OBJECTIVE. The purpose of our study was to describe and compare the CT and pathologic findings of atypical thymoma and thymic carcinoma.

MATERIALS AND METHODS. Twenty-seven consecutive patients (14 men, 13 women ranging in age from 22 to 77 years [mean age, 52 years]) with pathologically proven atypical thymoma (n = 9) and thymic carcinoma (n = 18) constituted the study population. The chest CT findings in each of the 27 patients were reviewed retrospectively in consensus by two chest radiologists. These findings were correlated with pathologic findings.

RESULTS. The tumors were located in the anterior mediastinum, and most tumors had a lobulated margin (24/27, 89%). Atypical thymomas were significantly smaller (mean, 4.7 cm) than thymic carcinomas (mean, 7.2 cm) (p = 0.041) on CT. The findings of invasion of the great vessels, lymph node enlargement, extrathymic metastases, and phrenic nerve palsy were seen only in patients with thymic carcinoma. The frequencies of necrosis, intratumoral calcification, pleural effusion, pleural implants, pericardial effusion, and obliteration of the mediastinal fat plane were not significantly different between atypical thymomas and thymic carcinomas (p > 0.05). Various histologic subtypes were included in thymic carcinoma. The tumor necrosis and calcification seen on CT were confirmed at pathologic examination.

CONCLUSION. When a large thymic tumor appears with invasion of the great vessels, lymph node enlargement, phrenic nerve palsy, or extrathymic metastases on CT, thymic carcinoma rather than atypical thymoma should be considered.

The nosology of thymic epithelial tumors is somewhat confusing [1–6]. Thymic epithelial tumors have been classified into three groups: benign thymoma, type 1 malignant thymoma (invasive thymoma), and type 2 malignant thymoma (thymic carcinoma) [7]. Type 1 malignant thymoma is diagnosed by the presence of local invasion or metastasis and shows cytoarchitecturally benign features indistinguishable from those of benign thymoma [6]. Type 2 malignant thymoma (thymic carcinoma), whether invasive or not, shows true malignant epithelial tumor features [8].

Recently, thymic epithelial tumors have been reclassified in consideration of their prognostic implication. The tumors include thymomas, atypical thymomas, and thymic carcinomas. Thymomas are further subclassified into medullary, mixed, and cortical thymomas. Of these three subcategories, cortical thymoma shows a rather locally aggressive clinical course. Thymic carcinomas, with a tendency to show local and distant metastases, comprise various histologic subtypes [9]. In addition, existence of a form of thymic epithelial tumors that is intermediate between thymomas and thymic carcinomas has been proposed. This intermediate form, which we call atypical thymoma, may emerge from benign cortical thymoma but differs histopathologically from the tumor by showing features of low-grade malignancy including cytologic atypia, large cell size, occasional mitotic figures, and aggressive behavior [6, 8, 10–13]. Despite these features of low-grade malignancy, atypical thymoma preserves a few hallmarks of thymic differentiation such as the organotypical features of normal thymus. Kirchner et al. [8] designated the tumors “well-differentiated thymic carcinoma.” Hofmann et al. [14] called these tumors epithelial or epidermoid thymoma. Suster and Moran [5, 13, 15] proposed the term “atypical thymoma” for these tumors because such lesions, although cellular, do not display the overt...
Thymic carcinoma is characterized by the loss of the organotypical features and histologic features of cytologic atypia similar to those seen in other conventional types of carcinoma. Thymic carcinoma is difficult to classify because of its histologic diversity and the inconsistency in correlating morphology with clinical behavior [9, 16, 17].

Between October 1994 and January 2000, either atypical thymoma (n = 9) or thymic carcinoma (n = 18) was diagnosed in 27 patients in a tertiary referral hospital. In 20 patients, the diagnosis was made on the basis of surgical resection (total or extended thymectomy in 18 and debulking surgery in two), and in the remaining seven patients the diagnosis was made at biopsy (percutaneous core needle biopsy in two, mediastinoscopic biopsy in two, incisional biopsy in two, and with video-assisted thoracoscopic surgery in one). The tumors were considered to be of primary thymic origin because the patients had neither evidence of a tumor in other primary sites nor abnormally elevated serum tumor markers such as α-fetoprotein or human chorionic gonadotropin.

The patients were 14 men and 13 women whose ages ranged from 22 to 77 years (mean, 52 years). Patients with atypical thymoma (n = 9, two men and seven women) ranged in age from 30 to 67 years (median, 50 years), and those with thymic carcinoma (n = 18, 12 men and six women) ranged from 22 to 77 years (median, 58 years).

When the tumors showed cytologic atypia, large cell size, occasional mitotic figures, and aggressive behavior with the preservation of organotypical features of a normal thymus, the tumors were classified as atypical thymoma [5, 8, 13, 15]. These tumors did not display the overt cytologic features of malignancy. When the tumors showed loss of organotypical features of the thymus (this is not observed in thymomas) and cytologic atypia, nuclear prominence, a high nucleocytoplasmic ratio, and regional necrosis, the tumors were classified as thymic carcinoma [6, 9]. On light microscopic and immunohistochemical staining examinations, the subtypes of thymic carcinomas were determined. Various histologic features of poorly differentiated nonkeratinizing squamous cell carcinoma (n = 10), well-differentiated squamous cell carcinoma (n = 2), small cell or neuroendocrine carcinoma (n = 3), large cell neuroendocrine carcinoma (n = 2), and clear cell carcinoma (n = 1) were seen in 18 patients with thymic carcinoma.

Twenty-one patients presented with chest pain or discomfort (n = 9), dyspnea (n = 5), symptoms indicating myasthenia gravis (n = 4), dry cough (n = 1), facial edema (n = 1), and general weakness (n = 1). The remaining six patients (two with atypical thymoma and four with thymic carcinoma [22%]) in whom the tumor was detected incidentally were asymptomatic. Four patients (4/9, 44%) with myasthenia gravis had atypical thymoma. One patient with large cell neuroendocrine thymic carcinoma had Cushing’s syndrome.

CT scans were available in all patients. The mean interval between pathologic diagnosis and CT scanning was 15 days (range, 2–35 days). CT consisted of helical scanning plus additional thin-section scanning using a HiSpeed Advantage scanner (General Electric Medical Systems, Milwaukee, WI) in 23 patients. When the main lesion site was identified in a scanogram (initial topography for a detailed CT section), unenhanced high-resolution CT was performed through the lesion with 1-mm collimation and at 5-mm intervals before the performance of helical CT. Helical CT was performed from the lung apices to the middle portion of both kidneys with 7-mm collimation and a pitch of 1.3. Scanning was performed after the IV injection of contrast medium (100 mL of iopamidol [Iopamiron 300; Bracco, Milan, Italy]) at a rate of 2 mL/sec with a power injector (MCT Plus; Medrad, Pittsburgh, PA). The image data were reconstructed using 7-mm collimation. In the remaining four patients, whose scanning was performed in other hospitals, scanning consisted of conventional CT from the level of the thoracic inlet to the level of the middle portion of the kidneys (10-mm collimation) with the IV administration of contrast medium. Scanning parameters were 120 kVp and 200 mA. All image data were reconstructed using the bone algorithm. CT was performed with the lung (window width, 1500 H; window level, –700 H) and mediastinal (window width, 400 H; window level, 20 H) windows.

Chast CT scans were assessed retrospectively in one session by two chest radiologists who were unaware of the final diagnosis. Decisions on the findings were reached by consensus. The CT analysis included the location, size, marginal characteristics, homogeneity, attenuation compared with chest wall muscle, and degree of enhancement of the tumor; the presence of tumor necrosis and calcification; and associated findings. The presence of mediastinal fat infiltration, invasion of the great vessels, pleural and pericardial effusion, pleural implants, lymph node enlargement, and metastases was also evaluated.

The location of the tumor was categorized as right, left, or midline in the anterior mediastinum. The longest diameter of the tumor was measured at the level where the axial tumor image appeared largest. Marginal characteristics were subdivided into smooth, lobulated, and irregular. The degree of enhancement of the tumor was recorded in Hounsfield units and was calculated from the difference in measured attenuation values on unenhanced (thin-section CT) and enhanced images (enhanced helical CT). This measurement was obtained in only 23 patients in whom both high-resolution and helical CT scans were available. Tumor necrosis was presumed to be present when a focal area of lower attenuation than the remaining large portion of enhancing tumor was seen on enhanced scans. The extent of tumor necrosis was semiquantified and recorded to the nearest 5% of tumor volume by combining the numbers of visible estimation of the necrotic low-attenuation area on each CT scan. Invasion of the great vessels was regarded as present when the tumor abutted and altered the contour of the corresponding vessels, and/or when overt tumor thrombosis and vascular occlusion were also present.

CT findings were compared between the two groups of patients (those with atypical thymoma and those with thymic carcinoma). Statistical differences in CT findings between the two groups were analyzed using the chi-square or Fisher’s exact test and the Mann-Whitney test [20]. Pathology specimens were available in all patients, and gross specimens were available in 20 patients who underwent surgical resection. An experienced lung pathologist reviewed all pathology specimens. The percentages of tumor necrosis and calcification of the main tumor were also evaluated. When mediastinal nodes were dissected, the presence of malignant cells in the nodes was analyzed. The presence of vascular invasion was also assessed.

Results

The tumors ranged in size from 1.8 to 12.6 cm (average, 6.4 cm). All tumors were located in the anterior mediastinum, either in the right side (n = 9), in the left side (n = 12), or in the midline (n = 6). Most tumors had lobulated margins (24/27, 89%). One atypical thymoma and one well-differentiated squamous carcinoma had smooth margins. One poorly differentiated nonkeratinizing squamous carcinoma was lobulated with an irregular margin.

The maximum diameter of thymic carcinoma (n = 9), 2.7–12.6 cm; average, 7.2 cm) was significantly larger than that of atypical thymoma (range, 1.8–8.8 cm; average, 4.7 cm) (p = 0.041). The tumors were either homogeneous (n = 12) (Figs. 1 and 2) or inhomogeneous (n = 15) (Figs 3 and 4), and most showed isosattenuation with the chest wall muscles without a significant difference between the two groups (p > 0.05). The mean degree of enhancement was 12.9 H (range, 3–36 H) in atypical thymoma and
Fig. 1.— Atypical thymoma in 35-year-old woman with myasthenia gravis.

A, CT scan using mediastinal window of unenhanced thin-section (1-mm) collimation obtained at level of azygos arch shows 18-mm left anterior mediastinal mass (arrows) with smooth margin. Mediastinal fat plane is well preserved.

B, Photomicrograph of histologic specimen shows organotypical features of thymic differentiation in low magnification. Note lobular pattern with intervening septa (solid arrows) and perivascular cystic spaces (open arrows). (H and E, ×40)

C, Photomicrograph of histologic specimen shows epithelial cells with atypical polygonal features (distinct epidermoid differentiation) (arrows). Cells are admixed with small lymphocytes (arrowheads). (H and E, ×200)

Fig. 2.— Thymic large cell neuroendocrine carcinoma in 22-year-old man with Cushing's syndrome.

A, Enhanced CT scan (7-mm collimation) obtained at subcarinal level shows 27-mm mass in right anterior mediastinum. Mass contains nodular calcification (arrow) and shows enhancement, with slightly higher attenuation than chest wall muscles. Fat plane between mass and adjacent mediastinal structure is not obliterated.

B, Photomicrograph of histologic specimen shows organoid growth pattern in low magnification. Note absence of organotypical features (interlobular septa and perivascular cystic spaces) of thymic differentiation. (H and E, ×40)
15.8 H (range, 2–54 H) in thymic carcinoma ($p > 0.05$). Areas of necrosis were seen in five (56%) of nine patients with atypical thymoma and in eight (44%) of 18 patients with thymic carcinoma. The extent of necrosis was 10–80% (mean, 27%) in atypical thymoma and 5–50% (mean, 23%) in thymic carcinoma. Intratumoral calcifications were observed in three patients (33%) with atypical thymoma and in 11 patients (61%) with thymic carcinoma ($p > 0.05$) (Figs. 2A and 3B). Most intratumoral calcifications were stippled except in two patients with poorly differentiated nonkeratinizing squamous cell carcinoma and large cell neuroendocrine carcinoma who had nodular calcification.

Pleural effusion was present in three patients (33%) with atypical thymoma and in seven patients (39%) with thymic carcinoma ($p > 0.05$) (Fig. 3C). Nodular or plaquelike pleural thickening was seen in one patient (11%) with atypical thymoma and in six patients (33%) with thymic carcinoma (Figs. 3C and 4C). A small amount of pericardial effusion was seen in two patients (22%) with atypical thymoma and in five patients (28%) with thymic carcinoma ($p > 0.05$). Obliteration of the mediastinal fat plane, suggesting invasion or simple adhesions, was seen in two patients (22%) with atypical thymoma and in six patients (33%) with thymic carcinoma (Figs. 3 and 4).

In seven (39%) of 18 patients with thymic carcinoma, invasion of the great vessels was suggested on CT (Fig. 3). The involved vessels were the right or left innominate vein ($n = 6$), the superior vena cava ($n = 1$), the aorta ($n = 1$), and the pulmonary trunk ($n = 1$). Lymph node enlargement ($> 1$ cm in the short-axis diameter) suggesting nodal metastasis was seen in eight (44%) of 18 patients with thymic carcinoma (Fig. 4B). The enlarged nodes were located in the right lower paratracheal ($n = 5$), subcarinal ($n = 3$), right upper paratracheal ($n = 2$), aortopulmonary window ($n = 2$), paraaortic ($n = 2$), paraesophageal ($n = 2$), hilar ($n = 2$), right cardiophrenic angle ($n = 2$), left upper paratracheal ($n = 1$), left lower paratracheal ($n = 1$), and right internal mammary chain ($n = 1$) areas. Metastases to the lung ($n = 4$) or liver ($n = 2$) (Fig. 4D) were observed in five (28%) of 18 patients with thymic carcinoma. Left diaphragmatic elevation suggesting phrenic nerve palsy was seen in one patient with thymic carcinoma. The findings of invasion of the great vessels, lymph node enlargement, extrathymic metastases, and phrenic nerve palsy were not seen in any patient with atypical thymoma. Our findings are summarized in Table 1.

Of 20 patients who underwent surgical resection, one (13%) of eight patients with atypical thymoma and nine (75%) of 12 patients with thymic carcinoma showed necrotic areas (range, 5–80%; mean, 23%) at histopathologic examination. The extent of necrosis was parallel to that seen on CT. Three (25%) of 12 patients with thymic carcinoma, who had calcification on CT, had intratumoral calcification. Of eight patients who had enlarged mediastinal lymph nodes on CT, four patients underwent lymph node dissection. Of these four patients, three patients had lymph node metastasis. Of seven patients with great vessel invasion seen on CT, pathologic specimens were available in five patients. Four (80%) of the five patients had vascular invasion at surgery and at pathologic examination. Conversely, in one patient in whom CT did not suggest vascular invasion, invasion of the left innominate vein was seen at surgery and at pathologic examination.

**Discussion**

The term “thymic tumor” (thymoma and thymic carcinoma) is used exclusively to designate neoplasms of the thymic epithelial cells, distinguishing the epithelial tumors from nonepithelial ones in the thymus such as lymphoma of the thymus, thymic carcinoid, germ cell tumor of the thymus, and thymolipoma [17, 18]. Primary thymic epi-
thelial neoplasm is presumed to form part of a spectrum of differentiation, regardless of the presence of local invasion [5, 8, 13, 15]. At one end of the spectrum, tumors appear with a high degree of organotypical differentiation simulating the normal thymus (thymomas). At the other end, tumors appear with loss of the organotypical features (the shaping of lobular units, palisading of epithelial cells around perivascular spaces, and abortive Hassall’s corpuscles) and with cytologic atypia that are designated thymic carcinoma. Between the ends of the spectrum, tumors exist that show combined features of thymoma and thymic carcinoma. These tumors show mild cytologic atypia. However, they still retain most of the organotypical features of differentiation of the normal thymus. These tumors are called atypical thymoma or well-differentiated thymic carcinoma [5, 8, 10–13].

Atypical thymoma or well-differentiated thymic carcinoma is characterized by low-grade malignancy. The tumors usually invade contiguous structures and frequently cause endo-thoracic (without extrathoracic) metastasis but are rarely fatal through local recurrence and progressive endo-thoracic spread [8]. Because the tumors maintain histopathologically the organotypical features of the thymus and show good prognosis, we prefer the term “atypical thymoma” to “well-differentiated thymic carcinoma.” The term “atypical thymoma” may also help to distinguish the tumors from thymic carcinoma.

Thymic carcinoma lacks the organotypical features of thymoma but has a high degree of histologic anaplasia [8, 16–21]. Various histologic subtypes of thymic carcinomas have been described [1, 17, 22]. These various histologic patterns exhibit the pluripotential nature of the thymic epithelial cell [17, 22]. The described subtypes include squamous cell (epidermoid) (36%), lymphoepithelioma-like (a form of poorly differentiated squamous cell) (32%), undifferentiated (anaplastic) (11%), small cell (8%), basaloïd (4%), sarcomatoid (4%), clear cell (2%), and mucoepidermoid (2%) carcinoma.
noma, and adenocarcinoma (1%) [1, 17]. In addition, neuroendocrine differentiation is a common feature [22, 23]. Our study also showed marked predominance of squamous cell carcinomas, including the well- and poorly differentiated subtypes (12/18, 67%), paralleling previous reports [1, 22, 23]. Some researchers differentiate thymic carcinomas with high-grade and those with low-grade histology. Well-differentiated squamous carcinoma, low-grade mucoepidermoid carcinoma, and basaloid carcinoma usually show a favorable prognosis and are included in low-grade histology. Other variants (high-grade histology) are aggressive and require multimodality treatment [1, 2, 7, 18, 24–26].

Thymic carcinoma has a poorer survival rate and is associated with more aggressive behavior than invasive thymoma [25, 27, 28]. In the series by Wick et al. [2], the average survival of patients who died of thymic carcinoma (18/20 patients) was 18 months. In the study by Suster and Rosai [1] of 60 patients with thymic carcinoma, survival at 1 year was 57%, at 3 years was 40%, and at 5 years was 33%. In the study by Blumberg et al. [3] of 43 cases of thymic carcinoma, survival was 65% at 5 years and 35% at 10 years. In Suster and Rosai’s study, the following morphologic features showed poor prognosis: poorly circumscribed infiltrating tumor margins, mitotic count greater than 10 in 10 high-power fields on microscopic examination, lack of lobular growth, and tumors of high-grade histology. The study by Blumberg et al. showed that survival depended on whether the inominate vessels were invaded [3].

Thymic carcinoma is rarely associated with such paraneoplastic syndromes as myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia [2, 6, 7, 25, 27]. To our knowledge, only four cases of myasthenia gravis associated with thymic carcinomas have been reported in the literature [1, 17, 29]. However, myasthenia gravis is frequently associated with thymomas and atypical thymomas. In one series [8], the percentage of myasthenia gravis associated with atypical thymomas was highest among all types of thymic epithelial tumors, as high as 77%. Explanations for the high frequency are that atypical thymoma with preservation of few organotypical thymic features may provide the minimal, but the most effective, prerequisite for the pathogenesis of myasthenia gravis. Our study showed lower frequency (44%) of myasthenia gravis with atypical thymoma than the previous report of Kirchner et al. [8]. The frequency of myasthenia gravis in our study was similar to that of thymoma (30–60%) [17].

CT findings of thymic carcinoma have been reported sporadically. Findings described include a large and highly aggressive anterior mediastinal mass; areas of necrosis, hemorrhage, calcification, or cyst formation; invasion of contiguous mediastinal structures and spread to intrathoracic sites; and frequent extrathoracic metastases [17–19]. The tumors occur in a broad age range of patients with an average age of 46 years, cause a low incidence of paraneoplastic syndromes, and show a poor prognosis [17–19]. In addition to the findings, we could see mediastinal or hilar nodal enlargement and phrenic nerve palsy in the thymic carcinomas.

Until now, to our knowledge, differential points of CT findings between atypical thymoma and thymic carcinoma have not been published. In our study, the differentiation between atypical thymoma and thymic carcinoma was difficult with the CT findings of attenuation, homogeneity, necrosis or calcification, pleural or pericardial effusion, pleural implants, and mediastinal fat obliteration. However, the findings of invasion of the great vessels, lymphadenopathy, phrenic nerve palsy, and lung or distant metastases were seen only in patients with thymic carcinoma and were helpful in differentiating the two entities. Tumors were significantly larger in thymic carcinoma (mean, 7.2 cm) than in atypical thymoma (mean, 4.7 cm). Only one patient with large cell neuroendocrine carcinoma had a small tumor (2.7 cm), and this patient showed clinical findings of Cushing’s syndrome. Therefore, with large invasive thymic tumors (great vessel invasion), the presence of mediastinal or hilar lymph node enlargement, phrenic nerve palsy, and hematogenous metastasis suggests a possibility of thymic carcinoma other than atypical thymoma.

Thymic carcinoid, lymphoma, malignant mediastinal germ cell tumor, and metastatic tumor to the thymus are difficult to differentiate from thymic carcinoma or atypical thymoma on the basis of CT findings alone. The tumors may show necrotic areas, variable enhancement, infiltrating behavior, and metastatic properties [18, 19, 30]. The presence of mediastinal or hilar lymph node enlargement, vascular invasion of the great vessels, and extrathymic metastases favors the diagnosis of thymic carcinoma. However, those findings may also be seen in lymphomas and malignant germ cell tumors.

In conclusion, thymic carcinomas have various histologic subtypes and show various CT findings in heterogeneous age groups of patients. When a large thymic epithelial tumor shows invasion of the great vessels, lymph node enlargement, phrenic nerve palsy, or extrathymic metastases, thymic carcinoma should be the proper diagnosis. The

### Table 1: CT Findings of Atypical Thymoma and Thymic Carcinoma

<table>
<thead>
<tr>
<th>Finding</th>
<th>Atypical Thymoma (n = 9)</th>
<th>Thymic Carcinoma (n = 18)</th>
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<tr>
<td>Homogeneity</td>
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<tr>
<td>Homogeneous</td>
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<tr>
<td>Inhomogeneous</td>
<td>6 (67)</td>
<td>9 (50)</td>
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<tr>
<td>Attenuation</td>
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<td>Low</td>
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<td>1 (6)</td>
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<tr>
<td>Iso</td>
<td>7 (78)</td>
<td>15 (83)</td>
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<tr>
<td>High</td>
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<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>5 (56)</td>
<td>8 (44)</td>
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<tr>
<td>Calcification</td>
<td>3 (33)</td>
<td>11 (61)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>3 (33)</td>
<td>7 (39)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pleural implant</td>
<td>1 (11)</td>
<td>6 (33)</td>
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</tr>
<tr>
<td>Pericardial effusion</td>
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<td>5 (28)</td>
<td>&gt;0.05</td>
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<tr>
<td>Mediastinal fat obliteration</td>
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<td>6 (33)</td>
<td>&gt;0.05</td>
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<tr>
<td>Invasion of great vessels</td>
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<td>7 (39)</td>
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<td>8 (44)</td>
<td>&lt;0.001</td>
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<td>Metastases</td>
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<td>5 (28)</td>
<td>&lt;0.001</td>
</tr>
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</table>

Note.—Numbers in parentheses are percentages.

*One patient had both lung and liver metastases.
frequency of necrosis, intratumoral calcification, pleural effusion, pleural implants, pericardial effusion, and obliteration of the mediastinal fat plane on CT is not helpful in differentiating between atypical thymomas and thymic carcinomas.

References