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Radiographic Predictors of Resectability in Thymic Carcinoma

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Abstract

Background: The aim of this study was to assess pre-operative computed tomography (CT) characteristics of thymic carcinomas and to investigate which features could predict an incomplete surgical resection. A secondary aim was to correlate pre-operative imaging features with Masaoka stage.

Methods: In this study, approved by our Institutional Review Board, two readers retrospectively reviewed pre-operative CTs at our tertiary referral oncology center between 1994 and 2014. Imaging features analyzed included tumor morphology, infiltration of surrounding mediastinal fat, loss of surrounding fat plane, degree of contact between tumor and great vessels and associated pulmonary or pleural abnormality. Surgical and pathological records were reviewed for completeness of surgical resection and Masaoka stage.

Results: Forty-one patients were included, with Masaoka stage I (n=3), II (n=4), III (n=12), and IV (n=22). Twenty-one patients (51%) had a complete surgical resection. Ten had microscopic residual disease (R1), with involved surgical margins at pathology and 10 patients had macroscopic residual disease (R2) at surgery. Besides lesion size, the feature associated with incomplete surgical resection was the degree of tumor contact with adjacent mediastinal vessels on the pre-operative CT ($p = 0.038$). Many of the more common features associated with incomplete resection were also more likely to be present in patients with late Masaoka stage (III/IV), including infiltration of the mediastinal fat, which was present in all 34 patients with Masaoka stage III/IV compared to 5 (71%) with stage I/II ($p=0.03$).

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Conclusions: Pre-operative CT imaging features may help to identify patients at risk for an incomplete surgical resection.

Classifications:

Computed tomography; CAT Scan; CT scan; mediastinum; thymoma; thymic carcinoma; thymectomy; thymus

Thymic carcinoma is a rare aggressive subtype of thymic epithelial tumors, representing less than 1% of thymic tumors (1). The latest World Health Organization (WHO) histological classification subdivided thymic tumors into thymomas and thymic carcinomas, reflecting differences in both histological appearance and also clinical behavior and prognosis(2). In comparison to thymomas, thymic carcinomas tend to present at a more advanced stage, have a more aggressive clinical course and a higher frequency of local lymph node and distant metastases, with lower survival rates (3, 4).

Due to the rare nature of thymic carcinomas, most studies on these tumors have small sample sizes, with often conflicting results about prognostic indicators and optimal management. A multimodality approach to treatment is generally used, but the current mainstay of treatment is surgical resection (5, 6). A complete surgical resection is an important prognostic indicator for patients with this disease and in predicting overall survival (6–8). A complete resection is not always possible and the value of performing an incomplete resection or debulking procedure is unclear. Studies have suggested a survival benefit from even an incomplete resection (7, 9), however another study did not find any significant difference in survival between patients who had debulking surgery and those who had no surgery (10). The ability to pre-operatively predict which patients are at risk for an incomplete resection could help avoid unnecessary surgery in a subgroup of patients who are unlikely to benefit.

Our aim was to assess pre-operative computed tomography (CT) characteristics of thymic carcinomas and to investigate which features could predict an incomplete surgical resection. A secondary aim was to correlate pre-operative imaging features with Masaoka stage.

Material and Methods

Patient Selection

The institutional review board at our institution issued a waiver of informed consent for this retrospective study, which was compliant with HIPAA. An electronic search of our histopathological database was performed to identify all patients with resected thymic carcinoma between September 1994 and September 2014. Patients who had resection of thymic carcinoma between these dates and who had a pre-operative CT scan available were included. We excluded patients with thymic carcinoma who did not undergo resection and those who did not have a pre-operative CT available. Picture archiving and communication system (PACS) records were reviewed for each patient and the pre-operative CT performed closest to the surgery date was selected for analysis.

Imaging Analysis

Pre-operative CT scans were reviewed retrospectively and independently by two radiologists (oncologic imaging fellows), who were blinded to clinical information and surgical outcome at time of image analysis. Where differences arose, they were resolved by a third, more experienced thoracic radiologist (17 years experience). The images were reviewed on a PACS (GE; Waukesha, WI). Many of the patients had been referred to our hospital following initial imaging elsewhere; therefore, CT protocols varied.

For image interpretation, we used standard report terms defined by the International Thymic Malignancy Interest Group (ITMIG) for mediastinal masses suspected as thymoma (11). To limit bias, readers underwent a training session on the application of these reporting criteria prior to starting the study. Imaging features analyzed included tumor size, attenuation, contour morphology and presence of tumor calcification. The relationship of the tumor to the mediastinum was evaluated, specifically, tumor infiltration of surrounding mediastinal fat suggesting breach of capsule, presence/absence of a fat plane between the tumor and vessels, and degree of contact with adjacent structures including vessels, heart, airway and esophagus (< 10%, 10–25%, > 25%). Scans were reviewed for changes in adjacent pulmonary parenchyma and presence of pulmonary nodules, lymphadenopathy, pleural effusions/nodularity or distant metastases.

Electronic medical records, including operative and histopathological reports were reviewed. We documented WHO histopathologic grade (B3 + C, C), Masaoka tumor stage (I/IIa/IIb/III/IVa/IVb) and completeness of resection (R0/R1/R2). We recorded patient age, sex, symptoms/diagnosis of myasthenia gravis, neoadjuvant therapy and clinical outcome, including recurrence or mortality.

Statistical Analysis

Fisher's exact test was used to examine associations of imaging features with completeness of surgical resection and Masaoka staging. The area under the empirical receiver operating characteristic (ROC) curve (AUC) analysis was estimated for maximum tumor size on completeness of resection. The sensitivity and the specificity of incomplete resection were estimated at the cutoff value maximizing the Youden's index. A test with p-value < 0.05 was considered statistically significant. Statistical analyses were performed in software package SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Our study group consisted of 41 patients who underwent resection of a thymic carcinoma. Patient characteristics are recorded in Table 1. All patients had pre-operative CTs available. Because the pre-operative CTs were mostly performed at other institutions, scan protocols varied. Most scans (82.9%, n=34) used 5 mm slice thickness; this varied from 3–7.5 mm. Most CTs (75.6%, n=31) were performed with intravenous contrast. No patient had a pre-operative MRI available.

Post-operatively, Masaoka stage was determined for each patient (Table 1). Most patients (n=34, 82.9%) were late stage-Masaoka stage III/IV. Most (n=31, 76%) had neoadjuvant

chemotherapy. Chemotherapy regimens were not standardized; however, all patients received platinum-based chemotherapy. Ten patients (24%) did not receive neoadjuvant chemotherapy. Of these, 3 had incomplete R1 resections. One of these patients was Masaoka stage IIB and the other two were stage IVA. No patient had neoadjuvant radiation therapy.

Twenty patients (48.7%) had an incomplete surgical resection; 10 with microscopic residual disease (R1), and 10 with macroscopic residual disease (R2) recognized during surgery, most frequently due to unresectable tumor around mediastinal vascular structures (Table 2, Figures 1–3). Almost all patients with an incomplete surgical resection were Masaoka stage III/IV (Tables 3–4). Most patients who had an incomplete surgical resection had received neoadjuvant chemotherapy; however, two had not. These patients were both classified as Masaoka stage IVA following surgery. Median time interval between the pre-operative CT and surgery was 30 days (range: 3–119 days).

Two features were significantly associated with an incomplete resection; degree of tumor contact with adjacent vessels on the pre-operative CT ($p = 0.038$) and larger maximum tumor size ($p=0.014$). Seventeen patients (85%) who had an incomplete resection had tumor contacting $>25\%$ of an adjacent mediastinal structure on the pre-operative CT, compared to 9 (45%) of patients who had complete resection. At the cutoff value of $>7.5\text{cm}$ maximum tumor size, sensitivity for incomplete resection was 0.55 (95%CI: 0.315–0.769) and the specificity was 0.905 (95%CI: 0.696–0.988) with AUC of 0.737 (95%CI: 0.583–0.891). Predictability of incomplete resection was not significantly improved by addition of the degree of tumor contact with adjacent mediastinal vessels to the tumor size (AUC= 0.766, the Wald test $p=0.205$). Many other imaging features were more common in patients who had an incomplete resection, including lack of surrounding fat plane, adjacent lung changes or presence of pleural effusion; however, sample sizes were small and these results were not statistically significant (Tables 4 and 5).

Many features that were more common in patients who had incomplete resection were also more likely to be present in patients with late Masaoka stage (III/IV). The relationship between pre-operative imaging features and Masaoka stage is outlined in Table 6. All 34 patients with Masaoka stage III/IV demonstrated infiltration of mediastinal fat compared to 5 (71%) with stage I/II, ($p=0.03$). Tumor size was significantly different between the early and late Masaoka stages ($p=0.039$). There was a trend of more stage III/IV patients 31 (91%) having loss of fat plane between tumor and great vessels compared to 4 (57%) stage I/II patients ($p=0.051$).

Comment

Thymic carcinoma is a rare aggressive tumor with limited published data regarding optimal disease management. As a result, the treatment pathways are not clearly defined, as shown by a recent survey from the ITMIG (12). It has been shown that a complete resection is the most important predictor of long term survival (4, 7, 8, 10, 13, 14). Identifying patients at risk of incomplete resection can help with the decision process in determining who might benefit from neoadjuvant therapy, or conversely, have limited benefit from surgery. Given

conflicting data on the benefits of incomplete resection (7, 9, 10), careful inspection of the pre-operative CT is an important tool in this aim.

Neoadjuvant chemotherapy is usually given to patients believed clinically to have late stage disease. However, three of our patients who had an incomplete surgical resection had not received neoadjuvant chemotherapy and two of these were eventually classified as Masaoka stage IVA. We have shown that tumor characteristics on pre-operative CTs can be used to help predict risk of incomplete resection, which can be used to guide neo-adjuvant treatment decisions, and aid patient counseling. To our knowledge, no other study has investigated the relationship between imaging features and the risk of incomplete resection in thymic carcinoma. Our results are similar to a study we published previously on patients with thymomas, which showed the significance of the relationship of tumor to adjacent vessels when predicting resectability (15). We also identified features that could be used to predict later stage, which was shown to be associated with overall survival in studies by Lee et al (6), Kondo et al (16) and Hosaka et al (17).

The rate of incomplete resection was 48.7%, similar to the rate found in a larger study by the European Society of Thoracic Surgeons and the ITMIG (18). In this analysis, 60% had a complete resection and 40% had an incomplete resection. Our rate was also similar to that in several smaller studies (19–21).

Our study had some limitations. This was a retrospective study, with inherent selection biases. Any patient deemed unresectable at presentation, or medically inoperable, would not have surgery and would not have been included. However, our aim was to study patients who were thought to be potentially resectable, as we felt that the pre-operative imaging features could help to guide the surgeon's management. Some of the imaging features evaluated were potentially subjective in nature. To reduce this possible bias, all readers trained on the use of standardized reporting terms (11). The use of two blinded readers, with the added benefit of a third opinion where differences arose, further reduced the potential impact of reader bias. We feel that the use of three readers in total makes the results applicable to everyday practice, when many different radiologists of differing experience levels will be reading these cases.

We chose to analyze the imaging features on the pre-operative CT scan closest to the date of surgery. However, many of our patients had a baseline CT at time of diagnosis, then neo-adjuvant chemotherapy, which may have altered tumor size and imaging characteristics by the time the pre-operative CT was performed. Many of the baseline pre-chemotherapy scans were not available for analysis, so comparison of pre- and post-treatment radiographic features was not possible. We feel that analyzing the immediately pre-operative CT was most relevant for our study; however, we acknowledge that decisions about neoadjuvant therapy are based on pretreatment imaging. In addition, the added value of MR imaging in thymic tumors has been increasingly recognized (22–26), none of our patients had an MRI available for review.

As is common with rare malignancies, smaller sample size precluded our ability to perform clinically meaningful multivariable analysis and detect statistically significant results. Thus,

larger prospective and multicenter retrospective studies are needed on this topic. Nevertheless, this study represents one of the larger study groups published on this rare tumor. In a recent review on thymic carcinoma, only two of the nine recently published papers on thymic carcinoma had larger patient numbers than ours, and none used pre-operative imaging findings to predict resectability(16, 19–21, 27–32).

In summary, we identified imaging features of thymic carcinoma on pre-operative CT that may help identify patients at risk of incomplete surgical resection. Based our results, we hope that radiologists and surgeons pay particular attention to the relationship of the tumor to adjacent mediastinal vessels as well as tumor size, as these were the features most associated with an incomplete resection. In the case of tumors with one, or both these features, then the patient should be advised that a complete resection may not be possible. We hope that our data can help to guide treatment pathways for thymic carcinoma in the future and aid in pre-operative counselling of these patients.

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Figure 1.

(A-C) 68-year-old female with prior breast cancer. Incidental finding of mediastinal mass and pleural nodules on chest radiograph. CT confirmed anterior mediastinal mass partially encasing the superior vena cava and brachiocephalic veins (A, B) with loss of mediastinal fat planes, as well as right pleural metastases (arrows, B, C). At surgery, tumor involved the superior vena cava, brachiocephalic and subclavian veins and a decision was made to perform a debulking procedure.

Figure 2.

(A, B) 42-year-old male, with incidental finding of a mediastinal mass on MRI spine. Pre-operative CT showed tumor encasing the left subclavian artery over >75% of its circumference with loss of fat planes between the mass, subclavian artery and aorta arch (A, B). At surgery, the tumor invaded the adventitia of the left subclavian artery origin and could not be completely resected.

Figure 3.
(A, B) 50-year-old female who presented with dyspnea and had a pericardial effusion drained. Subsequent CT demonstrated an anterior mediastinal mass, partially encasing the ascending aorta and main pulmonary artery, with loss of mediastinal fat planes (A, B). At surgery, tumor involved all the mediastinal great vessels and could not be completely resected.

Table 1:

Patient characteristics

Variables	Number	%
Age, mean (range), years	59.6 (37–82)	
Sex		
Male	18	44
Female	23	56
Myasthenia Gravis		
No	41	100
Yes	0	0
Completeness of resection		
R0	21	51
R1	10	24
R2	10	24
WHO histologic type		
B3 + C	1	2
C	40	98
Masaoka stage		
I	3	7
IIa	0	0
IIb	4	10
III	12	29
IVa	12	29
IVb	10	24
Neo-adjuvant chemotherapy		
Yes	31	76
No	10	24
Adjuvant treatment		
None	12	29
Chemotherapy alone	3	7
Radiation therapy alone	19	46
Combined chemoradiation	7	17
Maximum tumor size		
Mean $\pm$ SD (range) cm	6.3 $\pm$ 2.6 (2.5–12.1)	

Note: SD = standard deviation; WHO = World Health Organization

Table 2.

Surgical findings in patients with R2 resection

Patient	Surgical findings/Site of residual disease
1	Tumor invading through pericardium and into the myocardium which could not be completely resected.
2	Tumor involved the superior vena cava (SVC), innominate and subclavian veins and residual tumor was left on these vessels.
3	Tumor involved pulmonary artery and ascending aorta and residual tumor was left on these vessels.
4	Tumor involved SVC, ascending aorta and right ventricular outflow tract and residual tumor was left on these vessels.
5	Tumor invaded through pericardium into the right ventricle and could not be completely resected.
6	Tumor could not be completely resected from the hilum and gross residual disease was left here. Multiple miliary pleural metastases were seen at time of surgery and were not resected.
7	Tumor involved all the mediastinal great vessels and could not be completely resected.
8	Tumor involved the SVC and its junction with the innominate vein and residual tumor was left on these vessels.
9	Widespread tumor nodules involving the pericardium could not be completely resected. Intra-operative biopsies of internal mammary nodes were positive for tumor.
10	Tumor invaded the adventitia of the left subclavian artery origin and could not be completely resected.

Note: SVC = superior vena cava

Table 3.

Resection rates by Masaoka stage

Masaoka stage	R0 (%)	R1 (%)	R2 (%)
I (n=3)	3 (100)	0 (0)	0 (0)
IIb (n=4)	3 (75)	1 (25)	0 (0)
III (n=12)	8 (67)	2 (17)	2 (17)
IVa (n=12)	3 (25)	5 (42)	4 (33)
IVb (n=10)	4 (40)	2 (20)	4 (40)

Table 4.

Characteristics of Incompletely Resected Patients

Margin	Masaoka Stage	Neoadjuvant Chemotherapy	Maximum Preoperative Tumor Size (cm)	Heterogeneity	Fat Plane Separates Tumor From Adjacent Vessels	Peritumoral Fat Infiltration	Adjacent Vessel Abutment (%)	Adjacent Lung Changes	Pleural Effusion	LA
R1	3	Yes	9.4	Yes	No	Yes	>25%	No	No	Yes
R1	3	Yes	4.7	Yes	No	Yes	>25%	No	No	No
R1	4A	Yes	5.0	Yes	No	Yes	>25%	No	No	No
R2	4A	Yes	12.1	Yes	No	Yes	>25%	No	Yes	Yes
R1	4B	Yes	3.5	No	No	Yes	10No25%	No	No	Yes
R1	2B	No	6.4	Yes	No	Yes	>25%	No	No	No
R2	4A	Yes	9.5	Yes	No	Yes	>25%	No	No	No
R2	3	Yes	12.0	Yes	No	Yes	>25%	Yes	Yes	No
R2	3	Yes	11.1	Yes	No	Yes	>25%	No	No	Yes
R2	4A	Yes	13.0	Yes	No	Yes	>25%	Yes	No	No
R2	4A	Yes	6.5	Yes	No	Yes	10No25%	Yes	Yes	No
R2	4B	Yes	8.5	Yes	No	Yes	>25%	Yes	No	Yes
R1	4A	No	3.5	No	Yes	Yes	<10%	No	No	No
R2	4B	Yes	5.0	Yes	No	Yes	>25%	No	No	No
R2	4B	Yes	9.0	Yes	No	Yes	>25%	No	No	No
R1	4A	Yes	10.5	Yes	No	Yes	>25%	No	No	Yes
R2	4A	Yes	8.0	Yes	No	Yes	>25%	No	No	No
R1	4A	No	7.8	Yes	No	Yes	>25%	Yes	No	No
R1	4B	Yes	6.5	Yes	No	Yes	>25%	No	No	No
R1	4A	Yes	9.6	Yes	No	Yes	>25%	Yes	No	No

LA = lymphadenopathy.

Table 5.

Association of pre-operative CT features with risk of incomplete surgical resection.

	Complete resection (n=21)	Incomplete resection (n=20)	Univariate analysis
	N (%)	N (%)	Fishers exact test p value
Contour			0.232
Lobular	18 (86)	20 (100)	
Round	3 (14)	0 (0)	
Fat plane separating tumor from mediastinal vessels			0.184
Yes	5 (24)	1 (5)	
No	16 (76)	19 (95)	
Infiltration of peritumoral fat			0.488
Yes	19 (90)	20 (100)	
No	2 (10)	0 (0)	
Degree of abutment of adjacent vessel circumference			0.038
25%	12 (57)	3 (15)	
>25%	9 (43)	17 (85)	
Adjacent lung changes			0.238
Yes	2 (10)	5 (25)	
No	19 (90)	15 (75)	
Presence of any pleural effusion			0.232
Yes	0 (0)	2 (10)	
No	21 (100)	18 (90)	
Any lymphadenopathy			0.484
Yes	4 (19)	6 (30)	
No	17 (81)	14 (70)	
Pleural nodularity			0.326
Yes	5 (24)	8 (40)	
No	16 (76)	12 (60)	
Pulmonary nodules			0.758
Yes	12 (57)	10 (50)	
No	9 (43)	10 (50)	
			Wilcoxon rank sum test p value
Maximum size: median (range)	5.3 (2.5, 10.5)	7.9 (3.5, 12.1)	0.014

Table 6.

Association of pre-operative CT features with Masaoka stage

	Early stage (I/II) (n=7)	Late stage (III/IV) (n=34)	Univariate analysis
	N (%)	N (%)	Fishers exact test p value
Contour			0.070
Lobular	5 (71)	33 (97)	
Round	2 (29)	1 (3)	
Fat plane separating tumor from mediastinal vessels			0.051
Yes	3 (43)	3 (9)	
No	4 (57)	31 (91)	
Infiltration of peritumoral fat			0.026
Yes	5 (71)	34 (100)	
No	2 (29)	0 (0)	
Degree of abutment of adjacent vessel circumference			0.070
25%	5 (71)	10 (29)	
>25%	2 (29)	24 (71)	
Adjacent lung changes			0.321
Yes	0 (0)	7 (21)	
No	7 (100)	27 (79)	
Presence of any pleural effusion			0.999
Yes	0 (0)	2 (6)	
No	7 (100)	32 (94)	
Any lymphadenopathy			0.660
Yes	1 (14)	9 (26)	
No	6 (86)	25 (74)	
Pleural nodularity			0.077
Yes	0 (0)	13 (38)	
No	7 (100)	21 (62)	
Pulmonary nodules			0.991
Yes	4 (57)	18 (53)	
No	3 (43)	16 (47)	
			Wilcoxon rank sum test p value
Maximum size: median (range)	3.0 (2.5, 6.4)	5.8 (2.5, 12.1)	0.039