Research Reports

Differential Diagnosis of Invasive Thymoma and Thymic Carcinoma by CT Findings

□□□□□□ Chin J Radiol 1999□24(5)□179-184

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ABSTRACT

The clinical behavior and prognosis of invasive thymoma and thymic carcinoma are different, and computed tomography is the most widely applied and advanced imaging modality for diagnosis of these diseases. It is important to evaluate the usefulness of CT characteristics in their differentiation.

Retrospectively, we evaluated the CT findings of invasive thymoma and thymic carcinoma to determine the differential points between them. Seventeen patients with invasive thymoma and 25 patients with thymic carcinoma, that were confirmed by surgical resection or by fine needle biopsy, were included in this study. All tumors were located in the anterior mediastinal prevascular space. Special attention was given to the following CT findings: homogeneity, attenuation, invasion of adjacent cardiovascular structure, mediastinal lymph nodes, pleural implants, extrathymic metastases, and calcification. Univariate and multivariate analyses were performed with Fisher's exact test and binary logistic regression.

Invasion of adjacent cardiovascular structure was seen in three patients (17%) with invasive thymoma, and 20 patients (80%) with thymic carcinoma. Significant mediastinal lymphadenopathy was seen in two patients (12%) with invasive thymoma, and nine patients (36%) with thymic carcinoma. Pleural implants were observed in eight patients (47%) with invasive thymoma, and 12 patients (48%) with thymic carcinoma. Metastases to the lung, adrenal gland, liver, bone, spleen, or retroperitoneal lymph nodes were observed in 12 patients (48%) with thymic carcinoma, but were absent from patients with invasive thymoma.

According to Fisher's exact test, there are four significant signs by CT findings associated with differentiation between thymic carcinoma and invasive thymoma: (1) inhomogeneous mass content, (2) infiltration of adjacent pericardium, (3) encasement of great vessels, and (4) extrathymic metastases. Binary logistic regression analysis shows that thymic carcinoma is more likely rather than invasive thymoma with the presence of infiltration of adjacent pericardium and encasement of great vessels. Infiltration of adjacent pericardium is more predominant in predicting thymic carcinoma than is encasement of great vessels.

If a tumor can be attributed to thymic origin by fine needle cytological study or by biochemical stain, then thymic carcinoma would be more likely with the presence of infiltration of adjacent pericardium and encasement of great vessels on CT scan.

Key words: Thymus, CT; Thymus, neoplasms

INTRODUCTION

Thymomas are defined as tumors originating in the epithelial components of the thymus. Of all thymomas 70% to 80% are totally encapsulated and classified as benign, and the remainder represents the group of malignant thymomas. [1] According to Rosai and Levine, [2] malignant thymomas are classified into two types: type I, invasive thymoma; and type II, thymic carcinoma. Differentiation of a thymic carcinoma from an invasive thymoma is important because the former has more aggressive behavior and poorer prognosis than the latter. An invasive thymoma behaves as a malignant tumor despite its benign histologic appearance. The distinction between benign and invasive thymomas depends on the demonstration of local invasion or extrathymic metastasis. In the series of Verley et al. [3], the average survival of patients with invasive thymomas was 50% at 5 years and 35% at 10 years. Thymic carcinoma is a rare anterior mediastinal neoplasm that should fulfill the following criteria: (1) anterior mediastinal location and (2) absence of another primary tumor. Wick and associates [4] reported the average survival time of patients with thymic carcinoma to be 18 months in 18 of the 20 patients who died.

Reports of CT findings of invasive thymoma and thymic carcinoma are rare, and differences of CT findings between invasive thymoma and thymic carcinoma have not been adequately discussed. We retrospectively evaluated the CT findings of invasive thymoma and thymic carcinoma and the usefulness of CT characteristics in their differentiation.

MATERIALS AND METHODS

We retrospectively reviewed CT images of 17 patients with invasive thymoma and 25 patients with thymic carcinoma from 1984 to 1999. There were 11 men and six women in the invasive thymoma group, ranging in age from 22 to 75 years with a mean age of 50 years. There were 12 men and 13 women in the thymic carcinoma group, ranging in age from 20 to 78 years with a mean age of 54 years. The diagnosis was confirmed by surgical exploration of the mediastinum in 16 patients with invasive thymoma and 17 patients with thymic carcinoma. In one patient with invasive thymoma and eight patients with thymic carcinoma, core biopsy and percutaneous fine needle aspiration were performed to confirm the diagnosis. Two patients with invasive thymoma had myasthenia gravis, but none of the thymic carcinomas was associated with autoimmune disease.

Computed tomography was performed with a Somatom DR3 scanner (Siemens Medical System, Erlangen, Germany) and three Picker PQ series (PQ2000, PQ5000, PQ6000) scanners (Picker International, Highland Heights, Ohio) with 8-mm thick sections at 8-mm intervals after intravenous injection of 100 ml of iodinated contrast material. Special attention was given to the following CT findings: homogeneity, attenuation compared with chest wall muscle, invasion of adjacent cardiovascular structure (pericardium and great vessels), mediastinal lymph node enlargement, pleural implants, extrathymic metastases, and calcification. Univariate analyses of these CT findings were performed via Fisher's exact test (Table 1), and binary logistic regression model (forward stepwise) was acquired to define which CT findings play a significant role for differentiation of invasive thymoma from thymic carcinoma for multivariate analysis (Table 2).

Table 1. CT findings of invasive thymoma and thymic carcinoma

CT finding	Invasive thymoma (%) (n = 17)	Thymic carcinoma (%) (n = 25)	*p* value [1]
Homogeneity			
Inhomogeneous	4 (24)	16 (64)	0.014*
Attenuation			
Low	1 (6)	5 (20)	0.374
Invasion of adjacent cardiovascular structure			
Pericardium	1 (6)	14 (56)	< 0.001***
Great vessels	2 (12)	16 (64)	0.001**
Pleural implants	8 (47)	12 (48)	1.000
Mediastinal lymphadenopathy	2 (12)	9 (36)	0.151
Metastases	0	12 (48)	0.002**
Calcification	2 (12)	2 (8)	1.000
Direct invasion	2 (12)	3 (12)	1.000

1 By Fisher's exact test (two-tail); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2. Binary logistic regression model of invasive thymoma and thymic carcinoma

Factor	Regression coefficient [1]	SE[2]	*p* value [3]	Odds ratio with 95% confidence intervals[4]
Infiltration of pericardium	2.7229	1.1664	0.020*	15.224 (1.58,149.76)*
Encasement of great vessels	2.3101	0.9311	0.013*	10.075 (1.62,62.49)*
Constant	-1.0815	0.5181	0.037*	
Model Chi-square,	$p < 0.001$			

1 Logistic regression coefficients.
2 Standard error of regression coefficients.
3 Probability of test statistic, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
4 Expressed as observed odds ratio (lower confidence limit, upper confidence limit); * $p < 0.05$.

RESULTS

All tumors were located in the anterior mediastinal prevascular space. Maximal diameters of the invasive thymomas ranged from 3 to 10 cm, and thymic carcinomas ranged from 5 to 25 cm. Most invasive thymomas were homogeneous and as isodense as the chest wall muscle (figs. 1, 2), but most thymic carcinomas were heterogeneous with central lobulated necrosis (figs. 3, 4). The homogeneity depended on the size of the tumor mass and the degree of necrosis. The larger tumors showed a larger necrotic zone and lower attenuation. Thymic carcinomas frequently showed heterogeneous inner structure due to a greater necrotic zone than did invasive thymomas in our series (p < 0.05).

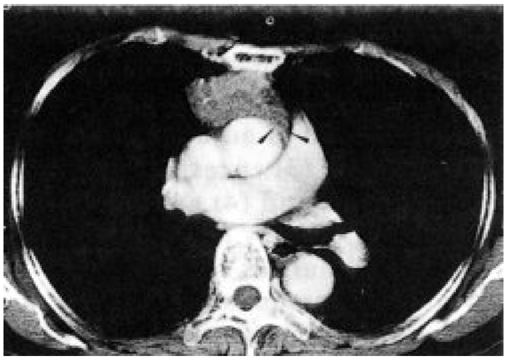


Fig. 1. Invasive thymoma in a 66-year-old woman. CT scan reveals an inhomogeneous mass involving the anterior mediastinum and obliteration of the periaortic fat plane (arrowheads) around the ascending aorta.

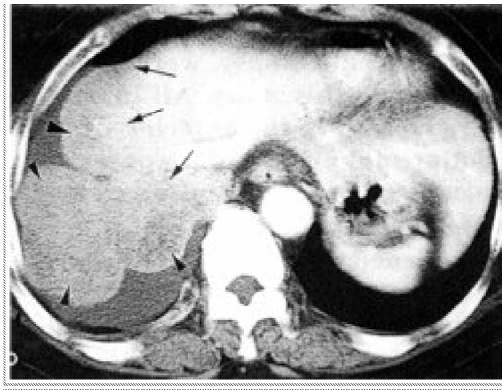


Fig. 2. Invasive thymoma in a 60-year-old woman. CT scan reveals multiple lobulated homogeneous mass lesions (arrowheads) abutting the right hemidiaphragm (arrows) and much pleural effusion in the right lower thoracic cavity.

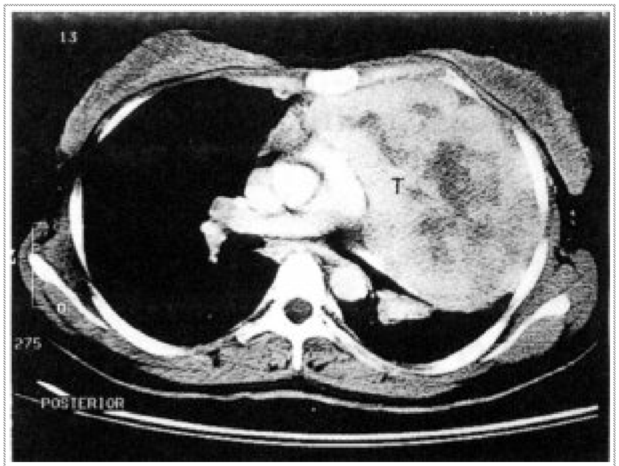
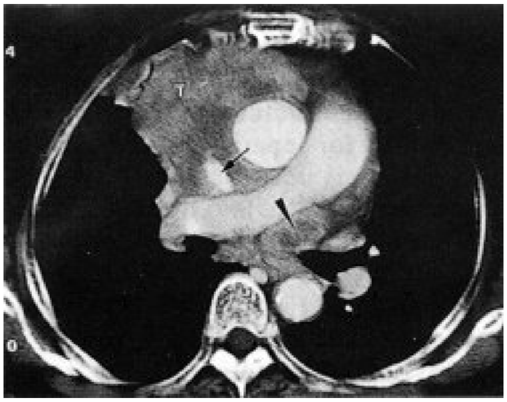


Fig. 3. Thymic carcinoma in a 20-year-old woman. CT scan reveals a huge inhomogeneous anterior mediastinal mass (T) with marked central lobulated necrosis and irregular infiltration of the left lung and great vessels.



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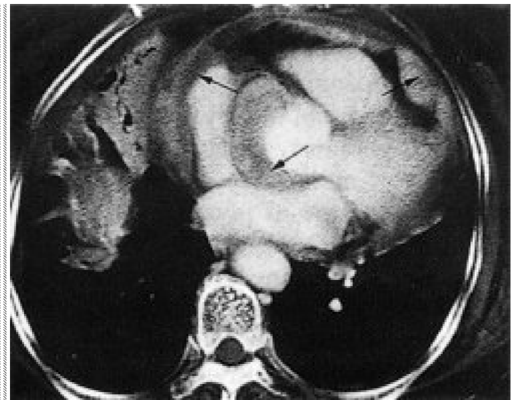

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Fig. 4. Thymic carcinoma in a 69-year-old woman. A. CT scan reveals a huge infiltrating anterior mediastinal mass (T) with marked central lobulated necrosis, with encasement of SVC (arrow), and enlarged mediastinal lymphadenopathy (arrowhead) with necrosis. B. General pericardial thickening (arrows) is recognized as irregular infiltration by the tumor mass.

Invasion to adjacent cardiovascular structures included obliteration of the mediastinal fat plane around great vessels, encasement of great vessels (figs. 3, 4a, 5), and irregular infiltration of pericardium with thickening (fig. 4b). Encasement of great vessels was seen in two patients (12%) with invasive thymoma, and 16 patients (64%) with thymic carcinoma. Irregular infiltration or thickening of the pericardium was seen in one patient (12%) with invasive thymoma, and 14 patients (56%) with thymic carcinoma.

In 20 out of 25 cases (80%) of thymic carcinoma, the CT images demonstrate encasement of great vessels or pericardial invasion, which include 16 cases (64%) with encasement of great vessels, 14 cases (56%) with thickened pericardium or pericardial effusion, and 10 cases (40%) with both of the above findings. There is one case (4%) with filling defect in SVC as an intravascular invasion by thymic carcinoma (fig. 5). Invasion of the mediastinal structure was almost always present in thymic carcinoma (80%); complete resection of these tumors is often difficult and impossible.

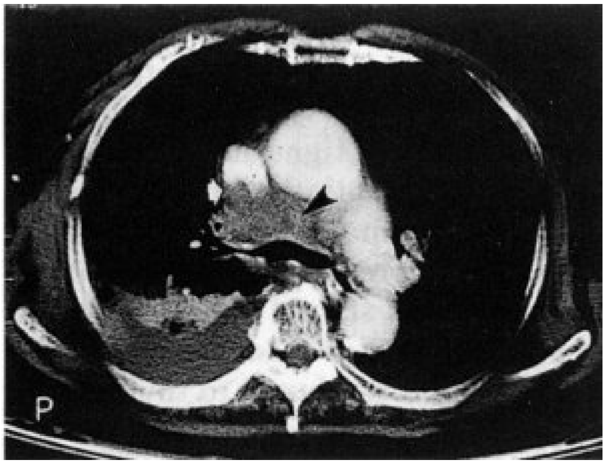

Fig. 5. Thymic carcinoma in a 69-year-old woman. CT reveals a local filling defect (arrow) at the posterior and lateral aspects of SVC from intravascular invasion, and enlarged pretracheal lymphadenopathy (arrowhead)

Distal pleural implants involving the pleura abutted from the chest wall, mediastinum, or diaphragm (fig. 2), and visceral pleura in fissures in eight patients (47%) with invasive thymoma, and 12 patients (48%) with thymic carcinoma. Pleural implants are one sign of invasiveness by presumed pleural seeding. The incidence of pleural implants in invasive thymoma is 50%-80% [14], whereas the incidence in thymic carcinoma is not discussed in the recent literature. There was no significant difference in the incidences of pleural implants between invasive thymoma and thymic carcinoma ($p > 0.05$) in this series.

Mediastinal lymphadenopathy (>1.5 cm in diameter) suggesting significant node metastases (figs. 4a, 5) was seen in two patients (12%) with invasive thymoma, and nine patients (36%) with thymic carcinoma. Direct invasion of the sternum, chest wall, and lower neck was seen in two patients (12%) with invasive thymoma, and three patients (12%) with thymic carcinoma. Small punctuate calcifications (fig. 6) were noted in two patients (12%) with invasive thymoma, and two patients (8%) with thymic carcinoma.

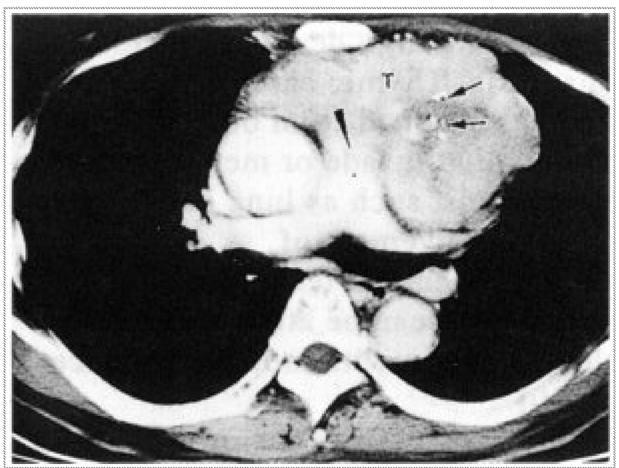

Fig. 6. Thymic carcinoma in a 62-year-old man. CT scan reveals one lobulated inhomogeneous anterior mediastinal mass (T) with punctate calcifications (arrows) and necrosis, and obliteration of the fat plane between mass and pulmonary trunk (arrowhead) as local invasion.

Metastases to the lung, adrenal gland, liver, bone, spleen, or retroperitoneal lymph nodes were observed in 12 patients (48%) with thymic carcinoma. There were eight cases with metastases to the liver, two cases to the lung, two cases to the bone, one case to the adrenal gland, one case to the spleen, and one case with retroperitoneal lymphadenopathy. Lung metastases were confirmed by open biopsy in two patients, and liver metastases were confirmed by percutaneous needle biopsy in six patients. No definite extrathymic metastasis was identified in the invasive thymoma group.

Table 1 summarizes the CT findings of invasive thymoma and thymic carcinoma, and results of univariate analysis by Fisher's exact test. In this study, attenuation, pleural implants, mediastinal lymphadenopathy, calcification, and local invasion seem not to show significant statistical differences between these two types of malignant thymomas (by Fisher's exact test, $p > 0.05$). According to Fisher's exact test, there are four significant signs by CT findings associated with differentiation between thymic carcinoma and invasive thymoma: (1) inhomogeneous mass content, (2) infiltration of adjacent pericardium, (3) encasement of great vessels, and (4) extrathymic metastases.

Two factors, including infiltration of adjacent pericardium and encasement of great vessels, are accepted by multivariate forward stepwise binary logistic regression analysis (Table 2, model Chi-square: $p < 0.001$) that separately present a correct prediction rate for invasive thymoma and thymic carcinoma of about 82.35% and 80% in our series. The other two factors (inhomogeneous mass content and extrathymic metastases) show no definite improvement in correct prediction for invasive thymoma and thymic carcinoma when they are added to the logistic regression model. The odds ratios with 95% confidence intervals of infiltration of adjacent pericardium and encasement of great vessels are 15.224 (1.58,149.76) and 10.075 (1.62,62.49) in the logistic regression model. If the 95% confidence interval around the observed odds ratio does not extend beyond 1, we can conclude that the odds ratios are statistically significant with a p value less than or equal to 0.05. Infiltration of adjacent pericardium and encasement of great vessels are statistically significant by odds ratio, and the exact probabilities of test statistics are listed in Table 2.

DISCUSSION

The term "thymoma" is restricted to primary tumors of the thymic epithelium. According to Rosai and Levine, [2] malignant thymomas are classified into two types: type I, invasive thymoma; and type II, thymic carcinoma. Seminoma, carcinoid, Hodgkin disease, non-Hodgkin lymphoma, and metastases to the thymus should be excluded, because CT findings of these malignant thymomas are not specific. [11-12]

Computed tomography is a good predictor of the invasive character and metastases of malignant thymomas. Obliteration of the mediastinal fat plane was one indicator of local invasion of a malignant thymoma. The presence of a fat plane reliably excluded local invasion, but the absence of a fat plane might be not necessary for local invasion, because fibrous adhesion without actual invasion presents the same CT findings. [13-14] Keen and Libshitz [15] and Zerhouni et al. [13] documented 94% and 91% accuracies of invasion to great vessel and/or pericardium, lung, and pleura on thin-section CT scans. In our series, local invasion to the pericardium and encasement of great vessels were recognized as a gross invasion on the CT scan, and all were proved histologically or surgically.

Invasive thymomas resemble benign thymomas, and lack histologic evidence of malignancy. The malignant nature of invasive thymomas is determined by local invasion or microinvasion of peripheral mediastinal structures, or rarely by metastases. In contrast to invasive thymomas, thymic carcinomas are composed of cytological malignant thymic epithelial cells and generally lack organoid features of benign or invasive thymomas, such as perivascular space rosette-like formation, gland-like formation, or abortive Hassall's corpuscles, but they have a high degree of histologic anaplasia. Thymic carcinomas should be distinguished from other epithelial tumors that invade or metastasize to the thymus, such as lung carcinoma. With improvement of immunochemical techniques, carcinomas can be attributed to thymic origin with more confidence. [5-10]

Invasiveness is a major prognostic factor in thymomas. The 5-year and 10-year survivals in the series of Verley and Hollmann [3] were 85% and 80% for the group with non-invasive thymomas, but only 50% and 35% for the group with invasive thymomas. Local invasion by invasive thymomas occurred at the chest wall, lower neck, pleura, great vessel, and pericardium in our series. They may also spread by pleural seeding. [16] Distal metastases including to liver, bone, adrenal gland, and lymph nodes occur in the late clinical course of malignant thymomas. Although there were no cases with distal metastases in the group of invasive thymoma in our series, there are distal metastases of invasive thymoma reported in the literature. Huang et al. [17] documented four of 34 patients with invasive thymoma demonstrating metastases to lung, bone, liver, spleen, and omentum.

In Wick's series [3], 19 of 20 cases (95%) of thymic carcinomas demonstrated gross invasion of contiguous mediastinal structures, such as the pericardium, lung parenchyma, phrenic nerve, and great vessels, and 13 of 20 cases (65%) demonstrated metastases to the lungs, liver, extrathoracic lymph nodes, adrenal glands, and bones. In our series, gross invasions of contiguous mediastinal structures were accounted for separately and discussed via univariate analysis as shown in Table 1. Invasion of the pericardium and encasement of great vessels showed significant statistical differences in Fisher's exact test, and were included in the binary logistic regression model to predict the possibility of thymic carcinoma rather than invasive thymoma. Distal metastases accounted for about 36% in the subgroup of thymic carcinomas and showed significant differences in Fisher's exact test between the two types of malignant thymomas, but there was no benefit in the binary logistic regression model.

Since there are various anterior mediastinal masses besides malignant thymoma, these signs should be used only for differentiation of invasive thymomas from thymic carcinomas under the impression of malignant thymoma, and should not be adapted to predict the tumor nature. If a tumor can be attributed to thymic origin by fine needle cytological study or by biochemical stain, a thymic carcinoma would be more likely than a invasive thymoma under the presence of infiltration of adjacent pericardium and encasement of great vessels

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Received: April 14, 1999 Accepted: August 23, 1999

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