Comparison of patterns of relapse in thymic carcinoma and thymoma

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Objective: Thymic carcinomas are considered to be more aggressive than thymomas and carry a worse prognosis. We reviewed our recent experience with the surgical management of thymic tumors and compared the outcomes and patterns of relapse between patients with thymic carcinoma and those with thymoma.

Methods: We performed a single-institution retrospective cohort study. Data included patient demographics, stage, treatment, pathologic findings, and postoperative outcomes.

Results: During the period 1995–2006, 120 patients with thymic tumors underwent surgical intervention, including 23 patients with thymic carcinoma and 97 patients with thymoma, as classified according to the World Health Organization 2004 histologic classification. The overall 5-year survival was significantly different between patients with thymic carcinoma and those with thymoma (thymic carcinoma, 53%; thymoma, 89%; $P = .01$). Data on relapse were available for 112 patients. The progression-free 5-year survival was also significantly different between patients with thymic carcinoma and those with thymoma (thymic carcinoma, 36%; thymoma, 75%; $P < .01$). Using multivariate analysis, thymic carcinoma and incomplete resection were found to be independent predictors of progression-free survival. Relapses in patients with thymic carcinoma tended to occur earlier, and occurred significantly more frequently at distant sites than in patients with thymoma (60% vs 13%, $P = .01$).

Conclusions: Patterns of relapse differ significantly between patients with thymic carcinoma and those with thymoma, with lower progression-free survival, earlier onset, and more distant relapses in patients with thymic carcinoma. Given the greater propensity for distant failures, the inclusion of systemic therapy in the treatment of thymic carcinoma might take on greater importance. Despite significantly higher rates of distant relapse, good overall survival in patients with thymic carcinoma can be achieved.

Surgical intervention is considered the mainstay of treatment for thymic tumors, but despite resection, relapses are common, and the optimal treatment approaches remain unclear. Disease progression after treatment tends to occur in the mediastinum or the pleural cavity, but some patients return with distant metastases.¹ Given that long-term survival is achievable with resection, freedom from disease progression might be a more useful metric.² However, prior studies on recurrence can be difficult to compare in the setting of differing histologic classifications, study periods spanning multiple decades, inadequate statistical analyses, and a focus on overall survival.

A more complete understanding of relapse patterns might lead to improved strategies for the prevention, surveillance, and treatment of recurrence. For thymoma, disease stage,

as defined by the Masaoka system, and completeness of surgical resection are considered the most consistent predictors of survival.^{3,4} Our knowledge of thymic carcinoma (TC) has been limited because of its rarity, but TC is considered to be more aggressive and carry a worse prognosis. The number of conflicting classification systems reflects the persistent confusion surrounding thymic tumors, and even the original World Health Organization (WHO) classification labeled TCs as “Thymoma (Type C).”⁵ Although the recent update of the WHO classification⁶ officially recognizes the distinction between TC and thymoma as separate and distinct histologic entities, they tend to be treated fairly similarly. We hypothesized that the patterns of relapse differ significantly between patients with TC and those with thymoma, reflecting different behaviors. We reviewed our recent experience with the surgical management of thymic tumors to define patterns and predictors of disease progression.

MATERIALS AND METHODS

We reviewed all patients undergoing resection for thymic epithelial tumors at Memorial Sloan-Kettering Cancer Center between January 1995 and December 2006. The institutional review board granted approval for this study on August 30, 2005. In this retrospective cohort study we included all patients with a pathologic diagnosis of thymoma or TC under the WHO (2004) histologic classification. All resected specimens were reviewed by one reference pathologist (W.T.) for the purposes of this study to confirm the diagnosis and the WHO classification. Patients who had

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Abbreviations and Acronyms	
PET	= positron emission tomography
PFS	= progression-free survival
SVC	= superior vena cava
TC	= thymic carcinoma
WHO	= World Health Organization

undergone prior resection, patients with a diagnosis of thymic carcinoid, and patients presenting with evidence of distant disease (Masaoka stage IVB) were excluded from this analysis.

Patient characteristics and outcomes were abstracted from medical records. The independent variables analyzed are listed in Table 1. Demographic variables included age as continuous and sex and race as categorical variables. Race categories were defined according to the Surveillance Epidemiology and End Results database definitions.⁷ Patient characteristics included pathologic Masaoka stage as a categorical variable, radiographic tumor size (longest diameter) as a continuous variable, and administration of preoperative therapy and postoperative therapy as dichotomous variables. Resection status was determined from the operative notes and the pathology reports. Resection status was dichotomized as complete if R0 with microscopically negative margins and incomplete if microscopically or grossly incomplete.

Outcome variables included time from operation to disease progression and site of progression. Because the proportion of incomplete resections was high, we used the term *disease progression* to encompass the occurrence of any treatment failure after resection. Disease progression was timed to the date of the first postoperative radiographic study that demonstrated progression or recurrence or was censored at the date of the most recent radiographic study documenting absence of disease. Site of progression was dichotomized as locoregional (confined to the mediastinum or pleural space) or distant (hematogenous) disease.

Patient characteristics were compared by using 2-tailed *t* tests for continuous variables, and χ^2 and Fisher's exact tests for categorical variables. Relapse was analyzed as a time to event rather than a binary outcome. Survival was estimated by using the Kaplan-Meier method. Because not all patients had complete resections, relapse was described in this study in terms of PFS rather than disease-free survival. Log-rank tests were used for univariate analysis of survival. Multivariate analysis was conducted by using the Cox proportional hazards method, incorporating clinically relevant and significant variables ($P < .10$) by means of univariate analysis into the model. Statistical analyses were conducted with STATA/IC 10.0 software (STAT-Corp, College Station, Tex).

RESULTS

One hundred twenty patients underwent resection during the study period and served as the basis for analysis of overall survival. Eighteen of these patients formed the basis for a prior study.⁸ Of the 120 patients, 3 underwent exploration only, and 5 were missing data on recurrence status, resulting in 112 patients for the analysis of disease progression. Median follow-up was 41 months (mean, 53 months) for death status and 26 months (mean, 34 months) for disease progression.

Patient characteristics are summarized in Table 1. The average age at the time of the operation for all patients in this study was 58 years, and the ratio of male to female patients was even overall. White patients (non-Hispanic and Hispanic) formed the predominant category in the distribution

TABLE 1. Patient characteristics

Variable	Thymic carcinoma (n = 23)	Thymoma (n = 97)	P value
Age (y)			
Mean	58.1 ± 2.6	58.1 ± 1.5	.99
Sex			
Male	15 (65)	46 (47)	.13
Female	8 (35)	51 (53)	
Race			
White	20 (87)	82 (85)	.96
Black	1 (4)	5 (5)	
Asian	2 (9)	9 (9)	
Other	0 (0)	1 (1)	
Size* (cm)			
Mean	7.0 ± 0.6	7.1 ± 0.4	.94
Stage			
I	1 (4)	24 (25)	.01
II	5 (22)	32 (33)	
III	12 (52)	20 (20)	
IVA	5 (22)	21 (22)	
Resection			
Complete	12 (52)	76 (78)	.01
Incomplete	11 (48)	21 (22)	
Preoperative therapy	18 (78)	42 (43)	.03
Postoperative therapy†	13 (59)	36 (38)	.06

Continuous variables are reported as means ± standard errors. Numbers in parentheses represent percentages. *n = 17 for thymic carcinoma and n = 94 for thymoma. †n = 22 for thymic carcinoma and n = 96 for thymoma.

of race. In the 111 patients with recorded tumor dimensions, the average tumor size was 7.1 cm in the longest diameter (range, 1.2–19 cm). There was no significant difference in age, sex ratio, race distribution, or tumor size between patients with TC and those with thymoma ($P > .10$). With regard to Masaoka stage, there was a significant difference in the distribution, with patients with TC having an appreciably greater proportion of higher stages (III and IVA). Overall, the proportion of complete resection (R0) was 73%, but patients with TC had a significantly lower proportion of R0 resections compared with those with thymoma (52% vs 76%, $P = .01$). Consistent with the higher stage and lower resection rate, a higher proportion of patients with TC underwent preoperative therapy (78% vs 43%, $P = .003$) and postoperative therapy (59% vs 38%, $P = .06$). Identical findings were obtained when comparing the 112 patients with data on disease progression, again with only stage, resection rate, preoperative, and postoperative therapy significantly different ($P < .05$).

Preoperative and postoperative therapy regimens are detailed in Table 2. The majority of patients who underwent preoperative therapy received chemotherapy alone in both groups. Two patients underwent concurrent chemoradiation in both groups. All chemotherapy regimens were platinum based. The most common regimens used in patients with TC were cisplatin–docetaxel (n = 4), cisplatin–doxorubicin–cyclophosphamide (n = 3), and carboplatin–paclitaxel

TABLE 2. Perioperative therapy

Regimen	Thymic carcinoma	Thymoma
Preoperative	18	42
Chemotherapy only	16 (89)	40 (95)
Chemoradiotherapy	2 (11)	2 (5)
Postoperative	13	36
Radiotherapy only	8 (62)	26 (72)
Chemotherapy only	0 (0)	5 (14)
Chemoradiotherapy	5 (38)	5 (14)

Numbers in parentheses represent percentages.

($n = 3$). The most common regimens used in patients with thymoma were cisplatin–etoposide ($n = 16$) and cisplatin–doxorubicin–cyclophosphamide ($n = 15$). Of the patients who underwent postoperative therapy, the majority underwent radiation therapy alone in both groups at a median dose of 5040 cGy (range, 2500–6600 cGy).

Overall survival was significantly lower at 5 years for patients with TC (53%) compared with that seen in patients with thymoma (89%, $P = .01$). Progression-free survival (PFS) was significantly different between patients with TC and those with thymoma ($P = .0002$). The PFS at 5 years for patients with TC was 36%, and it was 75% for patients with thymoma. The median PFS was 29 months for patients with TC and has not yet been reached for patients with thymoma. Univariate analysis of other additional factors predictive of PFS included Masaoka stage ($P < .0001$), resection status ($P < .0001$), preoperative therapy ($P < .0001$), and postoperative therapy ($P = .01$). Age, sex, race, and size were not found to be significant predictors ($P > .10$).

Multivariate analysis demonstrated that TC consistently predicted PFS after adjusting for Masaoka stage, resection status, and preoperative and postoperative therapy in the model (Table 3). TC (hazard ratio, 4.1; $P = .006$) and resection status (hazard ratio, 22.9; $P < .0001$) remained the only significant predictors of PFS in multivariate analysis. Stratifying by these 2 independent predictors, complete resection resulted in significantly greater PFS in both patients with TC ($P = .0001$, 70% vs 0% at 5 years) and patients with thymoma ($P < .0001$, 87% vs 28% at 5 years).

All stage I and II tumors were completely resected (R0). The extent of disease precluded resection of all gross tumor in 19 of 58 patients with stage III and IVA disease. The most

TABLE 3. Multivariate analysis of progression-free survival

Variable	Hazard Ratio	95% CI	P value
Thymic carcinoma	4.1	1.5–11.3	.006
Incomplete Resection	22.9	4.0–133	<.001
Stage			
III	1.4	0.2–10.5	.77
IVA	1.0	0.1–8.2	.97
Preoperative therapy	0.5	0.1–3.9	.52
Postoperative therapy	0.5	0.1–1.6	.22

CI, Confidence interval.

TABLE 4. Comparison of sites of progression

Site	Thymic carcinoma (n = 10)	Thymoma (n = 15)	P value
Distant	6 (60)	2 (13)	.01
Locoregional	4 (40)	13 (87)	

common reason for a grossly incomplete resection was invasion of the aorta ($n = 7$), followed by invasion of the heart ($n = 5$), invasion of the superior vena cava (SVC) in conjunction with other structures ($n = 3$), unresectable pleural disease ($n = 3$), and bilateral diaphragmatic involvement ($n = 1$).

Of 112 patients, 25 (22%) were found to have disease progression. The distribution of sites of progression is listed in Table 4. Disease progression occurred significantly more often at distant sites in patients with TC. In patients with TC, the majority of relapses ($n = 6$ [60%]) occurred at distant sites compared with only 2 (13%) in patients with thymoma ($P = .01$). The locations of disease progression are summarized in Table 5. Relapses in patients with thymoma were overwhelmingly intrathoracic, with the majority being pleura based. The only distant site of progression occurred in the lung (distinct from pleura-based metastases). In patients with TC, distant sites of progression included the lung, bone, brain, and liver. In the 25 patients with progression, relapse occurred earlier in those with TC, with a median time from operation to progression of 9 in patients with TC and 20 months in patients with thymoma (Table 6). The time to progression in those who relapsed was shorter in those who had incomplete resections (8 months) than in those with complete resections (29 months). Among all patients with progression, the majority (80%) of incomplete resections led to relapse in less than 3 years, as did all relapses in patients with TC, regardless of resection status.

DISCUSSION

The objective of this study was to characterize and compare the patterns of relapse between patients with TC and those with thymoma and identify independent predictors

TABLE 5. Location of progression

Location	Thymic carcinoma (n = 10)	Thymoma (n = 15)
Distant		
Lung	1	2
Bone	1	–
Bone, lung	1	–
Brain, bone	1	–
lung		
Liver	1	–
Liver, lung	1	–
Locoregional		
Pleura	2	8
Mediastinum	2	5

TABLE 6. Time to progression in patients with progression

Type	Time to progression (mo)		
	Overall	Complete	Incomplete
Thymic Carcinoma (n = 10)			
Median	29.4 (4.5–33.4)	22.7 (16.2–29.2)	7.8 (4.5–33.4)
Thymoma (n = 15)			
Median	19.5 (3.5–95.0)	45.7 (5.8–64.6)	13.2 (3.5–95.0)

of relapse. The principle findings are that TC and thymoma exhibit significantly different behavior, with higher stage, lower resectability, lower overall survival and PFS, more distant metastases, and earlier relapses. Our data support the notion that these 2 thymic tumors are clinically distinct entities with different biologies and add to our understanding of the patterns and natural history of relapse in thymic tumors. The clinical relevance of this study is strengthened by a relatively large sample drawn from a recent time period more reflective of current classifications and treatments.

Consistent with previous reports, overall survival and PFS were significantly worse in patients with TC in our population.^{3,9-11} Multivariate analysis demonstrated that TC and incomplete resection, but not stage, were strong independent predictors of PFS. These results are consistent with reports that WHO histology is independently predictive of recurrence and that Masaoka stage fails to predict outcomes in TC.^{10,11} In those reports size was noted to be an important prognosticator, but we were not able to confirm those findings in our population, possibly because of fewer tumors that reached their size cutoff (>8 cm).¹⁰

The extent of surgical resection is an important consideration given that complete resection is one of the primary determinants of outcome. Incomplete resections occurred only in Masaoka stage III and IVA thymic tumors. All stage I and II tumors were completely resected. The extent of disease precluded resection of all gross tumor in one third of patients with stage III and IVA disease, most commonly because of invasion of the aorta or the heart in the majority of cases. Although resection of the SVC was performed when that would permit a complete resection, the associated morbidity of an SVC reconstruction in conjunction with extrapleural pneumonectomy or chest wall resection was deemed unacceptable in 3 cases. Distribution of relapse sites differed significantly between patients with TC and patients with thymoma, with disease progression occurring at distant sites in the majority of relapses in patients with TC. These distant sites included the brain, liver, bone, and lung. The only thymoma distant metastasis occurred in the lung in our series, and others have noted the lung as the most common site of distant hematogenous metastases as well.¹² As with previous observations, pleural (locoregional) metastases appear to be most common mode of recurrence in patients with thymoma.^{10,12-15} Other extrathoracic sites in patients with thymoma have been re-

ported in the literature, including 3 patients who had brain and liver metastases.^{1,16} The 1 patient with thymoma with a lung metastasis originally presented with what is considered a low-grade histologic subtype (WHO A), serving as a cautionary note that no patient with a thymic tumor is immune from the potential for distant spread.

Our results should be interpreted in light of several limitations. The analysis of a single-institution experience raises the issue of external validity. However, this study population more accurately reflects contemporary management and might be more generalizable than prior study populations dating back multiple decades. The duration of follow-up was relatively limited, given the potential for recurrence years after treatment, but is a direct consequence of selecting a more contemporary study population. Nevertheless, significant differences in PFS were clearly evident early on between tumor types and resection status. The limited sample population is a function of the rarity of these tumors, but this study represents one of the larger experiences with TC in the past decade.¹⁷ Although surgical intervention is the mainstay of treatment, including only patients undergoing surgical management necessarily injects selection bias and fails to take into account the outcomes of those who might have been treated nonsurgically. Although patients were often followed with annual computed tomographic scans, not all patients had standardized follow-up, and recurrences might have come to light only when symptomatic or on serendipitous discovery. Conversely, patients who died might have had undetected recurrences. This, along with the average yearlong detection interval, will tend to overestimate the true time to progression. However, this is likely more reflective of the day-to-day reality of medical practice conditions.

Intuitively, relapses would most likely be expected to occur locally after incomplete resections. Although this appears to be the case with thymoma, the majority of patients with TC who had relapses presented with progression at distant sites, despite the best attempts at curative resection. This lends support to the idea that TC is a tumor with a more aggressive biology and might behave more like a systemic disease. The early time course of disease progression raises the possibility that distant micrometastases might already have been present at the time of treatment. The significantly higher frequency of distant failure in patients with TC raises the question of whether greater consideration should be given to the inclusion of systemic therapy when the diagnosis of TC is established.

The notion that different biologies are at work is reflected in reports observing differential expression patterns of tyrosine kinase receptors in thymic tumors. TCs tend to be c-kit positive and epidermal growth factor receptor negative, whereas thymomas tend to be epidermal growth factor receptor positive and c-kit negative.¹⁸⁻²⁰ The overexpression of c-kit in TC points to potential new avenues for targeted therapy, and at least 1 report has documented a clinical

response to imatinib, a tyrosine kinase inhibitor directed against c-kit.²¹

An alternative explanation might be that patients were understaged at the time of treatment, but with the exception of brain metastases, most of the other observed sites of distant relapse in these patients would have been encompassed by initial chest computed tomographic scans that included the upper abdomen. Several reports on the utility of positron emission tomography (PET) in thymoma suggest that this modality might be helpful in staging and might be particularly appropriate in cases of TC, given the higher potential for systemic disease.²²⁻²⁴

The high proportion of distant metastases raises further questions about the value of postoperative radiation in the treatment of thymic tumors.²⁵⁻²⁷ Postoperative therapy was not found to be an independent predictor of progression-free relapse, although selection bias must be acknowledged, and all distant relapses occurred in areas outside the radiation field. One hypothesis that has been advanced is whether concurrent induction chemoradiation might decrease the likelihood of recurrence.²⁸ By aiming for a pathologic complete response and sterilizing the tumor before surgical intervention, the possibility of shedding viable tumor cells through surgical manipulation might be lessened. These questions can only be answered through prospective controlled studies.

Our approach to preoperative biopsy has generally been to obtain a core biopsy specimen when there was suspicion of lymphoma or germ cell tumor or when the clinical appearance of a locally invasive thymic tumor raised consideration for preoperative chemotherapy. Well-circumscribed tumors typically proceed directly to resection. Distinguishing between thymoma and TC before resection would likely not alter the treatment course initially because locally advanced tumors would be treated with neoadjuvant chemotherapy in either case in our practice.

Patients with TC that progressed exhibited a tendency toward earlier relapse, as did patients with incomplete resections. In this series all patients with TC that progressed did so within the first 3 years, along with 80% of all patients with progression after R1 or R2 resection. Although it has been our practice to have annual follow-up, more frequent surveillance might be appropriate in the first few years in the setting of TC or incomplete resection. With our latest recurrence occurring at 95 months, we concur with others in advocating prolonged, if not lifelong, follow-up.^{14,29}

In conclusion, TC is a distinct entity from thymoma and, as a more aggressive tumor, has a higher propensity for distant spread, early relapse, and lower overall survival and PFS. Our results reiterate the importance of complete resection and the need for accurate pathologic diagnosis and vigilant surveillance after therapy. The propensity for distant failure places an emphasis on the need for better systemic therapies, and prospective efforts to improve our understanding of the biology and the optimal management of these tumors is imperative.

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Discussion

Dr John Handy (Portland, Ore). Dr Huang, nice job on the presentation. I thank the association for allowing me to discuss Memorial Sloan-Kettering's longstanding work in thymic malignancy, which dates back to the 1980s.

This is a retrospective report of a large series initiated to remedy the historical mixing of different histologic classifications, study periods spanning decades, and analytic end points, should it be disease-free survival or PFS. Therefore Sloan-Kettering has answered by using the World Health Organization classification. It is a contemporary series, and the end point is PFS. The objective was to define patterns and predictors of disease progression, and it is admirably accomplished in this data-filled article, the manuscript of which I received far in advance.

I have 3 questions. The high proportion of both TC and thymoma that received induction therapy indicated that the diagnosis was known preoperatively. What exactly is your preoperative workup? Do you perform biopsies in all patients? Who is getting PET scans?

Dr Huang. In general, the patients who are receiving induction therapy have come to us with a diagnosis from the outside, either with a needle biopsy or tissue obtained through the Chamberlain procedure. If the patients come to us presenting with a clinical stage III or IVA tumor, namely with invasion into the mediastinum or pleural disease, and they do not have biopsy results, we will proceed with either interventional radiology for a needle biopsy or do a Chamberlain procedure, if necessary. For any patients in whom we are considering induction therapy, they will not proceed to systemic therapy without a biopsy.

In terms of the utility of PET, we prefer to obtain PET scans on these patients, if possible, looking for distant metastases. This might be more relevant in the setting of TC. Sometimes these patients come to us from the outside already having had a PET scan. If not, we try to obtain one.

Dr Handy. Second, because TC fails distantly regardless of the completeness of the resection, are you rethinking induction chemotherapy, and what agents are you using nowadays?

Dr Huang. In terms of systemic therapy, we have traditionally been treating TCs with the same regimens with which we have treated thymomas in the past. The most commonly used regimens at our institution have been cisplatin, doxorubicin, and cyclophosphamide or cisplatin, and etoposide.^{1,2} We have been using those

for thymomas and TCs. However, recently, some of our oncologists have started to approach TCs as a different disease. Because they seem to be predominantly squamous in histology, we have been approaching some of these patients with a regimen, such as cisplatin and docetaxel, more like non-small cell lung cancer.

Several reports now have shown that there is a high proportion of thymic tumors that overexpress epidermal growth factor receptor,³ raising the possibility of using targeted therapies for these thymic tumors, and this is an area of active investigation.

Dr Handy. Finally, in light of this report and your publication last year of use of extended resection in stage IVA thymomas, how is Sloan-Kettering presently caring for these patients with thymoma? Who is receiving chemotherapy and radiation therapy, and what about resection, because these are local recurrences? Nice job on the presentation.

Dr Huang. In general, for the patients with early-stage disease that is smaller and well encapsulated, most will proceed straight to surgical intervention. The more challenging patients that we face are the patients with higher-stage, locally advanced disease, which present to us with clinically stage III or IVA tumors. These patients will typically need a biopsy to demonstrate their pathology and then proceed to induction therapy with one of the regimens that I mentioned before with the goal of treating to maximum response, usually about 4 cycles of treatment. At that point, they proceed to surgical resection if they are medically operable, where the goal is a total thymectomy with en-bloc resection as necessary. In some cases this might lead to extended resections, including extrapleural pneumonectomy, if necessary, in cases of extensive confluent disease, as recently reported by our group and others.^{4,5} After resection, every patient with an incomplete resection will receive radiation therapy post-operatively. Patients with stage III and IVA tumors will usually receive mediastinal radiation after complete resections. For those patients who have undergone extrapleural pneumonectomy, these patients have received hemithoracic radiation to the chest cavity akin to our approach to pleural mesothelioma.⁶

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