

Efficacy of computed tomography features in predicting stage III thymic tumors

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Abstract. Accurate assessment of the invasion of intrathoracic structures by stage III thymic tumors assists their appropriate management. The present study aimed to evaluate the efficacy of computed tomography (CT) features for the prediction of stage III thymoma invasion. The pre-operative CT images of 66 patients with confirmed stage III thymic tumors were reviewed retrospectively. The CT features of invasion into the mediastinal pleura, lungs, pericardium and great vessels were analyzed, and their sensitivity, specificity, positive predictive value (PPV), negative predictive value and accuracy were calculated. For mediastinal pleural and pericardial invasion, an absence of space between the tumor and the mediastinal pleura/pericardium with mediastinal pleural/pericardial thickening and pleural/pericardial effusion exhibited a specificity and PPV of 100%, respectively. For lung invasion, a multi-lobular tumor convex to the lung with adjacent lung abnormalities exhibited a specificity and PPV of 91.2 and 81.3%, respectively. For vessel invasion, the specificity and PPV were each 100% for tumors abutting $\geq 50\%$ of the vessel circumference, and for tumor oppression, deformation and occlusion of the vessel. In conclusion, recognition of the appropriate CT features can serve as a guide to invasion by stage III thymic tumors, and can facilitate the selection of appropriate pre-operative treatment.

Introduction

Thymic tumors, including thymomas and thymic carcinomas, are the most common primary neoplasms of the anterior mediastinum, with one study quoting an incidence of 2.5-3.2 per million individuals in the Netherlands (1). Thymic tumors should be considered malignant due to their tendency for local invasion, pleural dissemination and systemic metastases. In total, 30-60% of thymic tumors show various degrees of invasion into mediastinal fat and adjacent structures (2-5).

Based on the gross and microscopic invasive properties of the tumors at surgery, the International Thymic Malignancy Interest Group (ITMIG) has adopted the Masaoka-Koga staging system as the official staging system for thymic tumors (6-8). Usually, a complete resection can be achieved by surgery in patients at stage I or II. However, for stage III or IV tumors, particularly where there is locoregional spread into neighboring mediastinal organs (stage III tumors), neoadjuvant therapy provides a survival advantage (9-12). With recent advances in minimally invasive surgical techniques, certain patients with stage III thymic tumors have become eligible for surgical evaluation, but others will require neoadjuvant therapy prior to complete resection (13). In certain cases, patients who have undergone invasive procedures have ultimately been found to have an early-stage thymic tumor; while in others, the pre-operative stage of the tumor has been underestimated, resulting in surgical difficulties (14). Therefore, accurate assessment of tumor invasion into intrathoracic structures is of great value in deciding upon the appropriate management of stage III thymic tumors, and precise staging is important prior to making treatment decisions (15).

At present, computed tomography (CT) is the imaging modality of choice for the evaluation of mediastinal masses. Although there have been several studies focusing on the association between the Masaoka-Koga stage, CT findings and World Health Organization (WHO) histology (16-26), none of these studies were dedicated to an evaluation of CT features for predicting pathological staging. The present study was designed to evaluate the efficacy of CT features in predicting invasion by stage III thymic tumors and to assess whether the features can serve as a guide to selecting the appropriate therapeutic strategies.

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Patients and methods

Approval and consent. This retrospective study was approved by the Research Committees of the Shanghai Chest Hospital, Shanghai Jiao Tong University (Shanghai, China) and the Shanghai Jiao Tong University Affiliated Shanghai Sixth People's Hospital (Shanghai, China), and a waiver was obtained for informed consent. The study took place between July 2009 and June 2013.

Patient inclusion and exclusion criteria. Patients with pre-operative thymic tumors that had been confirmed by surgical resection and histological examination were enrolled in the present study. All patients were diagnosed with stage III thymic tumors on the basis of invasion into neighboring organs (i.e., the mediastinal pleura, lungs, pericardium or great vessels), as determined by surgical findings and histology. CT imaging was performed in all patients within the 2 weeks prior to surgery. All patients underwent complete tumor resection without pre-operative neoadjuvant therapy. Patients with incomplete data were excluded.

A total of 66 patients (44 males and 22 females) ranging in age from 18-77 years (median, 56 years) were enrolled. Of these, 9 patients presented with myasthenia gravis (MG), 34 with chest pain and a cough, and 7 with dyspnea, while 16 were asymptomatic.

Diagnostic criteria. The tumor stage was classified according to the ITMIG definition of details of the Masaoka-Koga staging system (27). All histopathological specimens were reviewed by an experienced pathologist according to the latest WHO classification (11). The classification included 7 subtypes of thymomas (types A, AB, B1, B1+B2, B2, B2+B3 and B3) and thymic carcinoma, which were determined in accordance with the morphology of epithelial cells and the lymphocyte-to-epithelial cell ratio (28).

Definition of stage III. According to the ITMIG definition of details of the Masaoka-Koga staging system (27), macroscopic or microscopic invasions into neighboring organs (i.e., the pericardium, great vessels or lungs) and any involvement (either partial or penetrating) of the mediastinal pleura were classified as stage III.

CT imaging. The CT examinations were performed using a Philips Brilliance 64-slice helical CT (Philips Brilliance, Cleveland, Ohio, USA). In all patients, the CT examinations used 64x0.625-mm collimation, a slice thickness of 5.00 mm, a slice increment of 5.00 mm, a pitch of 1.08, 120 kVp and 200 mA, and a 512x512 image matrix through the thorax prior to and after intravenous injection of a contrast medium (iohexol; 300 mg iodine/ml; 1.5 ml/kg) at a rate of 3.0 ml/sec. All CT images were captured at mediastinal (window width, 400-450 HU; window level, 30-50 HU) and lung (window width, 1,000-1,500 HU; window level, -650 to -500 HU) windows.

Image analysis. The CT features of the thymic tumors were reviewed independently by two radiologists with 15 and 8 years of experience, respectively. The radiologists were

blinded to each other, and to the clinical and pathological information. The radiologist with 15 years of experience reassessed the CT findings 1 month after the initial evaluation. The following anatomical and invasive characteristics were assessed: i) Tumor size: Long diameters were measured in the maximal cross-section CT images. ii) Tumor contours: Smooth, lobulated or irregular. iii) Tumor density: Homogeneous or heterogeneous. The heterogeneous density included gross unevenness and a CT value difference of 20 HU following administration of contrast medium. iv) Calcification: Yes or no. v) Necrosis/cystic components: Yes or no. A non-enhanced region with water density was regarded as either cystic or necrotic. vi) Invasion: The grading according to invasion, as assessed by CT features, is summarized in Table I. Any one of the findings listed in Table I suggested invasion into the organ.

Statistical analysis. Data were expressed as the mean \pm standard deviation for continuous variables and numbers with percentages for categorical variables. A P-value of <0.05 was interpreted as a statistically significant difference. The consistency of the assessments by the two radiologists and for the same radiologist prior to and after 1 month was assessed by a weighted κ coefficient. The diagnostic efficacy of the CT features in comparison with pathological findings was evaluated by their sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. For the statistical analyses, SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

Patients and disease characteristics. Among the 66 patients, all the thymic tumors were located in the anterior mediastinum; on the left side in 31 patients, on the right side in 27 patients and on the midline in 8 patients. The mean size was 5.6 ± 1.4 cm, ranging from 2.9-9.9 cm. On the basis of the WHO classification, thymic carcinomas were present in 25 patients (25/66, 37.9%), type B3 thymomas in 18 (18/66, 27.3%), type B2+B3 thymomas in 8 (8/66, 12.1%), type B2 thymomas in 10 (10/66, 15.2%), type B1+B2 thymomas in 3 (3/66, 4.5%) and type A thymomas in 2 (2/66, 3.0%). The pathological results for the 66 patients were as follows: Single organ invasion including pleural invasion in 5 cases and pericardial invasion in 18 cases; pleural and lung invasion in 9 cases; pleural and pericardial invasion in 6 cases; pericardial and vessel invasion in 2 cases; pleural, lung and pericardial invasion in 15 cases; pleural, pericardial and vessel invasion in 3 cases; and pleural, lung, pericardial and vessel invasion in 8 cases. Overall, there was pleural invasion in 46 cases (46/66, 69.7%), lung invasion in 32 (32/66, 48.5%), pericardial invasion in 52 (52/66, 78.8%) and vessel invasion in 13 (13/66, 19.7%).

The κ values ranged from 0.74-0.93, suggesting good agreement between the two radiologists, and prior to and after 1 month. The weighted κ coefficients for the two radiologists, and for the same radiologist prior to and after 1 month are shown in Table II.

CT features. On CT, the thymic tumors presented as oval-shaped in 14 patients (21.2%) and as an lobulated or irregular anterior mediastinal mass in 52 patients (78.8%).

Table I. Location and grade of invasion.

Location	Grade I	Grade II	Grade III	Grade IV
Mediastinal pleura	Irregular interface with absence of space between the tumor and mediastinal pleura only	Irregular interface with absence of space between the tumor and mediastinal pleura, with mediastinal pleural thickening, but without pleural effusion	Irregular interface with absence of space between the tumor and mediastinal pleura, with pleural effusion, but without mediastinal pleural thickening	Irregular interface with absence of space between the tumor and mediastinal pleura, with mediastinal pleural thickening and pleural effusion
Lung	Single lobular tumor convex to the lung, without adjacent lung abnormalities such as patchy inflammation or fibrosis of the adjacent lung parenchyma	Single lobular tumor convex to the lung with adjacent lung abnormalities	Multilobular tumor convex to the lung, without adjacent lung abnormalities	Multilobular tumor convex to the lung with adjacent lung abnormalities
Pericardia	Irregular interface with absence of space between the tumor and pericardium only	Irregular interface with absence of space between the tumor and pericardium, with pericardial thickening, but without pericardial effusion	Irregular interface with an absence of space between the tumor and pericardium, with pericardial effusion, but without pericardial thickening	Irregular interface with absence of space between the tumor and pericardium, with pericardial thickening and pericardial effusion
Great blood vessels	Tumor abutting <50% of the vessel circumference and absence of space between the tumor and blood vessel, without oppression, deformation and occlusion of the vessel	Tumor abutting ≥50% of the vessel circumference and absence of space between the tumor and blood vessel, without oppression, deformation and occlusion of the vessel	Tumor shows abutting ≥50% of the vessel circumference and deformation of the vessel oppression, with deformation and occlusion of the vessel	

Table II. Consistency estimates of the radiologist evaluations.

Mediastinal invasion	Grade	κ value	
		Of the same radiologist	Of the two radiologists
Pleural invasion	I	0.78	0.78
	II	0.89	0.81
	III	0.78	0.78
	IV	0.79	0.79
Lung invasion	I	0.89	0.89
	II	0.92	0.82
	III	0.93	0.82
	IV	0.92	0.84
Pericardial invasion	I	0.85	0.82
	II	0.84	0.80
	III	0.84	0.77
	IV	0.88	0.83
Vessel invasion	I	0.88	0.83
	II	0.78	0.78
	III	0.85	0.74

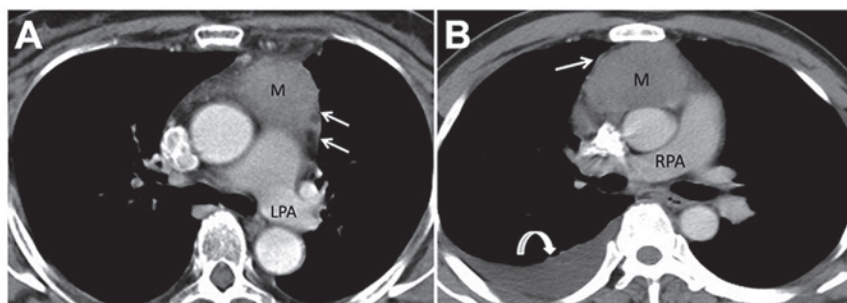


Figure 1. Examples of mediastinal pleural invasion. (A) A 56-year-old woman with a stage III thymic carcinoma (mediastinal pleural invasion). Contrast-enhanced chest computed tomography (CT) at the level of the left pulmonary artery (LPA) demonstrates a left anterior mediastinal mass (M) with an absence of space between the tumor and the mediastinal pleura, with mediastinal pleural thickening (straight arrows). (B) A 58-year-old man with a type B3 thymoma at stage III (mediastinal pleural invasion). Contrast-enhanced chest CT at the level of the right pulmonary artery (RPA) demonstrates a right anterior mediastinal mass (M) with absence of space between the tumor and the mediastinal pleura, with mediastinal pleural thickening (straight arrow) and right pleural effusion (curved arrow). The invasion was confirmed by the same experienced pathologist.

A heterogeneous density was exhibited in 51 patients (77.3%), 40 of whom (78.4%) exhibited necrotic and/or cystic components, and 19 of whom (37.3%) showed calcification.

Examples of CT images from patients with mediastinal pleural invasion are shown in Fig. 1. The manifestations of the tumor and the mediastinal pleura are shown in Table II. The majority of patients (39/66, 59.1%) had an irregular interface with an absence of space between the tumor and mediastinal pleura.

Examples of CT images from patients with lung invasion are shown in Fig. 2. Thymic tumors most often (21/66, 31.8%) presented as a single lobular mass convex to the lung, without adjacent lung abnormalities. There were 20 cases (30.3%) of

a multilobular mass convex to the lung, without adjacent lung abnormalities.

Examples of CT images from patients with pericardial invasion are shown in Fig. 3. Of the 66 CT images, the most common, in 32 (48.5%) patients, showed an irregular interface with an absence of space between the tumor and the pericardium.

Examples of CT images from patients with great vessel invasion are shown in Fig. 4. This was observed in 18 of the 66 CT images (27.3%).

Diagnostic efficacy. The diagnostic efficacies of the CT features in predicting stage III tumors are shown in Table III.

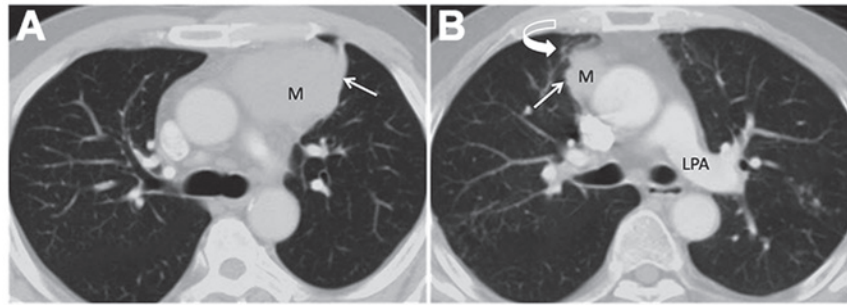


Figure 2. Examples of lung invasion. (A) A 53-year-old man with a stage III thymic carcinoma (left lung invasion). Contrast-enhanced chest computed tomography (CT) at the level of the carina of the trachea showing a left anterior mediastinal mass (M) with a single lobular shape convex to the superior lobe of the left lung, with adjacent lung parenchyma compression (straight arrow). (B) A 75-year-old man with a stage III thymic carcinoma (right lung invasion). Contrast-enhanced chest CT at the level of the left pulmonary artery (LPA) showing a right anterior mediastinal mass (M) with a multilobular shape convex to the superior lobe of the right lung (curved arrow), with patchy inflammation of the adjacent lung parenchyma (straight arrow). The invasion was confirmed by the same experienced pathologist.

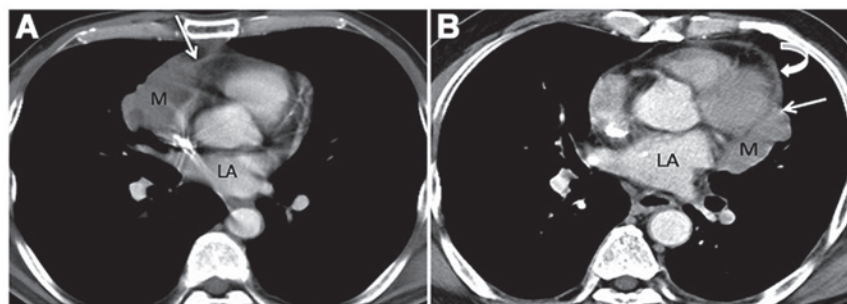


Figure 3. Examples of pericardial invasion. (A) A 57-year-old man with a type B2 thymoma at stage III (pericardial invasion). Contrast-enhanced chest computed tomography (CT) at the level of the left atrium (LA) shows a right anterior mediastinal mass (M) with an absence of space between the tumor and the pericardium, with pericardial thickening (straight arrow). (B) A 55-year-old man with a type B3 thymoma at stage III (pericardial invasion). Contrast-enhanced chest CT at the level of the left atrium (LA) shows a left anterior mediastinal mass (M) with an absence of space between the tumor and the pericardium (straight arrow), with pericardial thickening and pericardial effusion (curved arrow). The invasion was confirmed by the same experienced pathologist.

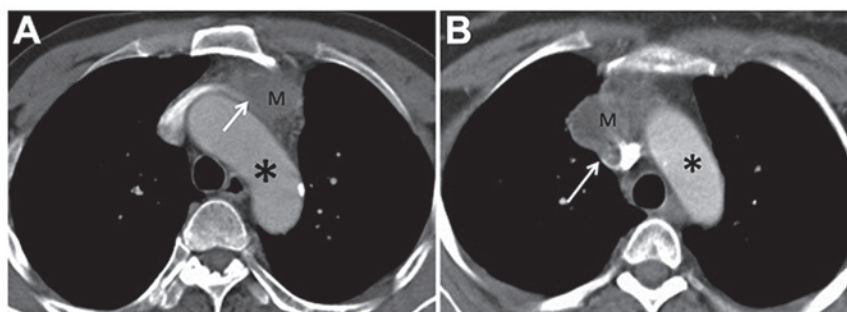


Figure 4. Examples of great vessel invasion. (A) A 62-year-old man with a type B3 thymoma at stage III (left brachiocephalic vein invasion). Contrast-enhanced chest computed tomography (CT) at the level of the aortic arch (*) shows a left anterior mediastinal mass (M) with an absence of space between the tumor and the left brachiocephalic vein (straight arrow). (B) A 41-year-old woman with a type B2+B3 thymoma at stage III (superior vena cava invasion). Contrast-enhanced chest CT at the level of the aortic arch (*) shows a right anterior mediastinal mass (M) with deformation and partial occlusion of the superior vena cava (straight arrow). The invasion was confirmed by the same experienced pathologist.

Mediastinal pleural invasion was diagnosed in 65 out of the 66 CT images and was confirmed by the pathology results in 46 cases. The specificity and PPV were each 100% for grade IV.

Lung invasion was diagnosed in 64 out of the 66 CT lung images and was confirmed by the pathology results in 32 cases. The specificity and PPV were 91.2 and 81.3%, respectively, for grade IV.

Pericardial invasion was diagnosed in 61 out of the 66 CT images and was confirmed by the pathology results in 52 cases. For grades II and IV, the specificity and PPV were each 100%.

Great vessel invasion was diagnosed in 18 of the 66 CT images and was verified by the pathology results in 13 cases. For grades II and III, the specificity and PPV were each 100%.

Table III. Diagnostic efficacy of CT features.

Site of invasion	Invasion on CT, n	Invasion on pathology, n	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Pleura							
Grade I	39	26	56.5	35.0	66.7	25.9	50.0
Grade II	19	15	32.6	80.0	79.0	34.0	47.0
Grade III	5	3	6.5	90.0	60.0	29.5	31.8
Grade IV	2	2	4.4	100.0	100.0	31.3	33.3
Lung							
Grade I	21	2	6.3	44.1	9.5	33.3	25.8
Grade II	7	4	12.5	91.2	57.1	52.5	50.0
Grade III	20	13	40.0	79.4	65.0	58.7	60.6
Grade IV	16	13	40.6	91.2	81.3	62.0	66.7
Pericardium							
Grade I	32	24	46.2	42.9	75.0	17.7	45.5
Grade II	12	12	23.1	100.0	100.0	25.9	39.4
Grade III	7	6	11.5	92.9	85.7	22.0	28.8
Grade IV	10	10	19.2	100.0	100.0	25.0	36.4
Great vessels							
Grade I	10	5	38.5	90.6	50.0	85.7	80.3
Grade II	5	5	38.5	100.0	100.0	86.9	87.9
Grade III	3	3	23.1	100.0	100.0	84.1	84.9

CT, computed tomography; NPV, negative predictive value; PPV, positive predictive value.

Discussion

The present study has illustrated pictorially the CT features of stage III thymic tumors. A focus was placed upon the association between the tumors and adjacent structures, such as the mediastinal pleura, lung, pericardium and great vessels. These CT features proved useful for the identification of tumor invasion for the radiologists and surgeons.

Studies have used CT for differentiating early (stage I and II) from advanced tumors (stage III and IV), according to the surgical classification of stages proposed by Masaoka-Koga (23-25). Preoperative CT features, such as large tumor size, lobulated tumor and infiltration of fat surrounding the tumor, suggest a high probability of Masaoka stage III or IV disease. However, it is challenging to accurately identify the stage of thymoma by the varying degree of fat obliteration between tumor and mediastinal structures (23,25). Proper management decisions for thymic tumors are based largely on the invasion site and the extent to which the tumors are present on CT imaging. It is key to determine to what extent the CT features agree with the pathological results. To the best of our knowledge, this is the first study that has focused on evaluating the efficacy of CT features in predicting stage III thymoma invasion. In the study, the most frequent invasive site was the pericardium, followed by the pleura, lungs and great vessels. The degree of invasion varied according to the association between the tumor and adjacent structures, and identifying true and false phenomena in the CT images proved to be challenging.

A previous study into the use of pleural invasion features to judge the tumor stage did not demonstrate the diagnostic accuracy of CT findings (25). In the present study, the signs of pleural invasion were subdivided into 4 grades to evaluate the efficacy of CT features in predicting stage III thymoma invasion. It was found that images suggesting an irregular interface with an absence of space between the tumor and pleura was the most invasive sign, and that this exhibited a higher sensitivity (56.52%) than the other signs evaluated. However, its PPV was just 66.67%. When the fat space disappeared and mediastinal pleural thickening or pleural effusion occurred simultaneously, the diagnostic specificity was as high as 80.00 and 90.00%, respectively. If all 3 signs occurred at the same time (grade IV), the specificity and PPV each reached 100%. Thus, as long as the absence of a fat space occurred with pleural thickening and/or pleural effusion, mediastinal pleural invasion can be confidently predicted. By contrast, mediastinal pleural invasion does not occur pathologically without these signs. In the present study, the sensitivity, NPV and accuracy of CT features for diagnosing mediastinal pleural invasion ranged from 4.35-56.52%, from 25.93-34.04% and from 31.82-50.00%, respectively. In the study by Tomiyama *et al* (24), infiltration of the pleura was identified by CT in only 5 out of 24 cases with surgically proven pleural infiltration. Although it was occasionally difficult to define mediastinal pleural invasion in the present patients, any attempt to focus more consistently on the mediastinal pleura represents a step forward (29). It has been reported that the results obtained using analyses of thinner or thicker sections

are not significantly different (24); therefore, further research, including magnetic resonance imaging analysis, is required to improve the diagnostic efficacy.

With the exception of a single lobular mass convex to the lung without adjacent lung abnormalities, the diagnostic specificities for the other 3 grades of CT lung invasion features were 91.18% for grade II, 79.41% for grade III and 91.18% for grade IV. Therefore, no lung invasion can be predicted in the absence of these CT characteristics. Since the specificity and PPV were 91.18 and 81.25%, respectively, in grade IV, a multilobular thymic tumor with adjacent lung abnormalities is the most important sign for diagnosing lung invasion via CT imaging. Lung invasion occurred more frequently in multilobular thymic tumors than in single lobular tumors in the present study. The 64 cases of lung involvement based on CT were verified pathologically in 32 patients. In a study by Zerhouni *et al* (30), in which the CT findings of 10 cases of invasive thymoma were reported, lung involvement was correctly diagnosed by CT in 6 patients. Tomiyama *et al* (24) reported that infiltration of the adjacent lung was identified by CT in only 1 out of 9 cases with histologically proven pulmonary infiltration. This difference in CT findings compared with the present study was presumably due to the different disease stages.

The identification of pericardial invasion is also an essential step prior to surgery, as it may affect the therapeutic strategy. In grades II and IV in the present study, all cases of pericardial invasion identified by CT were confirmed by the pathology results, and the diagnostic specificity and PPV were each 100%. As long as there was an absence of a fat space, with pericardial thickening with or without pericardial effusion on CT imaging, pericardial invasion could be confirmed pre-operatively. Since the diagnostic specificity and PPV for grade III were 92.86 and 85.71%, respectively, the CT characteristics of an absence of space between the thymic tumor and pericardium with pericardial effusion are useful in predicting pericardial invasion.

It has been reported that thymic carcinomas have a higher prevalence of great vessel invasion than thymomas (13,17). By contrast, the present study found that invasive thymomas (61.5%; 8/13) had a higher prevalence of great vessel invasion than thymic carcinomas (30.8%, 4/13). The exclusion of inoperative cases in the present study may have contributed to this finding. The diagnostic specificities and PPVs for CT findings in grades II and III were 100%. The CT manifestations of tumors abutting $\geq 50\%$ of the vessel circumference or oppression, deformation and occlusion of the vessels definitely suggested vessel invasion. Since the specificity for just an absent fat space (grade I) was 90.57%, it can be confidently predicted that no vessel invasion is present if there is space between the tumor and blood vessels. The NPVs and diagnostic accuracies for the other 2 grades ranged from 84.13-86.89% and from 84.85-87.88%, respectively. Therefore, a lack of invasion can be confidently diagnosed in the absence of these CT features. However, the diagnostic sensitivities for all 3 grades were as low as 23.08-38.46%. Possible reasons for this were patient selection bias and the incomplete resection of certain invaded vessels, which would have resulted in negative pathology findings.

The present study has certain limitations that should be considered alongside the results. The study was retrospective; therefore, there was no way of comparing the predictive value

of CT features with any other method of evaluating stage III thymic tumors prior to treatment. Also, the study sample size was quite small due to the limited number of patients; multi-center studies including more patients would provide more evidence for these results, as well as providing evidence of the reproducibility of the CT grading of the thymic tumor features.

In summary, in the first study to focus on evaluating the efficacy of CT features in predicting stage III thymoma, CT features were found to be effective. Consequently, familiarity with CT features for predicting stage III thymic tumors facilitates diagnostic accuracy, and thus may be useful in optimizing patient treatment.

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