Prognostic Factors for Cure, Recurrence and Long-Term Survival After Surgical Resection of Thymoma

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Introduction: To determine long-term outcome and risk factors for recurrence after thymectomy.

Methods: Patients who underwent thymectomy (n = 262) for a thymic tumor (1986–2010) were identified from a prospective database. Patients were classified according to World Helath Organization (WHO) histologic classification, Masaoka staging system, and completeness of resection. Risk factors for recurrence: WHO histology, tumor size, Masaoka stage and completeness of resection were analyzed.

Results: Of 262 patients, 51% were female, median age was 55 years, and 39% had myasthenia gravis. Median follow-up was 7.5 years, median tumor size was 5.4 cm, and Masaoka stage distribution was: I (25%), II (47%), III (17%), IV (4%), and (7%) not classified. Of 200 patients classified under the WHO system, there were (7%) type A, (22%) type AB, and (71%) type B; 83% had complete resection. One-hundred and sixty-nine patients received adjuvant radiotherapy, eight adjuvant chemoradiotherapy and 14 neoadjuvant chemoradiotherapy. Overall survival was 95% at 5 years, 91% at 10 years and 91% at 15 years. Recurrence occurred in 12 patients and disease-related death in four patients. Five patients underwent re-resection for recurrence with survival of 2–15 years. Only Masaoka stage and tumor size were associated with statistically significant risk of recurrence on multivariate analysis.

Conclusion: Resectable thymoma is associated with excellent prognosis. Aggressive resection of recurrent disease yielded excellent long-term results. Higher Masaoka stage is associated with a greater chance of incomplete resection. Higher Masaoka stage and increasing tumor size are independent factors associated with recurrence.

Key Words: Thymoma, Survival, Thymectomy, Recurrence, Risk factors

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Epithelial tumors of the thymus gland are rare neoplasms that exhibit significant histologic heterogeneity. This has contributed to long-standing controversy and uncertainty regarding best predictors of outcome. More recently, however, multivariate analyses performed in several retrospective case series have demonstrated tumor Masaoka stage and completeness of resection to be consistent independent prognostic factors.[1–3]

Although the World Helath Organization (WHO) histologic classification[4] has been increasingly adopted as the classification of choice, recent multivariate analyses have generally not shown it to be of independent prognostic value.[2,3,5] There is, however, consensus that many of these tumors are relatively indolent and are associated with excellent long-term survival of greater than 75% at 10 years, warranting aggressive surgical 50 intervention.

This retrospective study of a large cohort of thymoma patients was carried out to further the understanding of the association between survival and WHO histology, tumor size, Masaoka stage, and completeness of resection.

MATERIALS AND METHODS

This study was approved by the Research Ethics Board of University Health Network (Toronto General Hospital [TGH] and Princess Margaret Hospital). All patients with thymic tumors who underwent thymic resection at TGH between 1986 and 2010 were reviewed in this retrospective cohort. Data were collected from a prospectively maintained database, and all electronic and archived paper charts were reviewed. All surgical pathology assessments were performed at TGH. Staging was recorded according to the Masaoka staging system and extent of resection was defined as microscopically complete versus incomplete. In patients in whom resection was performed in the very early years, thymoma capsule invasion anteriorly even in the absence of extension outside of capsule used to be reported as "margin positive". However, after careful review, the investigators (surgeons and pathologists) felt this to be inaccurate considering that this aspect of the thymic capsule lies immediately posterior to the sternum where there is no other anatomical tissue to form a classic "surgical margin". Hence, it was felt that such cases should be considered as complete resections. This reporting method was adopted and is used consistently in all cases performed since that early

TABLE 1. All Thymic Tumors Resected (1986–2010; 262)

WHO histology	Non-WHO classification		Thymic Ca
200	43		19
	Lattes-Bernatz 24	"Benign thymoma" 19	None included in statistical analysis

Aside from variation in the reporting of histology all variables (Masaoka stage, tumor size etc.) were available on all above 243 cases.

WHO, World Helath Organization.

period. Although the indications for adjuvant radiotherapy have evolved over the period of this study, in general, in all incomplete resections and stage 2b or greater, radiotherapy has generally been recommended. Neoadjuvant therapy was recommended only sparingly on an individual basis mostly in the context of downsizing larger tumors in the hope of achieving an R0 resection. Histologically, the WHO classification was used in many cases (200 of 262). Cases reported early in this cohort were either reported according to Lattes Bernatz[24] or thymoma not otherwise specified or "benign thymoma,"[19] as older slides were no longer physically available for review (Table 1). Follow-up was performed every 6 months for the first 2 years and then yearly with computed tomography thorax. Histological WHO type C (undifferentiated/poorly differentiated thymic carcinoma cases (n = 19) are reviewed in this report for completeness of the experience. However, this subtype is largely considered a separate entity and therefore is not included in any statistical analysis.

Descriptive statistics were reported as medians with ranges for continuous variables and frequencies and proportions for categorical variables. Recurrence-free survival was calculated using the Kaplan-Meier method. Recurrence-free survival was defined as the time from surgery date to first recurrence (when identified on computed tomography scan either on routine follow-up or when done for clinical indications), death from disease, or last follow-up. There were very few events to analyze overall survival. Differences between survival curves were analyzed by Log-rank test. Multivariate analyses were performed using Cox-proportional hazard regression models. Hazard ratios and 95% confidence intervals were estimated from the multivariate model. Two-sided tests were applied. Results are considered significant if the p value is less than 0.05. An exhaustive search for potential cutoffs for tumor size was performed to determine the optimal size with the maximum effect between the large tumor and small tumor subgroups. All the other analyses are performed using SAS 9.2 (SAS Institute, Cary, NC).

TABLE 2. Demographic and Treatment Data by Masaoka Stage

	Masaoka Stage			
Characteristic	**I**	**II**	**III**	**IV**
Gender (M/F)	29/36	49/74	30/15	2/8
Age (median, years)	56	54	57	51
Completeness of resection (R0—Y/N)	64/1	108/15	25/20	3/7
Adjuvant radiotherapy (Y/N)	17[a]/48	111/12	36/9	5/5
Neoadjuvant chemoradiation (Y/N)	0/65	5/118	8/37	1/9
Adjuvant chemoradiation	0/65	1/122	1/44	2/8

[a]Radiotherapy was administered to many stage I patients as they were felt to be R1 resection at the anterior margin and so initially classified as stage II as described in methods.

RESULTS

Of 262 patients, 133 (51%) were female, median age was 55 years (range 16–86), and 39% had myasthenia gravis. Median follow-up was 7.5 years (maximum 25 years; minimum 1 year) and median tumor size was 5.4 cm (maximum 17.5 cm, mininimum 1 cm). The Masaoka stage distribution was: I, 65 (25%); II, 123 (47%); III, 45 (17%); and IV, 10 (4%). The pathological diagnosis of "benign and otherwise not classified thymoma" was reported in 19 (7%) of patients early in the cohort. Of 200 patients with known WHO staging, the histologic distribution was: type A, 14 (7%); AB. 44 (22%); and B, 142 (71%). Forty-three were classified only according to Lattes-Bernatz and Rosai systems all of which involved patients also early on in data collection before the WHO classification was adopted at TGH. Two-hundred patients (83%) had a complete resection (R0) and 43 (17%) had an incomplete resection (41 R1: microscopic-positive margins, two R2: grossly positive margins). One-hundred and sixty-nine patients received adjuvant radiotherapy, four received adjuvant chemoradiotherapy, and 14 received neoadjuvant chemoradiotherapy. Table 2 describes characteristics and treatment

TABLE 3. Masaoka Stage Versus World Helath Organization (WHO) Histology

	WHO Histology					
Masaoka Stage	**A**	**AB**	**B1**	**B2**	**B3**	**Total**
I	6	10	8	17	6	47 (23.5%)
II	6	29	14	43	13	105 (52.5%)
III	2	4	6	14	12	38 (19.0%)
IV	0	1	2	3	4	10 (5.0%)
Total	14 (7.0%)	44 (22.0%)	30 (15.0%)	77 (38.5 %)	35 (17.5%)	200[a]

[a]There were 24 patients who were classified using the Lattes-Bernatz histology criteria (Table 3) and 19 patients from the earliest portion of the series who were classified as "benign, not otherwise classified—thymoma". The latter were classified as stage I.

