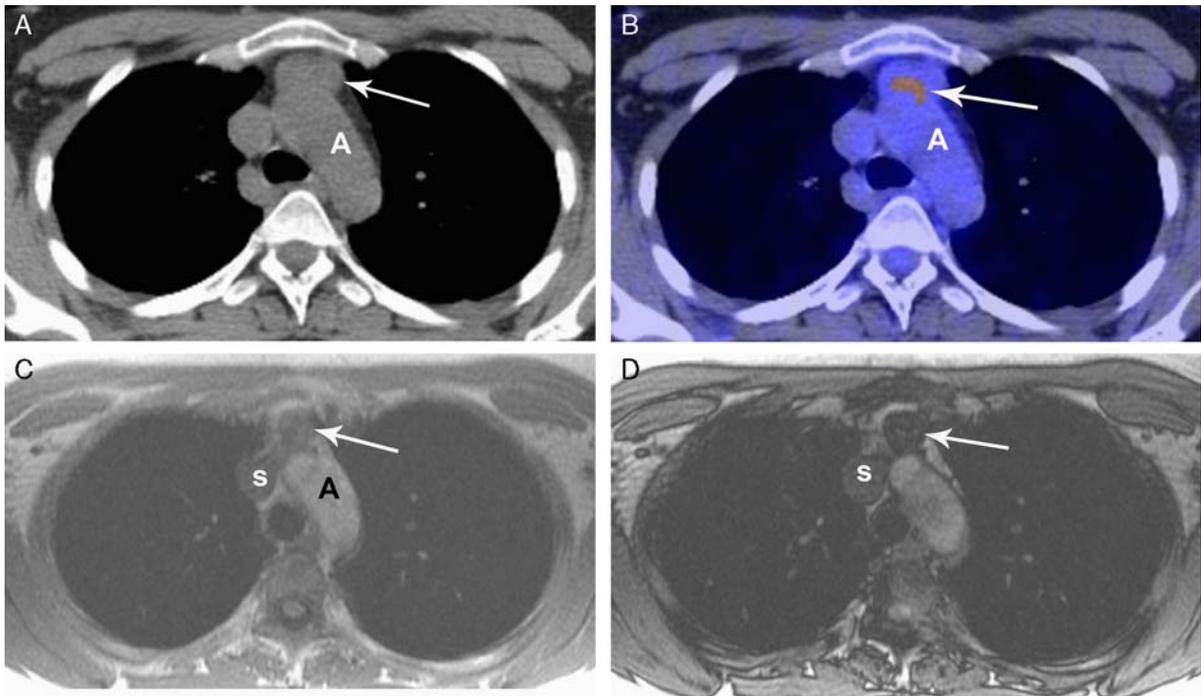
FIGURE 10. A 32-year-old woman with thymic hyperplasia. A, Unenhanced chest CT at the level of the aortic arch (A) shows mass-like enlargement of the thymus (arrow). B, Fused FDG PET-CT shows FDG uptake in the anterior mediastinal mass (arrow) above the mediastinal background activity. C, Transverse in-phase T1-weighted MRI image shows mass-like enlargement of the thymus without preservation of its normal triangular morphology (arrow). D, Opposed-phase gradient-echo T1-weighted MRI image shows decreased signal intensity within the thymus (arrow), a finding that is consistent with hyperplastic thymus. A indicates transverse aorta; S, superior vena cava.

decrease on out-of-phase images relative to in-phase images, whereas signal decrease is absent in thymoma (Fig. 10). Despite the elegance and 100% accuracy of this approach as described in the literature,[72,73] there has been a case report describing a normal thymus in which no signal drop was seen.[74]

FDG-PET/CT is not as useful in differentiating thymoma from thymic hyperplasia. Thymic hyperplasia has been known to be associated with increased FDG activity. Although the results of a study assessing 5 patients with thymic hyperplasia and 14 patients with thymoma suggested that the FDG activity of thymic hyperplasia is lower than that of thymoma,[58] a larger study assessing 160 patients without thymoma showed that the FDG SUV_{max} of patients with thymic hyperplasia can be as high as 7.3,[75] a value that overlaps with thymoma uptake. Thus, FDG uptake in thymic enlargement can be seen in both benign (thymic hyperplasia) and malignant processes.

Although many surgeons biopsy the anterior mediastinal mass before surgery, some surgeons advocate thymectomy without biopsy for small anterior mediastinal masses suggestive of thymoma. The importance of reaching the correct diagnosis with imaging cannot be overstated with this latter approach, as treatment differs significantly among the various anterior mediastinal tumors. Early-stage thymic epithelial malignancies and mature teratoma are resected, and germ cell tumor and lymphoma are treated with chemotherapy and/or radiation therapy, whereas thymic cyst is usually watched. With this approach, FDG-PET/CT may prove useful, as the SUV_{max} of thymoma is relatively low compared with those of other anterior mediastinal tumors. However, the FDG uptake does not differ substantially from those of other malignancies that can present as an anterior mediastinal mass, such as thymic carcinoma, lymphoma, paraganglioma, or nonseminomatous germ cell tumor.[62,76] It is for this reason that Luzzi et al[76] suggested that any anterior mediastinal mass whose SUV_{max} is > 5 not be resected without biopsy because of the possibility that it may be more aggressive than thymoma or even a nonsurgical disease such as lymphoma.

Similar to FDG-PET/CT, MRI was shown in a study to differentiate between thymoma and other anterior mediastinal tumors. In this study, which assessed 59 patients with an anterior mediastinal mass, 31 thymomas and 28 nonthymoma lesions, dynamic MRI with sequential images at 30 seconds for 5 minutes after administration of gadopentetate dimeglumine showed that the mean peak of the time intensity curve was significantly shorter for thymoma, only 1.5 minutes, than for nonthymoma tumors, 3.2 minutes.[45]

CONCLUSIONS

Although rare, thymoma is the most common primary neoplasm of the anterior mediastinum. Imaging plays a crucial role in the diagnosis and staging of thymoma and in the follow-up monitoring of patients treated for this tumor, and CT is the recommended cross-sectional imaging modality.

CT has been proven superior to MRI in the diagnosis of anterior mediastinal masses, but further studies are needed to confirm whether MRI can replace CT for the staging of thymoma and for follow-up of patients who have undergone treatment for this disease. FDG-PET/CT is useful for the initial evaluation of patients with an anterior mediastinal mass or for staging of thymic cancer, but its efficacy in patients with thymoma has not been proven.

Because patients with advanced-stage thymoma receive neoadjuvant chemotherapy, radiologists should be familiar with the imaging features of advanced-stage thymoma to identify such patients before surgery.

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CME-SAM EXAMINATION

Please mark your answers on the ANSWER SHEET.

After completing this CME-SAM activity, physicians should be better able to:
- Identify the epidemiology of thymic epithelial neoplasms.
- Compare the relative advantages and disadvantages of CT, MRI, and FDG-PET for the evaluation of thymic epithelial neoplasms.
- Accurately apply the 2004 WHO classification and clinical Masaoka-Koga staging system.

*1. Which of the following paraneoplastic syndromes is MOST COMMONLY associated with thymoma?
    (a) Hypogammaglobulinemia
    (b) Myasthenia gravis
    (c) Pure red cell aplasia
    (d) Cushing syndrome

Please see the following references for further study:
1. Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. *Mt Sinai J Med.* 1971;38:497–537.
2. Cameron RB, Loehrer PJ Sr, Thomas CR Jr. Neoplasms of the mediastinum. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:845–858.

*2. In regards to the clinical Masaoka-Koga staging of a newly diagnosed thymoma, which of the following statements is CORRECT?
    (a) By CT, a 2-cm mediastinal lymph node is suggestive of stage III thymoma.
    (b) A 2-cm FDG-avid nodule in the ipsilateral major fissure constitutes stage IVb disease.
    (c) It is most important to distinguish between stage I + II and stage III + IV disease.
    (d) The clinical Masaoka-Koga staging is assigned by the radiologist, the pathologic staging by the surgeon.

Please see the following references for further study:
1. Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. *J Thorac Oncol.* 2011;6:S1691–1697
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*3. In regards to imaging of an anterior mediastinal mass, which of the following statements is CORRECT?
   (a) MRI is superior to CT in the diagnosis of most anterior mediastinal tumors.
   (b) SUV_{max} of thymic carcinoma is significantly higher than SUV_{max} of thymoma.
   (c) FDG-PET is more accurate than CT for monitoring thymoma patients for disease recurrence.
   (d) FDG SUV_{max} can differentiate between lymphoma and type C thymoma.

Please see the following references for further study:
   1. Tomiyama N, Honda O, Tsubamoto M, et al. Anterior mediastinal tumors: diagnostic accuracy of CT and MRI. *Eur J Radiol*. 2009;69:280–288.
   2. Kaira K, Endo M, Abe M, et al. Biologic correlation of 2-[18F]-fluoro-2-deoxy-D-glucose uptake on positron emission tomography in thymic epithelial tumors. *J Clin Oncol*. 2010;28:3746–3753.
   3. Kaira K, Murakami H, Miura S, et al. 18F-FDG uptake on PET helps predict outcome and response after treatment in unresectable thymic epithelial tumors [published online ahead of print December 21, 2010]. *Ann Nucl Med*. 2011;25:247–253.

*4. A 10-cm anterior mediastinal mass abutting the superior vena cava is seen on a low-dose chest CT scan done as screening for lung cancer. Biopsy confirms this to be a thymoma. The patient had documented anaphylaxis to iodinated contrast agents two years ago. The thoracic surgeon is asking you to stage this thymoma for treatment planning. Which imaging modality would be the best choice for this patient?
   (a) Magnetic resonance imaging
   (b) Contrast-enhanced CT
   (c) FDG-PET/CT
   (d) Indium-111 Octreotide SPECT

Please see the following references for further study:
   1. Benveniste MFK, Moran CA, Mawlawi O, et al. FDG PET-CT aids in the preoperative assessment of patients with newly diagnosed thymic epithelial malignancies. *J Thorac Oncol*. In press.
   2. Sung YM, Lee KS, Kim BT, et al. 18F-FDG PET/CT of thymic epithelial tumors: usefulness for distinguishing and staging tumor subgroups. *J Nucl Med*. 2006;47:1628–1634.
   3. Lastoria S, Vergara E, Palmieri G, et al. In vivo detection of malignant thymic masses by indium-111-DTPA-D-Phe1-octreotide scintigraphy. *J Nucl Med*. 1998;39:634–639.

*5. In regards to the 2004 WHO classification of thymoma, which statement is true?
   (a) This classification is used for selection of the surgical approach.
   (b) Type B3 has a worse outcome than combined type A through B2.
   (c) Type B1 thymomas are usually larger than type AB thymomas.
   (d) Type A is assigned when the tumor is completely encapsulated.

Please see the following references for further study:
   1. Benveniste MFK, Moran CA, Mawlawi O, et al. FDG PET-CT aids in the preoperative assessment of patients with newly diagnosed thymic epithelial malignancies. *J Thorac Oncol*. In press.
   2. Suster S, Moran CA. Histologic classification of thymoma: the World Health Organization and beyond. *Hematol Oncol Clin North Am*. 2008;22:381–392.

*6. Which of the following statements in regard to thymoma epidemiology is correct?
   (a) The ratio of male to female incidence is 2:1.
   (b) The incidence declines after the age of 60 years.
   (c) Thymoma is more common in whites than in other ethnic groups.
   (d) The incidence is higher in smokers than in nonsmokers.

Please see the following reference for further study:
   1. Engels EA. Epidemiology of thymoma and associated malignancies. *J Thorac Oncol*. 2010;5(10 Suppl 4):S260–S265.

**ANSWER SHEET FOR JOURNAL OF THORACIC IMAGING
CME-SAM PROGRAM EXAM
MARCH 2013**

Please answer the questions on pages 81–82 by filling in the appropriate circles on the answer sheet below. Please mark the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

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5. Ⓐ Ⓑ Ⓒ Ⓓ
6. Ⓐ Ⓑ Ⓒ Ⓓ

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions below.

Please rate these activities 1 (minimally) to 5 (completely)   **1 2 3 4 5**

These activities were effective in meeting educational objectives   ○ ○ ○ ○ ○

These activities were appropriately evidence-based   ○ ○ ○ ○ ○

These activities were relevant to my practice   ○ ○ ○ ○ ○

Please rate your ability to achieve the following objectives,   Pre-test   Post-test
both before and after this activity: 1 (minimally) to 5 (completely)   **1 2 3 4 5   1 2 3 4 5**

1. Identify the epidemiology of thymic epithelial neoplasms.   ○ ○ ○ ○ ○   ○ ○ ○ ○ ○

2. Compare the relative advantages and disadvantages of CT, MRI, and FDG-PET   ○ ○ ○ ○ ○   ○ ○ ○ ○ ○
    for the evaluation of thymic epithelial neoplasms.

3. Accurately apply the 2004 WHO classification and clinical Masaoka-Koga staging system.   ○ ○ ○ ○ ○   ○ ○ ○ ○ ○

How many of your patients are likely to be impacted by what you learned from this activity?

○<20% ○20-40% ○40-60% ○60-80% ○>80%

Do you expect that these activities will help you improve your skill or judgment within   **1 2 3 4 5**
the next 6 months (1 – definitely will not change, 5 – definitely will change)   ○ ○ ○ ○ ○

How will you apply what you learned from these activities (mark all that apply):

In diagnosing patients ○   In making treatment decisions ○

In monitoring patients ○   As a foundation to learn more ○

In educating students and colleagues ○   In educating patients and their caregivers ○

As part of a quality or performance improvement project ○   To confirm current practice ○

For maintenance of board certification ○   For maintenance of licensure ○

How committed are you to applying these activities to your practice in the ways   **1 2 3 4 5**
 you indicated above (1 – minimally, 5 completely)   ○ ○ ○ ○ ○

Did you perceive any bias for or against any commercial products of devices?   **Yes**   **No**
If yes, please explain: ○   ○

How long did it take you to complete these activities ____hours ____minutes

What are your biggest clinical challenges related to radiology?

[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)

Mail the completed Answer Sheet by March 31, 2014 to:

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