Using the World Health Organization Classification of Thymic Epithelial Neoplasms to Describe CT Findings

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OBJECTIVE. Our purpose was to assess the CT features of various subtypes of thymic epithelial neoplasms on the basis of the 1999 World Health Organization classification.

MATERIALS AND METHODS. Thymic epithelial neoplasms in 53 patients who underwent thymectomy were retrospectively assessed histologically according to the 1999 World Health Organization classification. Type A and B neoplasms correspond to thymomas and type C, to thymic carcinoma. The study included four patients with type A, 14 with type AB, nine with type B1, 14 with type B2, four with type B3, and eight with type C epithelial tumors. Two observers independently assessed the CT scans without knowledge of the histologic findings.

RESULTS. Type A tumors were more likely to have smooth contours on CT (4/4, 100%) and round shapes (3.5/4, 88%) than any other type of thymic epithelial tumor (all, $p < 0.05$). Type C tumors had a higher prevalence of irregular contours (6/8, 75%) than any other type of thymic epithelial tumor (all, $p < 0.05$). Calcification was more frequently seen in type B1 (4/9, 44%), type B2 (8.5/14, 61%), and type B3 (3/4, 75%) tumors than in type AB (2/14, 14%) and type C (0.5/8, 6%) tumors (all, $p < 0.05$).

CONCLUSION. Smooth contours and a round shape are most suggestive of type A thymic epithelial tumor, whereas irregular contours are most suggestive of type C tumor. Calcification is suggestive of type B tumors. CT is of limited value, however, in differentiating type AB, B1, B2, and B3 tumors.

Thymic epithelial tumors have been traditionally classified into two main types: thymoma, which may be encapsulated or invasive and is histologically benign; and thymic carcinoma, which is a heterogeneous group of neoplasms that are histologically malignant. The prognosis of patients with thymomas varies considerably. Therefore, several classifications have been proposed for these tumors [1–10]. The classifications were aimed at reflecting invasiveness and prognosis [11–14]. However, there have been major criticisms of the various classifications and a lack of consensus on their value in prognosis [15–17]. More recently, a simple classification of the thymic epithelial tumors into thymoma, atypical thymoma, and thymic carcinoma has been proposed [18].

In 1999, the World Health Organization (WHO) proposed a consensus classification of thymic epithelial tumors [19]. This classification takes into account the morphology of epithelial cells as well as the ratio of epithelial cells to lymphocytes. It was recently reported that the WHO histologic classification reflects both the clinical and the functional features of thymic epithelial tumors [20]. Furthermore, histologic appearance reflects the oncologic behavior of thymoma if this novel classification system is used. Thus, the WHO histologic classification system may contribute to the clinical practice for the assessment and treatment of patients with thymoma [21]. On the basis of the previously reported results, the preoperative diagnosis according to the WHO histologic classification system should have an important implication in determining treatment strategy.

The aim of our study was to assess the CT features of the various subtypes of thymic epithelial tumors in the WHO classification.

Materials and Methods

CT images were available for retrospective review in 55 patients with thymic epithelial tumors who underwent CT of the chest at our institution on a variety of scanners as part of patient evaluations between April 1990 and October 2000. Two of the 55 patients with thymic cancer diagnosed at biopsy, who received chemotherapy and radiation but not surgical resection because of metastasis, were excluded from the analysis. The remaining 53 patients

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in whom a definitive diagnosis of thymic epithelial tumors was established by thymectomy formed the basis of our study (27 men and 26 women; age range, 26–74 years; mean, 52.3 years).

The surgical specimens were reviewed by an experienced pathologist, and the tumors were divided into six subtypes on the basis of the 1999 WHO classification. This classification is as follows: type A, tumor composed of a homogeneous population of neoplastic epithelial cells having spindle and oval shapes, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes; type AB, tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes, with sharp or indistinct segregation of the two patterns; type B1, tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla; type B2, tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a predominant population of lymphocytes (perivascular spaces are common); type B3, tumor predominantly composed of epithelial cells having a round or polygonal shape and exhibiting mild atypia, admixed with a minor component of lymphocytes (foci of squamous metaplasia and perivascular spaces are common); type C, tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to thymus, but rather analogous to those seen in carcinomas of other organs. The classification of type A, AB, B1, and B2 tumors does not specify which tumor types are encapsulated thymomas and invasive thymomas, but the classification of type B3 and C tumors corresponds to atypical thymoma and thymic carcinoma, respectively. All tumors were staged on the basis of the presence and extent of transcapsular invasion into adjacent mediastinal tissues as determined by surgical findings and confirmed at microscopic examination [22].

CT of the abnormal areas consisted of 3- to 10-mm-collimation sections. Protocols consisted of 10-mm-collimation contiguous sections through the thorax (14 patients), 7-mm collimation (five patients), or 5-mm collimation (34 patients). In 11 of the 34 patients with images obtained using 5-mm-collimation sections, additional images with 3-mm-collimation sections of the tumor were obtained. IV-administered contrast medium was used in all patients. The time interval between CT and thymectomy was 1–112 days (median, 19 days).

CT scans were randomized and then reviewed separately by two independent chest radiologists. The observers were aware that the patients had thymic epithelial tumors but did not know histologic subtypes.

CT scans were assessed for the size (short and long axis), contour, shape, attenuation of the tumor, presence of focal areas of low attenuation in the tumor, and presence of calcification in the tumor. The shape was classified as round if the long- to short-axis ratio was less than 1.5, oval if the ratio was equal to 1.5 or greater and less than 3.0, and plaque if the ratio was equal to or greater than 3.0. The distribution and location of calcification were noted. The distribution of calcification was classified as focal or multifocal. The location of calcification was classified as central if there was a predilection of abnormalities in the inner third of the tumor, peripheral if there was a predominance of abnormalities in the outer third of the tumor, and random if there was no predominance. The pattern of enhancement was recorded as homogeneous or heterogeneous, and the degree of enhancement was evaluated as less than that of chest wall muscle, equal to that of chest wall muscle, and higher than that of chest wall muscle by visual estimation. The presence of pleural effusion, pericardial effusion, and mediastinal and hilar lymphadenopathy (short-axis diameter >10 mm) was also assessed.

The differences in the prevalence of each CT finding among WHO histologic types were analyzed using the chi-square test; when small numbers invalidated the chi-square approximation, the Fisher's exact test was used. The differences in size among WHO histologic types were assessed using Scheffe's F test. The data used for analysis were averages of values for the two observers.

Results

The 53 primary tumors included 45 thymomas (four of type A, 14 of type AB, nine of type B1, 14 of type B2, four of type B3), and eight thymic carcinomas (type C) (Table 1). The proportion of invasive tumors with reference to WHO classification was 25%, 43%, 44%, 71%, 100%, and 100% in type A, AB, B1, B2, B3, and C tumors, respectively (Table 1).

Long- and short-axis diameters (mean ± SD) of tumors in each WHO histologic type were 2.75 ± 0.46 cm, 2.15 ± 0.49 cm in type A; 5.49 ± 1.68 cm, 3.72 ± 1.58 cm in type AB; 5.14 ± 2.11 cm, 3.13 ± 1.29 cm in type B1; 3.97 ± 1.14 cm, 2.39 ± 0.67 cm in type B2; 5.13 ± 3.06 cm, 3.28 ± 1.13 cm in type B3; and 6.59 ± 2.29 cm, 4.06 ± 1.99 cm in type C tumors, respectively. Long- and short-axis diameters of type C tumors were significantly greater than those of type A and B2 tumors ($p < 0.01$).

Type A tumors were more likely to have smooth contours (4/4, 100%) and a round

TABLE 1 **Clinical Stage and Incidence of Invasive Tumors According to the World Health Organization Classification [19]**

Type of Thymic Tumor	No. of Cases	Clinical Stage					Incidence of Invasive Tumors (%)
		I	II	III	IVA	IVB	
A	4	3	1	0	0	0	25
AB	14	8	5	1	0	0	43
B1	9	5	2	2	0	0	44
B2	14	4	6	3	1	0	71
B3	4	0	1	3	0	0	100
C	8	0	0	5	1	2	100
Total	53	20	15	14	2	2	62

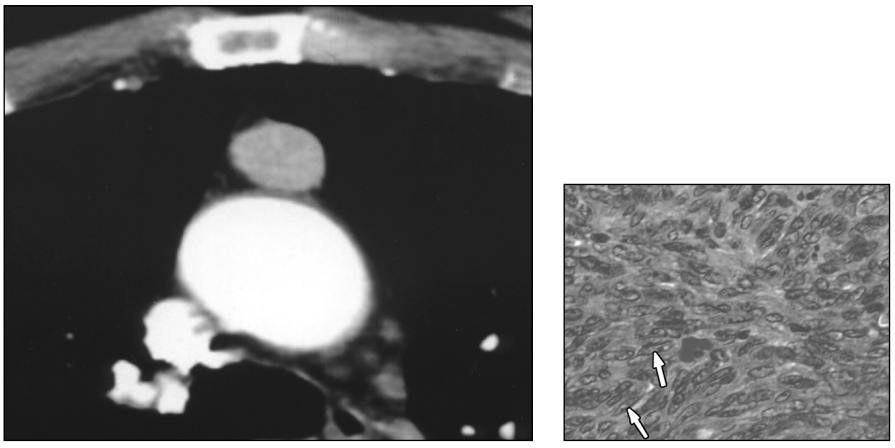


Fig. 1.—Type A tumor in 57-year-old woman.
A, Contrast-enhanced CT scan (5-mm collimation) obtained at level of azygos arch shows homogeneous anterior mediastinum mass with smooth contours and round shape. Mass was confirmed histopathologically as noninvasive thymoma (stage I, encapsulated thymoma).
B, Photomicrograph of histopathologic specimen shows spindle tumor cells (*arrows*) with no nuclear atypia (spindle cell type). Note small number of lymphocytes. (H and E, ×200)

shape (3.5/4, 88%) (Fig. 1) than type AB (6.5/14, 46% and 1/14, 7%, respectively) (Fig. 2); type B1 (3.5/9, 39% and 0/9, 0%, respectively) (Fig. 3); type B2 (4.5/14, 32% and 1/14, 7%, respectively); type B3 (0.5/4, 13%, and 0.5/4, 13%, respectively); and type C tumor (1/8, 13% and 1.5/8, 19%, respectively) (all, $p < 0.05$) (average of two observers) (Table 2). Type C tumors had a higher prevalence of irregular contours (6/8, 75%) than type A (0/4, 0%), type AB (1/14, 7%), type B1 (1/9, 11%), type B2 (2.5/14, 18%), and type B3 tumors (0.5/4, 13%) (all, $p < 0.05$). Calcification was more frequently seen in type B1 (4/9, 44%), type B2 (8.5/14, 61%) (Fig. 4), and type B3 tumors (3/4, 75%) than in type AB (2/14, 14%) and type C tumors (0.5/8, 6%) (all, $p < 0.05$). Heterogeneous enhancement was more often seen in type B3 (3/4, 75%) (Fig. 5) and type C tumors (7/8, 87%) than in type A (0.5/4, 12%), type AB (3.5/14, 25%), type B1 (3/9, 33%), and type B2 tumors (3.5/14, 25%) (all, $p < 0.05$). Pleural effusions were found in one (7%) of 14 cases of type AB, one (11%) of nine cases of type B1, and three (38%) of eight cases of type C; pericardial effusions were found in one (7%) of 14 cases of type AB and in three (38%) of eight of cases of type C. Mediastinal and hilar lymphadenopathy was seen in one (7%) of 14 cases of type AB and 3.5 (43%) of eight cases of type C tumors (Fig. 6), but not in any other types of thymoma. Metastasis of mediastinal lymph nodes removed at surgery were confirmed in one (type AB) of 45 cases of thymoma and four of eight cases of thymic cancer (type C) histopathologically.

The combination of homogeneous enhancement and a high degree of enhancement was seen in three (75%) of four cases of type A, nine (64%) of 14 cases of type AB, 1.5 (17%) of nine cases of type B1, three (21%) of 14 cases of type B2, zero (0%) of four cases of type B3, and zero (0%) of eight cases of type C tumors.

Agreement on the findings seen on each CT scan between two observers was 44 (83%) of 53 for contour, 43 (81%) of 53 for shape, 46 (87%) of 53 for attenuation of the tumor, 45 (85%) of 53 for low attenuation in the tumor, 51 (96%) of 53 for presence of calcification within the tumor, 51 (96%) of 53 for presence of pleural effusion, 47 (89%) of 53 for presence of pericardial effusion, 49 (92%) of 53 for presence of mediastinal and hilar lymphadenopathy, 50 (94%) of 53 regarding the pattern of enhancement, and 44 (83%) of 53 for the degree of enhancement.

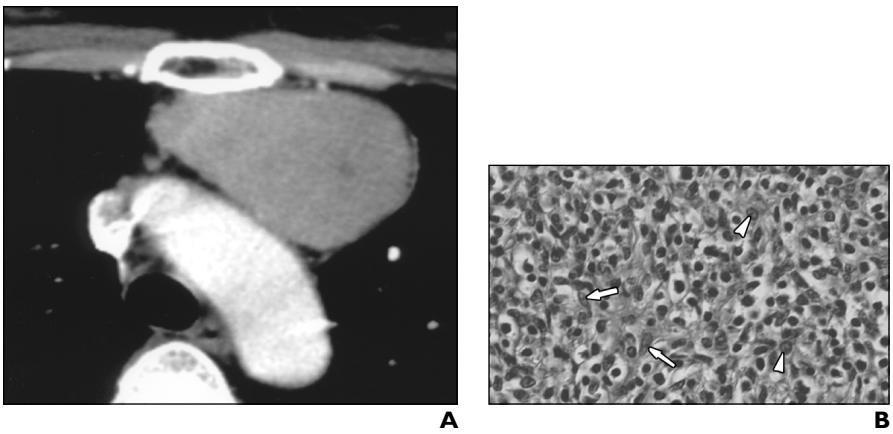


Fig. 2.—Type AB tumor in 55-year-old woman.
A, Contrast-enhanced CT scan (3-mm collimation) obtained at level of aortic arch shows oval mass in anterior mediastinum. Mass shows homogeneous enhancement with slightly higher attenuation than that of chest wall muscles.
B, Photomicrograph of histopathologic specimen shows lymphocyte-rich tumor with spindle (*arrows*) to oval (*arrowheads*) tumor epithelial cells (mixed type). Mass was confirmed histopathologically as noninvasive thymoma (stage I, encapsulated thymoma). (H and E, ×200)

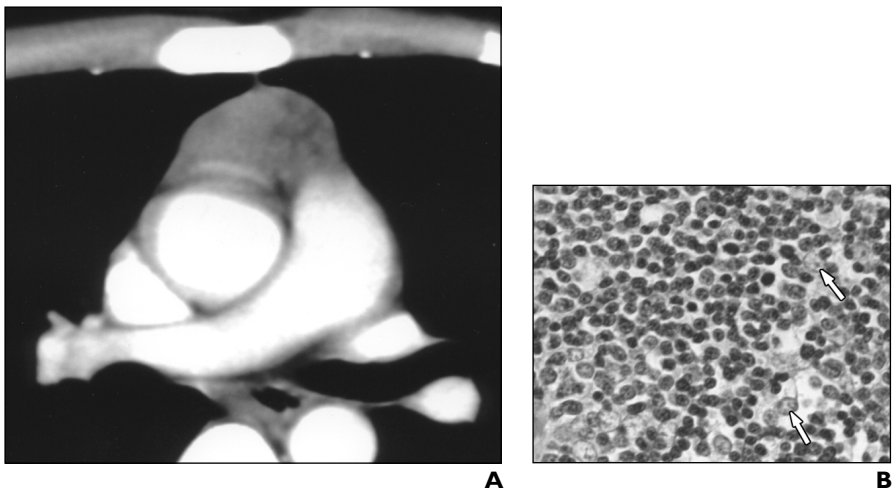


Fig. 3.—Type B1 tumor in 26-year-old woman.
A, Contrast-enhanced CT scan (7-mm collimation) obtained at right main pulmonary artery level shows mass at anterior mediastinum. Note smooth contours and oval shape of mass, which enhances heterogeneously with low attenuation.
B, Photomicrograph of histopathologic specimen shows predominance of lymphocytes and scattered tumor epithelial cells (*arrows*), resembling thymic cortex (lymphocyte-rich type). Mass was confirmed histopathologically as noninvasive thymoma (stage I, encapsulated thymoma). (H and E, ×200)

Discussion

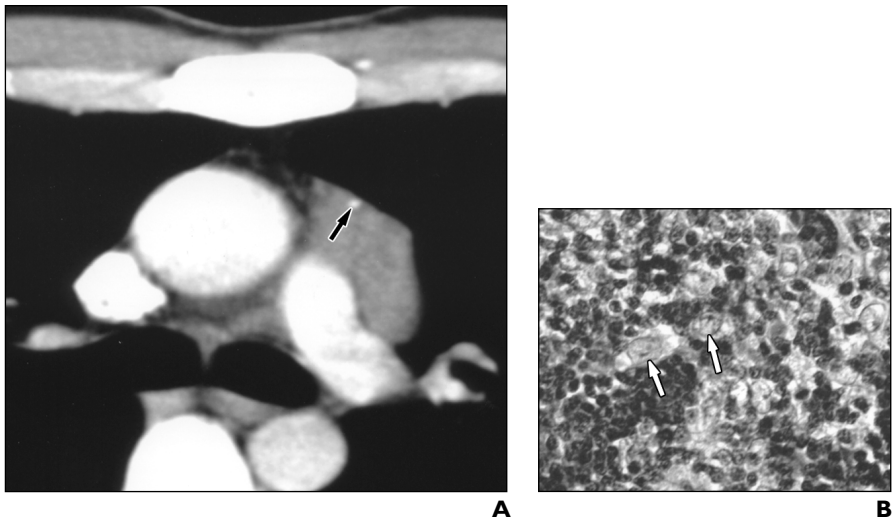
The 1999 WHO consensus classification of the thymic epithelial tumors is based on the morphology of epithelial cells and the ratio of epithelial cells to lymphocytes [19]. The relationship of the WHO classification and previous histologic classifications is as follows: type A corresponds to spindle cell type or medullary type thymoma; AB corresponds to mixed type; B1 corresponds to lymphocyte-rich type, lymphocytic type, predominantly cortical type, or organoid type; B2 corresponds to cortical type; B3 corresponds to epithelial type, squamoid type, or atypical thymoma, well-differentiated thymic carcinoma; and type C corresponds to thymic carcinoma.

The WHO histologic classification has been shown to reflect the clinical features of thymic epithelial tumors and to correlate with prognosis [20, 21]. The preoperative prediction of WHO histologic subtypes of thymic tumors may help clinical practice in the following situations: first, because type A, AB, or B1 thymomas have a less aggressive nature than type B2 or B3 thymomas, type A, AB, or B1 thymomas have more chances of complete resection than type B2 or B3 thymomas, even when CT findings suggest tumor invasion to the surrounding

TABLE 2 **CT Findings of Thymic Epithelial Tumors Based on the World Health Organization (WHO) Classification [19]**

CT Findings	WHO Classification					
	Type A (*n* = 4)	Type AB (*n* = 14)	Type B1 (*n* = 9)	Type B2 (*n* = 14)	Type B3 (*n* = 4)	Type C (*n* = 8)
Contour						
Smooth	4 (100)	6.5 (46)	3.5 (39)	4.5 (32)	0.5 (13)	1 (13)
Lobulated	0 (0)	6.5 (46)	4.5 (50)	7 (50)	3 (75)	1 (13)
Irregular	0 (0)	1 (7)	1 (11)	2.5 (18)	0.5 (13)	6 (75)
Shape						
Round	3.5 (88)	1 (7)	0 (0)	1 (7)	0.5 (13)	1.5 (19)
Oval	0.5 (13)	11 (79)	4.5 (50)	7.5 (54)	1.5 (38)	4.5 (56)
Plaque	0 (0)	2 (14)	4.5 (50)	5.5 (39)	2 (50)	2 (25)
Area of low attenuation	0.5 (13)	5.5 (39)	5.5 (61)	3.5 (25)	3 (75)	5 (63)
Calcification	1 (25)	2 (14)	4 (44)	8.5 (61)	3 (75)	0.5 (6)
Focal	1 (25)	0 (0)	4 (44)	4.5 (32)	1 (25)	0.5 (6)
Multifocal	0 (0)	2 (14)	0 (0)	4 (29)	2 (50)	0 (0)
Central	0 (0)	0 (0)	1 (11)	1.5 (11)	2 (50)	0 (0)
Peripheral	1 (25)	2 (14)	3 (33)	6 (43)	1 (25)	0.5 (6)
Enhancement pattern						
Homogeneous	3.5 (88)	10.5 (75)	6 (67)	10.5 (75)	1 (25)	1 (13)
Degree of enhancement						
Less than chest wall muscle	0 (0)	0 (0)	2 (22)	2.5 (18)	0 (0)	0.5 (6)
Equal to chest wall muscle	0.5 (13)	2 (14)	4.5 (50)	7.5 (54)	1 (25)	2 (25)
Greater than chest wall muscle	3.5 (88)	12 (86)	2.5 (28)	4 (29)	3 (75)	5.5 (69)
Pleural effusion	0 (0)	1 (7)	1 (11)	0 (0)	0 (0)	3 (38)
Pericardial effusion	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	3 (38)

Note.—Numbers and percentages of cases are actually averages of values for the two observers. Numbers in parentheses represent percentages.



A

B

Fig. 4.—Type B2 tumor in 35-year-old man.
A, Contrast-enhanced CT scan (5-mm collimation) obtained at carinal level shows slightly heterogeneous anterior mediastinum mass with plaque shape. Mass contains punctate peripheral calcification (*arrow*). Invasion of pericardium was confirmed at surgery (stage III, invasive thymoma).
B, Photomicrograph of histopathologic specimen shows moderate lymphocyte infiltration and plump tumor cells (*arrows*) with vesicular nuclei and distinct nucleoli (cortical type). (H and E, ×200)

organs. Therefore, patients with type A, AB, or B1 thymomas could be primarily treated by surgical resection, whereas patients with type B2 or B3 thymomas might require preoperative induction chemotherapy or radiation therapy. Second, because type A thymoma is the least invasive tumor, endoscopic surgery might be adopted more reasonably than with other types of thymomas. Third, although even subtotal resection of tumor contributes to the survival of patients with thymomas (type A, AB, B1, B2, or B3 tumors) when adequate adjuvant therapy is added, long-term survival cannot be expected for patients with thymic carcinoma (type C tumor, in case of incomplete resection). Thus, type C tumors require the exact preoperative diagnosis when involvement of the surrounding organs is suspected. Therefore, prediction of type C tumor by CT findings seems important to the recommendation of preoperative biopsy, such as needle biopsy.

In our study, smooth contours were present in all type A tumors, and the prevalence was decreasing from type A, AB, B1, B2, B3, to C tumors. Irregular contours were seen in none of type A tumors and in a small number of type AB, B1, B2, and B3 tumors, and irregular contours were found in 75% of type C tumors. It is reported that irregular tumor margin is suggestive of capsular invasion of thymoma (i.e., invasive thymoma and thymic carcinoma) [23, 24].

Jung et al. [25] found that atypical thymomas were significantly smaller than thymic carcinomas. In our study, long- and short-axis diameters of type C tumor were significantly longer than those of type A and B2 tumors, but there was no significant difference between type C tumors and type AB, B1, and B3 tumors.

Sone et al. [26] found a higher prevalence of calcification in invasive thymomas. In that study, calcification was present in four of 10 invasive thymomas and in none of the lesions of the seven patients with noninvasive thymoma. Recently, Tomiyama et al. [27] reported that calcification was found in 14.5 (54%) of 27 cases of invasive thymomas and six (26%) of 23 cases of noninvasive thymomas. In our study, calcification was found in 44% of type B1, 61% of type B2, and 75% of type B3 tumors. Do et al. [28] reported that calcification was found in one (10%) of 10 cases of thymic carcinoma and two (17%) of 12 cases of invasive thymoma. Jung et al. [25] reported calcification to be found in three (33%) of nine cases of atypical thymoma and 11 (61%) of 18 cases of thymic carcinoma. In our study, calcification was found in only 6% of type C tumors, which

corresponds to that of thymic carcinomas, and the prevalence of calcification was lower than in any type of thymic epithelial tumors.

In our study, areas of low attenuation were seen in 61% of type B1, 75% of type B3, and 63% of type C tumors. Tomiyama et al. [27] reported that areas of low attenuation were found significantly more often in patients with invasive thymoma than in patients with noninvasive thymoma. Although it is not clear why the prevalence of areas of low attenuation in type B2 tumors was low compared with that of type B1 and B3 tumors, areas of low attenuation were found significantly more often in patients with type B1, B3, and C tumors, which have a greater malignant potential than type A tumors.

Do et al. [28] reported that mediastinal lymphadenopathy was found in four (40%) of 10 cases of thymic carcinoma and one (8%) of 12 cases of invasive thymoma, and thymic carcinoma was more commonly associated with mediastinal nodes than invasive thymoma. Jung et al. [25] also reported that lymph node enlargement was found in eight (44%) of 18 cases of thymic carcinoma and in zero (0%) of nine cases of invasive thymoma; there was a significant difference between the two. The results of our study are similar, mediastinal lymphadenopathy being present in 43% of type C tumors, 7% of type AB, but not in any other types of thymic epithelial tumors.

Morgenthaler et al. [29] reported that attenuation is more heterogeneous in invasive thymoma after IV administration of contrast material. Tomiyama et al. [27] reported that homogeneous enhancement was found in 11 (41%) of 27 cases of invasive thymoma and 15 (65%) of 23 cases of noninvasive thymoma ($p < 0.05$). Enhancement degree whether less than, equal to, or greater than that of chest wall muscle was seen with similar frequency in noninvasive and invasive thymomas. In our study, heterogeneous enhancement was found in 75% of type B3 and 88% of type C tumors and in approximately 10–30% in other types of thymomas. Heterogeneous enhancement was present significantly more often in patients with type B3 thymoma and in those with type C thymoma (thymic carcinoma). A high degree of enhancement was found in 88% of type A, 86% of type AB, 75% of type B3, and 69% of type C tumors, and it was more often seen in these tumors than in type B1 and B2 tumors. Although the reason for the low enhancement of type B1 and B2 is not clear, it is conceivably related to the fact that these subtypes of thymoma are both lymphocyte-rich tumors.

Our study has several limitations. Some factors, including variation in section thickness, low numbers of each type of tumor, visual estimation of the image, observer variation, and the extensive delay between CT and surgery in some patients, could have affected interpretive outcome such as evaluation of presence of calcification in the tumor, degree of enhancement, and potential changes in tumor size and histol-

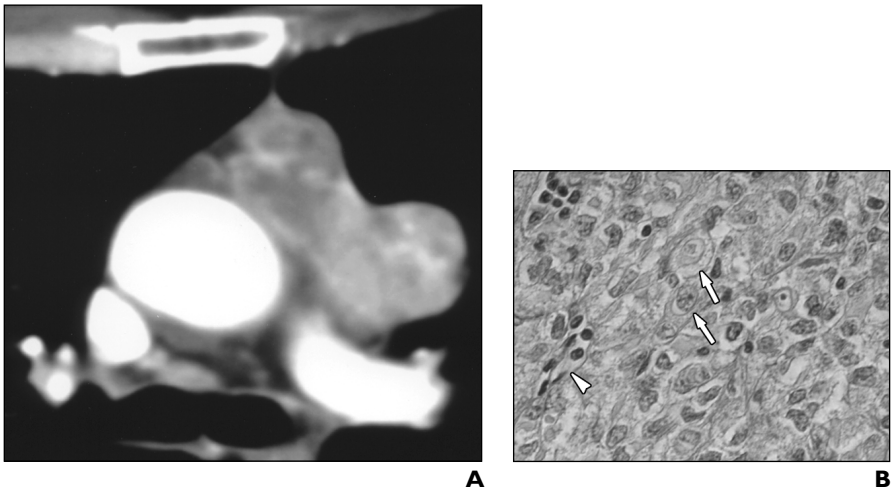


Fig. 5.—Type B3 tumor in 74-year-old man.
A, Contrast-enhanced CT scan (7-mm collimation) obtained at carinal level shows lobulated contour mass at anterior mediastinum. Mass shows heterogeneous enhancement with multiple areas of decreased attenuation. Invasion of left lung and pericardium was confirmed at surgery (stage III, invasive thymoma).
B, Photomicrograph of histopathologic specimen shows sheet of tumor epithelial cells (*arrows*) with small number of lymphocytes and perivascular space (*arrowhead*) (well-differentiated thymic carcinoma). (H and E, ×200)

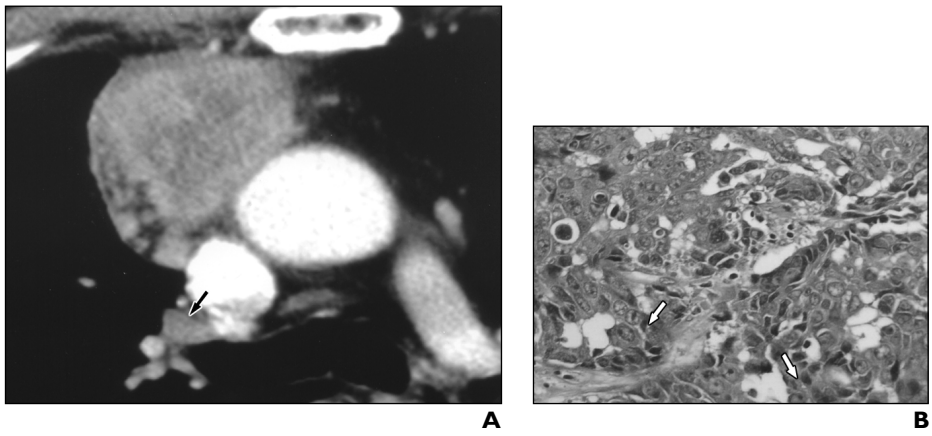


Fig. 6.—Type C tumor in 73-year-old man.
A, Contrast-enhanced CT scan (3-mm collimation) obtained at carinal level shows heterogeneous anterior mediastinum mass with irregular contour. Note enlarged lymph node in right hilum (*arrow*). Invasion of right lung and pericardium and metastasis to right hilar node were confirmed at surgery (stage III, invasive thymoma).
B, Photomicrograph of histopathologic specimen shows nests of thymic carcinoma cells with atypical nuclei and with some squamous differentiation (i.e., intercellular bridges [*arrows*]) (thymic carcinoma). (H and E, ×200)

ogy. Moreover our study is a retrospective review of charts rather than a prospective identification of each tumor type.

In conclusion, smooth contours and a round shape are most suggestive of type A tumor. Irregular contours and mediastinal lymphadenopathy are most suggestive of type C tumor. Calcification is suggestive of type B1, B2, and B3 tumors. The combination of homogeneous enhancement and a high degree of enhancement is suggestive of type A and AB tumors. CT is of limited value, however, in differentiating type AB, B1, B2, and B3 tumors.

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