Thymoma is a rare mediastinal neoplasm but is the most common primary neoplasm of the anterior mediastinum. There have been only a few published reports assessing this disease. Furthermore, many of these reports are from a single institution and span several decades, which may lead to potentially misleading conclusions related to diagnosis, staging, and treatment. Computed tomography is the imaging modality of choice for evaluating thymoma and can help distinguish thymoma from other anterior mediastinal abnormalities. Tumor stage and extent of resection are the most important prognostic factors. Tumors that are encapsulated and are amenable to complete resection have a good prognosis, whereas invasive and unresectable tumors have a poor prognosis regardless of their histologic characteristics. Radiologists must be aware of the full spectrum of imaging findings of thymoma, the standard guidelines for diagnostic evaluation, and how imaging findings affect therapeutic decisions.

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Introduction
Thymoma is the most common primary neoplasm of the anterior mediastinum (1). Early-stage and appropriately treated advanced-stage thymomas have an excellent prognosis. However, because of the rarity of thymoma, there are few published series assessing this disease, many of which are single-institution studies spanning several decades, which may lead to potentially misleading conclusions related to diagnosis, staging, and treatment. Misleading terms such as benign thymoma are no longer acceptable, since all thymomas are malignant tumors and have the potential to metastasize. Nevertheless, despite the ambiguous terminology and poor description of methods of patient selection and treatment in the few published thymoma studies, valuable information can be gleaned from the existing literature. Radiologists are key members of the multidisciplinary team required to evaluate patients with thymoma and must be aware of the imaging findings that impact treatment.

Because progress in the understanding of thymic malignancies can be accomplished only through international collaboration, the International Thymic Malignancy Interest Group (IT-MIG) was recently formed to provide a scientific infrastructure for the study of these lesions and to foster collaborative research, in which radiology plays a crucial role.

In this article, we describe the epidemiologic, pathologic, and clinical features of thymoma and discuss this disease entity in terms of classification, staging, treatment, imaging evaluation, differential diagnosis, and recurrence and follow-up.

Epidemiologic, Pathologic, and Clinical Features
Thymic neoplasms are rare tumors that account for less than 1% of all adult malignancies, with reported incidences of one to five cases per 1 million people per year (2). The primary epithelial neoplasms of the thymus are thymoma and thymic carcinoma, with thymoma being more common. Thymic carcinoma is a more aggressive disease that is often diagnosed with needle biopsy before treatment planning; it has been discussed elsewhere (3).

Thymomas typically occur in patients older than 40 years of age, are rare in children, and affect men and women equally (1). Most thymomas are solid neoplasms that are 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. 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 (4).

Thymoma is being diagnosed in a growing number of asymptomatic patients due to the increased use of chest computed tomography (CT). Symptoms (when present) are usually related to local effects of the neoplasm, including compression and invasion of adjacent structures, and can manifest as dysphagia, diaphragm paralysis, or superior vena cava syndrome. Up to one-third of patients with thymoma have chest pain, dyspnea, or cough (5). Systemic complaints and paraneoplastic syndromes are typically due to the secretion of hormones, antibodies, or cytokines by the tumor. Myasthenia gravis associated with thymoma occurs most frequently in women. Between 30% and 50% of patients with a thymoma have myasthenia gravis, whereas 10%–15% of patients with myasthenia gravis have a thymoma (6). Ten percent of patients with a thymoma have hypogammaglobulinemia, whereas 5% have pure red cell aplasia (7). Thymomas are also associated with various autoimmune disorders such as systemic lupus erythematosus, polymyositis, and myocarditis (8).

Classification
The histologic typing of thymoma is complex and has been the source of controversy for many years. Thymomas are composed of neoplastic epithelial cells and nonneoplastic lymphocytes and exhibit marked histologic variability. In 1999, the World Health Organization (WHO)

<p>| Table 1 | WHO Classification Schemes for Thymoma |</p>
<table>
<thead>
<tr>
<th>Description</th>
<th>1999 WHO Classification</th>
<th>2004 WHO Classification</th>
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<tbody>
<tr>
<td>Spindle cells</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Mixed spindle cells and lymphocytes</td>
<td>AB</td>
<td>AB</td>
</tr>
<tr>
<td>Lymphocytes &gt; epithelial cells</td>
<td>B1</td>
<td>B1</td>
</tr>
<tr>
<td>Mixed lymphocytes and epithelial cells</td>
<td>B2</td>
<td>B2</td>
</tr>
<tr>
<td>Predominance of epithelial cells</td>
<td>B3</td>
<td>B3</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>C</td>
<td>Thymic carcinoma</td>
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</tbody>
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Note.—Adapted, with permission, from reference 3.
Consensus Committee published a histologic classification scheme for tumors of the thymus. Thymomas were classified into six separate histologic subtypes (types A, AB, B1, B2, B3, and C) on the basis of the morphology of the neoplastic epithelial cells together with the lymphocyte–epithelial cell ratio. An updated version of the WHO classification scheme was published in 2004 (2). It retained the earlier classifications of A–B3 thymomas but relegated type C to a separate category (thymic carcinoma), and also acknowledged that certain types of thymoma do not fall into any of these categories (Table 1).

Both the WHO classification scheme of 1999 and the updated version of 2004 were found to lack inter- and intraobserver reproducibility and clinical predictive value (9,10). To complicate matters, several WHO subtypes often coexist in the same tumor, which makes classification challenging—particularly at needle biopsy, which may not yield a sample of the predominant tumor subtype (Fig 1) (10). Today, histologic classification primarily distinguishes thymic carcinoma from the different types of thymoma (11). Currently, the histologic classification of thymoma has no clinical implications, and management decisions rest primarily on the stage of disease and the completeness of resection.
Staging

Many different staging systems for thymoma have been proposed (12–15). The Masaoka-Koga staging system (13) is the most commonly used and is the staging system recommended by the ITMIG (16), since it has been shown to correlate with survival in multiple series (17). 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 a neighboring organ such as the pericardium, great vessels, or lung; and stage IV, by pleural or pericardial dissemination (IVa) or lymphatic-hematogenous metastasis (IVb). The focus of staging has been on pathologic stage (ie, as defined after resection). However, clinical stage (imaging assessment prior to initiation of treatment) is of greater clinical importance, especially because surgery is not always the first step in treatment (16,18). Once the thymus has been removed, there is loss of orientation of the thymus. Without good communication between the surgeon performing the thymectomy and the pathologist, there may be failure to recognize certain tissue (eg, mediastinal pleura) in the specimen, which may lead to incorrect staging (16). In addition, good communication between the radiologist and surgeon is important for optimal preoperative planning and specimen handling (19). Alerting the surgeon to areas of concern can ensure that he or she uses a mediastinal board for specimen handling, thereby preserving orientation of the thymus once the specimen is delivered to the pathologist. The two factors that most strongly correlate with prognosis are staging and completeness of surgical resection (14,20–22).

The radiologist must be familiar with (a) the advantages and disadvantages of each imaging modality, and (b) the information it may offer with respect to thymoma staging and treatment planning.

Treatment

Because completeness of resection is a major prognostic factor (20–22), surgical resection is the cornerstone of treatment of patients with thymoma (18). When incomplete resection occurs, as when microscopic disease remains at the surgical site, postoperative radiation therapy is recommended to achieve complete disease eradication. This is why careful handling and identification of resection specimens by the surgeon and proper communication with the pathologist are essential, so that areas of concern can be identified for the planning of radiation therapy.

Stage I thymoma is treated with surgical resection alone (Table 2). There is no role for adjuvant radiation therapy or chemotherapy because it does not provide any survival benefit (17,18).

Stage II thymoma is also treated with extended thymectomy. Routine adjuvant radiation therapy is not recommended for stage IIa disease (microscopic capsular invasion) but is recommended for stage IIb disease (eg, invasion into surrounding fat, close surgical margins, tumor adherent to but not penetrating the pericardium). Chemotherapy is not recommended for stage II disease (17).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
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<tr>
<td>I</td>
<td>Complete surgical resection</td>
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<tr>
<td>II</td>
<td>Complete surgical resection; if resection is incomplete, postoperative radiation therapy</td>
</tr>
<tr>
<td>III</td>
<td>Neoadjuvant chemotherapy followed by complete surgical resection;* if resection is incomplete, postoperative radiation therapy</td>
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<tr>
<td>IVa</td>
<td>Neoadjuvant chemotherapy followed by complete surgical resection;* if resection is incomplete, postoperative radiation therapy</td>
</tr>
<tr>
<td>IVb</td>
<td>Palliative chemotherapy</td>
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Note.—Adapted, with permission, from references 17 and 18. *For stage III or IVa tumors, adjuvant chemotherapy may be considered, but data are insufficient to routinely recommend its use after complete resection.
Figure 2. Thymic hyperplasia in a 23-year-old woman with Ewing sarcoma. (a) Contrast material–enhanced chest CT scan obtained prior to the initiation of chemotherapy shows the triangular morphology of the normal thymus (arrow). (b) Contrast-enhanced chest CT scan obtained 3 months after completion of chemotherapy shows diffuse enlargement of the thymus with preservation of its triangular shape (arrow), findings that are consistent with thymic hyperplasia.

The goal of treatment in stage III disease is complete resection. Patients with locally advanced thymomas typically receive neoadjuvant chemotherapy to allow effective resection (23,24), since complete resection—even of advanced disease—improves survival (20,25). Recent reports suggest that neoadjuvant therapy provides a survival advantage compared with adjuvant therapy in patients with stage III thymomas (26–28). Postoperative radiation therapy is recommended, and postoperative chemotherapy is considered, in cases of incomplete resection of stage III thymomas (17,18).

Treatment of stage IVa thymomas is similar to that of stage III lesions. Stage IVb thymomas should be treated with chemotherapy with palliative intent.

The radiologist’s main role is to distinguish early disease (stages I and II) from advanced disease (stages III and IV), since postoperative Masaoka-Koga staging cannot be used to guide decisions about neoadjuvant therapy (13,14).

Imaging Evaluation

The role of imaging is to initially diagnose and properly stage thymoma, with emphasis on the detection of local invasion and distant spread of disease, to identify candidates for preoperative neoadjuvant therapy (ie, those with stage III or IV disease). Imaging of treated patients is directed at identifying resectable recurrent disease, since patients with completely resected recurrent disease have similar outcomes as those without recurrence (29,30).

Nonneoplastic thymic enlargement must not be confused with thymoma. The normal thymus in young children and the hyperplastic thymus may mimic a mediastinal mass. The normal adult thymus is not visible at chest radiography but has a triangular shape at CT and magnetic resonance (MR) imaging and is best visualized at the level of the aortic arch. Thymic hyperplasia characteristically manifests at CT as a diffusely and symmetrically enlarged thymus with smooth borders and preservation of the normal thymic shape (Fig 2). Occasionally, however, thymic hyperplasia may alter the normal thymic shape, manifest as a focal thymic mass, or even demonstrate 2-[fluorine-18] fluoro-2-deoxy-d-glucose (FDG) uptake, mimicking thymoma (31). In a study by Nicolau et al (32) of 45 patients with myasthenia gravis who underwent chest CT followed by thymectomy, 22 patients were found to have lymphoid follicular hyperplasia. In the majority of patients (77%),
Figure 3. Hyperplastic thymus in a 25-year-old woman with myasthenia gravis. (a) Transverse in-phase T1-weighted MR image shows diffuse enlargement of the thymus without preservation of its normal triangular morphology (arrow). (b) Opposed-phase gradient-echo T1-weighted MR image shows decreased signal intensity within the thymus (arrowhead), a finding that is consistent with hyperplastic thymus. (Fig 3 courtesy of Loren Ketai, MD, Department of Radiology, University of New Mexico, Albuquerque, NM.)

Figure 4. Invasive thymoma in an asymptomatic 57-year-old man. Posteroanterior (a) and lateral (b) chest radiographs demonstrate a large, unilateral right anterior mediastinal mass with lobular contours (arrow).

Figure 5. Drawing illustrates a normal pediatric thymus, which may extend to the inferior border of the thyroid gland. After puberty, the thymus involutes and will rarely be recognized in the thoracic inlet, although thymomas may occasionally occur in this cephalic location.
the thymus was normal appearing or diffusely enlarged; however, the remaining patients (23%) presented with a thymic mass mimicking thymoma (32). When differentiation between nonneoplastic thymic enlargement and thymoma cannot be achieved at CT or conventional MR imaging, chemical shift MR imaging with in-phase and out-of-phase gradient-echo sequences can be helpful. This technique helps identify the normal fatty infiltration of the normal or hyperplastic thymus, which unlike thymoma manifests with homogeneously decreased signal on out-of-phase images relative to in-phase images (Fig 3) (33,34).

Radiographically, thymoma typically manifests as a unilateral, well-marginated anterior mediastinal mass with smooth or lobulated contours, located anywhere from the thoracic inlet to the cardiophrenic angle (Figs 4, 5). Thymoma may produce thickening of the anterior junction line or may be seen as a nodule or mass in the retrosternal region at lateral chest radiography. Radiographic signs of locally advanced disease include irregular borders with adjacent lung elevation and elevation of the hemidiaphragm due to phrenic nerve involvement (Fig 6). Pleural nodularity is indicative of pleural metastases (stage IVa disease) (Fig 7).

CT is the imaging modality of choice for evaluating thymoma and can help distinguish thymoma from other anterior mediastinal abnormalities. Extensive mediastinal lymphadenopathy, pleural effusions, and pulmonary metastases are more characteristic of other neoplastic processes (eg, thymic carcinoma or lung cancer) than of thymoma. Thymoma typically manifests as a 1–10-cm mass (mean, 5 cm) with smooth (Fig 8) or lobulated contours that characteristically arises from one lobe of the thymus. However, bilateral mediastinal involvement can also occur (3). Intravenous contrast material should be administered if not contraindicated, since vessel evaluation is important for staging. Homogeneous enhancement is characteristic, although heterogeneity can be seen in about one-third of thymomas due
Stage III thymoma in an asymptomatic 41-year-old man. Contrast-enhanced chest CT scan shows a 17-cm left anterior mediastinal mass (M), which has heterogeneous enhancement and invades the superior vena cava (⋆) and collateral circulation (arrows). The mass proved to be rich in epithelial cells (WHO type B3).

To necrosis, cystic change, or hemorrhage. Soft-tissue nodules in a cystic anterior mediastinal lesion should alert the radiologist that the lesion is a cystic neoplasm (cystic thymoma) rather than a congenital cyst (3). Calcification may occur and can be punctate, linear along the capsule, or coarse and within the tumor.

Thymomas may result in vascular invasion (Fig 9), pleural involvement, or pericardial dissemination. Direct signs of vascular involvement include (a) an irregular vessel lumen contour, (b) vascular encasement or obliteration, and (c) endoluminal soft tissue, which may extend into cardiac chambers (3). Pleural dissemination (“drop metastases”) manifests at CT as one or more pleural nodules or masses, which can be smooth, nodular, or diffuse and are almost always ipsilateral to the anterior mediastinal tumor (Fig 10). Pleural effusion is uncommon, even in the presence of extensive pleural metastases (35).

CT has been thought to have a limited role in the detection of tumor invasiveness (36), even though there have been very few systematic studies comparing CT findings and thymoma invasiveness. The majority of studies assessing the thymus have included either thymic hyperplasia or thymic carcinoma, have not provided statistical analysis of the thymoma patient group alone, and have usually described these tumors with reference to the WHO classification system rather than the clinically used Masaoka-Koga staging system (37–42). However, three new studies have compared Masaoka-Koga stage with CT findings.
In two retrospective studies assessing 50 and 58 patients with thymoma, respectively (43,44), the authors tried to distinguish stage I thymoma from more advanced disease (stages II–IV) and found that partial or complete obliteration of fat planes around the tumor was not helpful in making this distinction. However, lobulated or irregular contours, cystic or necrotic regions within the tumor, and multifocal calcifications were more suggestive of invasive thymoma at univariable analysis.

In an attempt to distinguish between patients who require neoadjuvant therapy before surgery (ie, those with stage III or IV disease) and those who do not (ie, those with stage I or II disease), the authors of a third study comparing the CT findings in 99 patients with thymoma found that CT was useful in making this distinction (45). The CT characteristics that showed a significant association with stage III and IV disease at multivariable analysis were a primary tumor 7 cm or larger (Fig 11), infiltration of the fat surrounding the tumor (Fig 12), and lobulated tumor contours.

Several CT studies have correlated CT appearance with WHO histologic classification. Two of these studies yielded contradictory results: One study found that thymomas with lobulated contours were associated with type B2 and B3 tumors (37), whereas the other study showed that CT is of limited value in differentiating types A, AB, and B1 from types B2 and B3 (41). Tomiyama et al (40) found that type A thymomas were more likely to have smooth contours, but that CT
Figure 13. Thymoma in a 54-year-old woman with facial swelling. (a) Contrast-enhanced gradient-echo T1-weighted MR image shows an intermediate-signal-intensity mass (M) with invasion of the superior vena cava (arrow). (b) Oblique FIESTA (fast imaging employing steady-state acquisition) MR image demonstrates encasement of the right coronary artery (arrowhead), which precluded complete surgical excision of the mass.

Figure 14. WHO type B1 thymoma in a 47-year-old woman with left-sided neck pain. (a) Axial T1-weighted MR image shows a rounded intermediate-signal-intensity mass (M) in the anterior mediastinum. (b) Axial fat-suppressed T2-weighted MR image demonstrates a 6-cm anterior mediastinal mass (M) with high signal intensity at the level of the ascending aorta (Ao). The mass was diagnosed as a lymphocyte-rich WHO type B1 thymoma at resection.

was of limited value in differentiating types AB, B1, B2, and B3. These conflicting results may be due in part to the limitations of the WHO classification scheme or the small size of these CT studies (45–76 patients).

With advances in multidetector CT technology, the use of MR imaging in the evaluation of thymoma has decreased. However, when the intravenous administration of iodinated contrast material is contraindicated, MR imaging is used for the assessment of local tumor invasiveness (Fig 13). At MR imaging, thymomas manifest with low to intermediate signal intensity on T1-weighted images, and with high signal intensity on T2-weighted images (Fig 14) that may approach the signal intensity of fat (46,47). Fat-suppression techniques may be useful in differentiating surrounding fat from thymoma. Heterogeneous signal intensity is present in tumors with necrosis, hemorrhage, or cystic change. Cystic changes and intratumoral necrosis manifest with low signal intensity on T1-weighted images and high signal intensity on T2-
weighted images. In addition, fibrous septa within the tumor and associated nodularity can be seen as low-signal-intensity regions, which help differentiate cystic thymoma from congenital cysts (Fig 15). The appearance of hemorrhage may vary according to its age. Low signal intensity due to hemosiderin deposition may be seen on T1- and T2-weighted images. Although CT is superior to MR imaging in the depiction of calcification within thymomas, MR imaging can occasionally reveal fibrous septa within the mass, as well as permit better evaluation of the tumor capsule. Visualization of the capsule and of septa within a tumor has been shown to be associated with a less aggressive histologic appearance (41). Sakai et al (48) studied 31 patients with thymoma using dynamic MR imaging and showed that mean peak time was delayed in advanced-stage thymomas (stage III) compared with earlier-stage tumors.

Nuclear medicine techniques are not currently used for the evaluation of thymic neoplasms. Indium-111 octreotide shows uptake in thymoma and is used to identify patients who may respond to treatment with octreotide, which is considered to be the second- or third-line therapy when conventional chemotherapy fails (49). The precise role of FDG positron emission tomography (PET) in the management of thymomas is unclear. One difficulty is that increased physiologic FDG uptake by a normal or hyperplastic thymus is common, especially in children and in adults younger than 40 years of age (Fig 16). Studies
that have assessed FDG PET of thymoma are small, with the majority including thymic cancers (50,51). A study of 33 patients with thymic epithelial cancer—eight with low-risk thymoma (WHO types A, AB, and B1), nine with high-risk thymoma (WHO types B2 and B3), and 16 with thymic cancer—showed that FDG PET was not able to help distinguish low-grade from high-grade thymoma, but that thymic cancers tended to have higher FDG activity (51). In an internal review at M.D. Anderson Cancer Center, 31 patients with thymoma underwent FDG PET/CT prior to surgery. The FDG uptake as assessed on the basis of maximum standardized uptake value was variable and could not help distinguish early-stage (stages I and II) from advanced-stage (stages III and IV) disease ($P = 0.66$). Currently, FDG PET/CT may highlight metastatic disease (Figs 17, 18), but its exact role in the management of thymoma has not yet been defined.

**Differential Diagnosis**

The differential diagnosis for anterior mediastinal tumors includes other primary thymic malignancies (eg, thymic carcinoma, thymic carcinoid tumor), nonthymic tumors (eg, lymphoma, germ cell tumor, small-cell lung cancer), and mediastinal metastasis. Patient age and gender, tissue composition as assessed at CT, ancillary CT findings, and evidence of tumor invasiveness are helpful in developing the differential diagnosis for anterior mediastinal masses. For example, thymoma rarely manifests with lymphadenopathy, pleural effusions, or extrathoracic metastases. When one or more of these findings are seen, a diagnosis other than thymoma is more likely. Some anterior mediastinal masses have a typical appearance. For example, a cystic anterior mediastinal mass with intrinsic fat attenuation typically represents a mature teratoma. Malignant germ cell neoplasms almost exclusively affect men and are more common in patients younger than 40 years of age.

**Recurrence and Follow-up**

Thymoma is an indolent disease that requires a lengthy follow-up. It is important to identify recurrence early, while complete resection can be achieved. In doing so, outcomes similar to those of patients without tumor recurrence after initial resection are obtained, with 5-year survival rates ranging from 65% to 80% (29,30). ITMIG follow-up recommendations suggest that, at a minimum, chest CT should be performed annually for 5 years after surgical resection, and then alternated with annual chest radiography until year 11, followed by annual chest radiography alone (16), since late recurrences are not uncommon. The reported average time to recurrence of a completely resected thymoma is approximately 5 years (range, 3–7 years) (16). One study suggested a correlation with tumor stage and showed a mean time to recurrence of 10 years in patients with stage I thymoma, compared with 3 years in patients with stages II–IV thymoma (52). Patients with resected stage III
or IVa thymoma, thymic carcinoma, incomplete resection, or other high-risk tumors should undergo CT every 6 months for 3 years. Although use of MR imaging can help limit radiation dose, its ability to help detect early recurrence compared with CT has not been assessed.

**Conclusions**

Although thymoma is a rare tumor, it is the most common primary neoplasm of the anterior mediastinum. Imaging plays an essential role in the diagnosis, staging, and follow-up of thymoma, and CT is the cross-sectional imaging modality of choice. Tumor stage and extent of resection are the most important prognostic factors. Tumors with a favorable outcome are those that are encapsulated and amenable to complete resection. Invasive and unresectable tumors have a poor prognosis regardless of their histologic characteristics. Radiologists should be familiar with the imaging features of advanced-stage thymoma so that they can identify candidates for preoperative neoadjuvant therapy, thereby having a positive impact on patient outcomes.

**Figure 18.** Pleural recurrence in a 38-year-old woman with previously treated stage IVa thymoma. (a) Postoperative baseline CT scan shows normal right basilar pleura adjacent to the attachment of the diaphragm to the chest wall (arrow). (b) Follow-up contrast-enhanced chest CT scan obtained 2 years later shows increased diaphragmatic pleural thickening (arrow). (c) Axial fused FDG PET/CT image shows FDG-avid pleural recurrence (arrow).

**Disclosures of Potential Conflicts of Interest.**


**References**


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Teaching Points

Role of Imaging in the Diagnosis, Staging, and Treatment of Thymoma

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