Thymoma: a review of the clinical and pathological findings in 65 cases

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Introduction: Although rare, thymoma is the most common tumour of the anterior mediastinum. In an effort to assess the clinical and pathologic characteristics of this tumour and to determine whether clinicopathologic stage or histopathologic classification correlates with clinical outcome, in the Department of Pathology and the Department of Surgery at the University of Saskatchewan we reviewed all cases of thymoma registered in the province of Saskatchewan using the database of the Saskatchewan Cancer Centre. **Methods:** In 65 patients with a diagnosis of thymoma or thymic carcinoma identified from the Saskatchewan Cancer Centre database between Jan. 1, 1960, and Dec. 31, 2000, we studied the presentation, diagnostic investigations, therapeutic interventions, tumour size, postoperative course, clinical stage, histopathologic classification, disease recurrence and mortality. **Results:** Of the 65 patients, 17 (26%) were asymptomatic and 11 (17%) had symptoms consistent with myasthenia gravis. Surgical resection is most commonly performed through a median sternotomy and frequently requires en bloc resection of one or more adjacent structures. The overall survival of patients with thymoma was found to correlate with the clinical stage as described by Masaoka and colleagues and with complete tumour resection. A trend to clinicopathologic correlation was observed when applying the histologic classification systems of Suster and Moran and the World Health Organisation, but this trend was not statistically significant. **Conclusions:** Thymoma is a rare tumour with a variable clinical presentation. Clinical outcome correlates with clinical stage and the ability to achieve complete tumour resection.

Introduction : Bien que rare, le thymome est la tumeur du médiastin antérieur la plus courante. Afin d'évaluer les caractéristiques cliniques et pathologiques de cette tumeur et d'établir s'il existe un lien entre le stade clinicopathologique ou la classification histopathologique et l'issue clinique, nous avons utilisé la base de données du centre de cancérologie de la Saskatchewan pour passer en revue, au Département de pathologie et au Département de chirurgie de l'Université de la Saskatchewan, tous les cas de thymome enregistrés en Saskatchewan. **Méthodes :** Nous avons étudié le tableau clinique, les tests diagnostiques, les interventions thérapeutiques, la taille de la tumeur, le traitement après l'intervention, le stade clinique, la classification en histopathologie, la récidive et la mortalité chez 65 patients atteints d'un thymome ou d'un carcinome thymique enregistrés dans la base de données du centre de cancérologie de la Saskatchewan entre le 1er janvier 1960 et le 31 décembre 2000. **Résultats :** Des 65 patients, 17 (26 %) ne présentaient pas de symptôme et 11 (17 %) avaient des symptômes compatibles avec ceux de la myasthénie. L'exérèse est pratiquée le plus souvent par sternotomie médiane et exige fréquemment l'ablation monobloc d'au moins une structure adjacente. On a démontré une corrélation entre, d'une part, la survie globale des patients atteints d'un thymome, et d'autre part, le stade clinique décrit par Masaoka et ses collègues et l'exérèse complète. L'application des systèmes de classification histologique de Suster et Moran et de l'Organisation mondiale de la Santé a révélé une tendance à une corrélation avec le stade clinicopathologique, mais cette tendance n'était pas significative sur le plan statistique. **Conclusions :** Le thymome est une tumeur rare dont le tableau clinique varie. L'issue clinique est en corrélation avec le stade clinique de même qu'avec la capacité de parvenir à une exérèse complète.

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Thymoma, a rare neoplasm arising from the epithelial cells of the thymus gland, is variable in its presentation, ranging from an asymptomatic incidental finding on chest radiography, to signs and symptoms consistent with a local mediastinal disorder, to an unusual paraneoplastic syndrome. Although rare, it is the most common tumour of the anterior mediastinum, accounting for up to 50% of such tumours.[1,2] In general, thymoma is associated with a good prognosis, and clinical staging rather than histologic classification provides the most important prognostic information.

Owing to its rarity, only a few large case series have been reported elucidating the clinical and pathological characteristics of thymomas.[1,3–6] These studies have included diagnoses and treatment for thymoma over many years, during which time diagnostic modalities and potential therapies have changed considerably. In addition, histopathologic classification systems have evolved.[7] Despite the existence of multiple histologic classification systems, none has been clearly demonstrated to be superior to the others; few studies have demonstrated a strong correlation between histopathologic classification and patient outcome. The changes in diagnosis and treatment and the lack of a universally used histopathologic classification system have made comparative studies and reference to the thymoma literature cumbersome.

In an attempt to add to the current body of information concerning the clinical and pathological characteristics of thymoma, we reviewed 65 consecutive cases identified over the past 40 years in Saskatchewan, a province with a relatively stable population of about 1 million people. In doing so, thymomas were classified according to previously established staging and histopathologic classification systems, and according to the histopathologic classification system recently introduced by the World Health Organisation (WHO).[8–11]

Methods

A retrospective review of the Saskatchewan Cancer Centre database was performed after ethics approval to identify all consecutive patients with a diagnosis of thymoma or thymic carcinoma between 1960 and 2000, inclusive. Data were collected from the cancer centre and hospital records. Follow-up data were obtained from hospital and physician records.

All slides were re-examined by a single pathologist, and each case was classified according to 2 different classification systems. The first, chosen for its simplicity, was that described by Suster and Moran,[9] who classified thymic epithelial neoplasms as thymoma, atypical thymoma or thymic carcinoma, based on the degree of cellular differentiation and atypia. The second classification system chosen was the recent WHO's International Histological Classification of thymic tumours, which classifies tumours as type A, AB, B1, B2, B3 or C, based on the predominant cell type.[10–13] A third classification system described by Marino and Muller-Hermelink[14] classified thymomas histogenetically, describing them as cortical, medullary or mixed. Although this classification is well known and likely the most widely accepted classification system, it has been criticized for its lack of reproducibility in everyday practice[15] and was therefore not used in this study. Operative records and histologic review were used to stage patients according to the clinical staging system devised by Masaoka and colleagues:[16] stage I (macroscopically and microscopically encapsulated), stage II (macroscopic invasion of mediastinal fatty tissue or microscopic invasion into the capsule), stage III (macroscopic invasion into surrounding structures) or stage IV (pleural or pericardial implants or lymphogenous or hematogenous metastases).

Clinical data collected included demographic information, such as age and sex, presenting symptoms, investigations and therapeutic interventions. Surgical data included surgical approach, procedure performed, the presence or absence of tumour invasion, and immediate operative complications. Follow-up data included the presence or absence of recurrent disease, survival status and cause of death if applicable. Survival functions were estimated to 5 and 10 years according to the Kaplan–Meier statistical method, and comparisons made with use of the log-rank test.

Results

Clinical features

The Saskatchewan Cancer Centre database yielded 65 patients who had a diagnosis of thymoma, giving an annual accrual of 1.6 patients per year. All cases were confirmed to be of primary thymic epithelial origin after review of the histologic findings. In 3 cases the diagnosis was made at autopsy, with histologic confirmation of thymoma or thymic carcinoma. Patient age at presentation ranged from 32 to 77 years (mean 55 yr). A slight female preponderance was detected, with 38 (58%) females and 27 (42%) males being affected.

Of the 65 patients, 48 (74%) presented with symptoms secondary to their disease (Table 1); the remaining 17 (26%) were asymptomatic at the time of diagnosis. In all the asymptomatic patients the diagnosis was made as the result of an incidentally discovered mass on a chest radiograph. Among symptomatic patients, chest pain was the most common presenting complaint (15 [23%] patients). Symptoms consistent with myasthenia gravis accounted for the second most frequent presentation, affecting 11 (17%) patients.

Sixty-three patients underwent preoperative investigation. Two patients died before investigations could be performed. Of the 63 patients who underwent investigation,

2 did not undergo surgery: in one case, the patient died as a result of tumour compression of the pulmonary artery and microscopic pulmonary tumour embolization; in the other, surgical intervention was not attempted because of pleural, pulmonary and paraspinal metastases diagnosed by fine-needle aspiration biopsy. A summary of the preoperative investigations performed is given in Table 2. All of the 60 chest radiographs obtained were positive for a mass. Computed tomography was performed in 42 cases; all the scans demonstrated a mass, only 4 clearly identified invasion, with another 5 being suggestive but not conclusive. Fine-needle aspiration biopsy, performed in 14 cases, correctly diagnosed thymoma in 7 (50%). Mediastinoscopy was performed in 10 cases but was diagnostic in only 1.

In the 61 patients who underwent surgery, median sternotomy was the preferred operative approach (48 [79%] patients). Other approaches included left anterolateral thoracotomy (7 [11%] patients), right anterolateral thoracotomy (5 [8%] patients), and right posterolateral thoracotomy (1 [2%] patient).

Of the operative procedures performed on the 61 patients (Table 3), 10 (16%) were open biopsy alone. The remainder consisted of total thymectomy (24 [37%]) or total thymectomy with partial en bloc resection of an adjacent structure(s) (27 [44%]). In 7 (14%) of the 51 patients who had surgical resection, the operating surgeon considered the resection incomplete. Pathological review revealed incomplete resection in an additional 18 cases for a total of 25 (49%) incomplete resections. There was 1 intraoperative death, from hemorrhage as the result of a laceration to the left atrium.

Among the 51 patients who underwent surgical resection, 22 (43%) received adjuvant radiotherapy, with 2 of these also receiving chemotherapy. Of the 22 patients, 4 had incomplete surgical and pathological resection, 14 had complete surgical resection but incomplete pathological resection, and 4 had complete surgical and pathological resection. Postoperative radiotherapy was largely reserved for patients with more extensive disease, with 19 of 22 patients being stage III or IV. Nine of the 10 patients who had an open biopsy without resection received radiotherapy, with 5 of these patients also receiving chemotherapy. The only patient who did not receive radiotherapy in the unresected group was lost to follow-up.

Pathologic features and follow-up

Tumours ranged in size from 1.5–16 cm in maximum dimension (mean 8.8 cm). In patients having myasthenia gravis, tumour size averaged 7.8 cm. Disease staging by Masaoka's system was as follows: stage I, 23 (35%) patients; stage II, 13 (20%) patients; stage III, 19 (29%) patients; stage IV, 10 (15%) patients. A summary of the distribution of tumours by histopathologic classification is provided in Table 4.

Follow-up ranged from 2 months to 27 years (mean 7.1 yr). Overall and disease-free survival were assessed according to clinical stage and histopathologic classification. Survival functions were estimated with the use of Kaplan–Meier curves and comparisons were made by the log-rank test.[17] In estimating survival, the outcome of interest was death

Table 1

Presenting Symptoms and Signs in 65 Patients With Thymoma

Presenting symptom/sign	Patients, no. (and %)
Asymptomatic	17 (26)
Chest pain	15 (23)
Myasthenia gravis	11 (17)
Cough	10 (15)
Shortness of breath	7 (11)
Fatigue	4 (6)
Venous obstruction	3 (5)
Weakness	3 (5)
Malaise	2 (3)
Back pain	2 (3)
Dysphagia	2 (3)
Hemoptysis	2 (3)
Hematologic syndrome	1 (2)
Myalgia	1 (2)
Wheezing	1 (2)
Night sweats	1 (2)
Numbness	1 (2)
Weight loss	1 (2)

Table 2

Preoperative Investigations Performed on 63 Patients With Thymoma

Investigation	Patients, no. (and %)
Chest radiography	60 (95)
Computed tomography of chest	42 (67)
Fine-needle aspiration biopsy	14 (22)
Bronchoscopy	11 (17)
Mediastinoscopy	10 (16)
Tomography of chest	5 (8)

Table 3

Operative Procedures Performed on 61 Patients with Thymoma

Operative procedure	Patients, no. (and %)
Biopsy of mass	10 (16)
Thymectomy alone	24 (37)
+ pleurectomy	7 (11)
+ pericardectomy	5 (8)
+ pleurectomy, pericardiectomy and wedge resection of lung	4 (6)
+ pleurectomy and pericardiectomy	3 (4)
+ pericardiectomy and wedge resection of lung	3 (4)
+ wedge resection of lung	2 (3)
+ pleurectomy and wedge resection of lung	1 (2)
+ pericardiectomy and resection of inominate vein segment	1 (2)
+ pleurectomy and resection of innominate vein segment	1 (2)

(event), and time to the occurrence of death was the survival time. Censoring occurred in this study if the patient was still alive or tumour recurrence had not occurred.

According to Masaoka's staging, median patient survival was significantly improved for stages I, II and III disease than for stage IV disease ($p < 0.01$). With the post hoc test for multiple comparisons, the median survival for patients with stage IV disease was significantly worse than for patients with stage I ($p < 0.01$) and stage II ($p < 0.05$) disease, and the median patient survival for stage III disease was significantly ($p < 0.05$) worse than for patients with stage I disease. Five- and 10-year survival rates according to Masaoka's staging are provided in Table 5, and survival curves are shown in Fig. 1.

Table 4

Histopathologic Classification in 65 Patients With Thymoma

Classification	Patients, no. (and %)
Suster and Moran	
Thymoma	38 (58)
Atypical thymoma	14 (22)
Thymic carcinoma	13 (20)
World Health Organisation	
A	6 (9)
AB	12 (18)
B1	14 (22)
B2	2 (3)
B3	19 (29)
C	12 (18)

Estimated survival curves using the Suster–Moran classification system (Fig. 1) demonstrated that the median survival time for patients with thymic carcinoma was significantly lower than for patients with thymoma and atypical thymoma ($p < 0.01$) (Table 6). Similar analyses, using the WHO classification (Fig. 1), identified a trend toward clinicopathologic correlation that was not statistically significant; this was attributed to dilution of patient numbers across 6 categories. Analyses of tumour recurrence as the measured outcome showed a definite trend dependent upon the WHO and Suster–Moran classifications. None achieved statistical significance.

Completeness of surgical resection was found to correlate with clinical outcome, with a statistically significant better survival time of 15.91 years in the completely resected group compared with 7.13 years in the incompletely resected group ($p < 0.001$).

Discussion

Although a diversity of neoplasms may arise in the thymus, the term thymoma specifically denotes a tumour of thymic epithelial cell origin. Confusion regarding the nomenclature of primary thymic tumours is long-standing and persists today, primarily in regard to the distinction between malignant thymoma and thymic carcinoma. This confusion stems from the finding that malignant thymoma can invade locally or even metastasize but remains a distinct histologic entity based on its bland cytologic characteristics. Further, multiple histopathologic classification systems have been described for thymoma, with most incorporating thymic carcinoma. Of clinical importance is the distinct biologic behavioural difference between thymoma and thymic carcinoma. The former tends to be indolent and is associated with a relatively good prognosis, whereas the latter behaves aggressively and is associated with a poor prognosis (less than one-third of patients survive 5 yr after diagnosis).[3] Moreover, thymomas are much more common than their histologically malignant counterparts; less than 2% of primary thymic tumours demonstrate overt carcinoma on histologic examination.[17,19]

Previous clinicopathologic studies have produced conflicting results with regard to the ability of histopathologic analysis to predict biologic behaviour. However, the clinical stage of the tumour, determined by the degree of encapsulation and presence of invasion or metastases, has been a more reliable prognostic indicator, with the staging system of Masaoka being the most commonly applied. The findings from our review of 65 cases of thymoma identified over a 40-year period support the ap-

Table 5

Outcome for 65 Patients With Thymoma, According to the Masaoka Staging System

	Masaoka stage			
Outcome of interest	I ($n = 23$)	II ($n = 12$)	III ($n = 20$)	IV ($n = 10$)
Death, no.				
Death	8	4	9	8
Censored	15	8	11	2
Survival				
Mean, yr	17.1	18.1	8.8	5.1
Median, yr	15.0	20.0	9.0	2.0
5-yr survival, % of pts.	88	71	61	48
10-yr survival, % of pts.	80	71	45	16

Table 6

Outcome for 65 Patients With Thymoma, According to the Suster–Moran Classification

	Suster–Moran classification		
Outcome of interest	Thymoma ($n = 38$)	Atypical thymoma ($n = 14$)	Thymic carcinoma ($n = 13$)
Death, no.			
Died	13	5	11
Censored	25	9	2
Survival			
Mean, yr	16.8	10.4	4.3
Median, yr	17.0	8.0	1.0
5-yr survival, % of pts.	80	90	23
10-yr survival, % of pts.	76	46	23

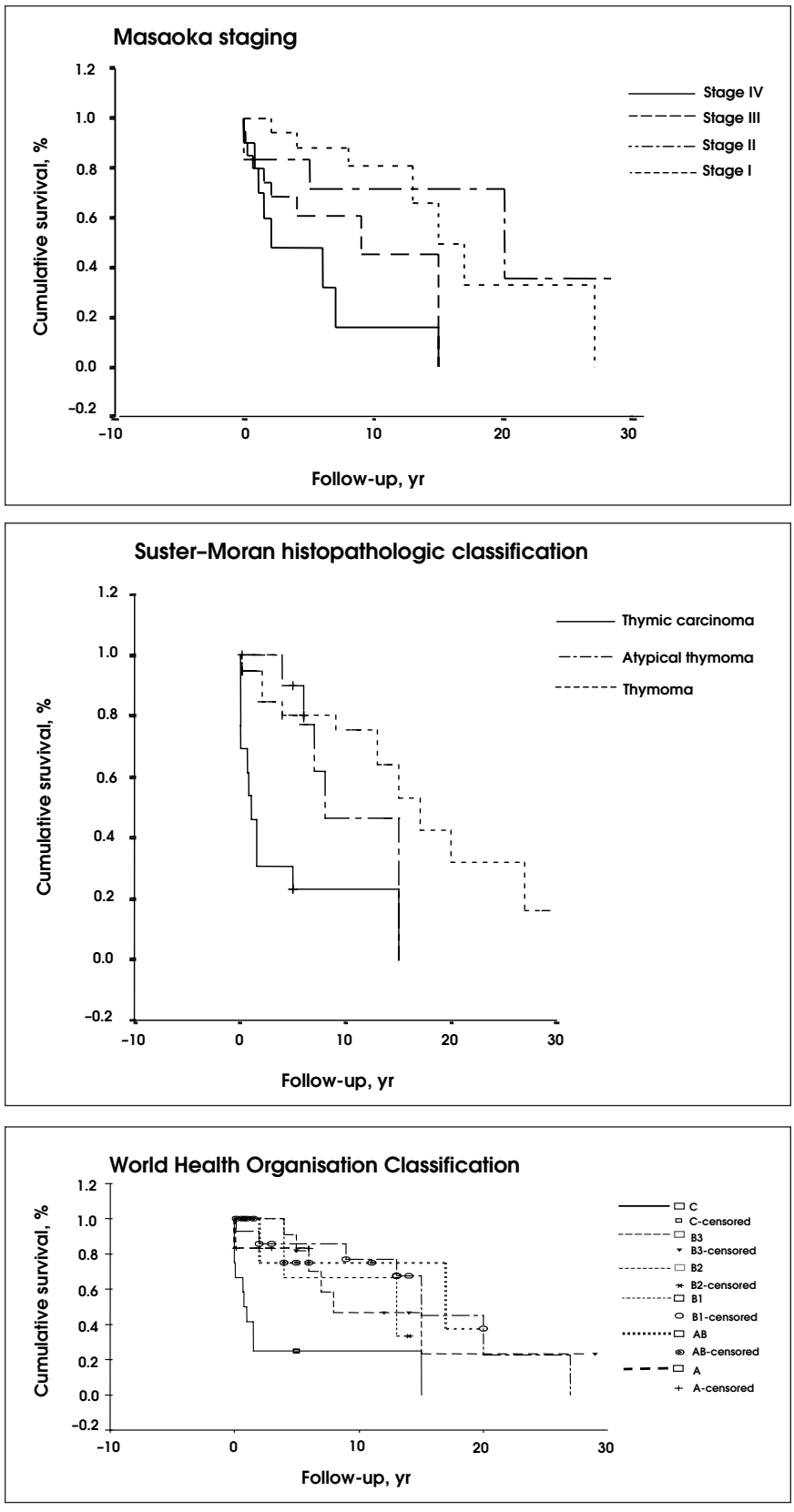

FIG. 1. Survival functions according to the Masaoka staging system (top), the Suster-Moran classification (centre) and the World Health Organisation classification (bottom) in 65 patients with thymoma, when the outcome of interest was death.

plication of clinical stage as a prognostic indicator. The histopathologic classification of Suster and Moran suggested a trend to clinicopathologic correlation, but this was not statistically significant. The same was true for the histopathologic classification system recently introduced by the WHO. A statistically significant correlation between histologic characteristics and outcome may not have been demonstrated owing to the small number of patients, a consequence of the rarity of this tumour. The finding in our series of double the survival for patients who had a complete resection confirms that this factor is highly predictive of patient outcome as has already been demonstrated.

With respect to the clinical features of thymoma, the majority of patients in our series (74%), as in others,[12] presented with symptomatic disease. Symptoms attributed to myasthenia gravis were found in only 17% (47% if patients having thymic carcinoma are excluded) of cases. Previous studies have found a similar incidence of myasthenia gravis with thymoma ranging from 30%–60%.[20,21] Most series have found that thymic tumours are smaller in patients with myasthenia gravis, yet we found relatively large tumours, averaging 7.8 cm, in these patients.

In terms of diagnosis, chest radiography was the most commonly performed investigation, with 100% of chest films suggestive of a mass. Computed tomography was performed in 42 cases, and all demonstrated a mass, but only 4 of 30 scans in patients with invasive thymomas correctly identified invasion. This may not be surprising: Tomiyama and colleagues,[22] evaluating the CT features of invasive thymoma, reported that no single finding was consistent with invasion; the presence of a lobulated or irregular contour, areas of low attenuation and multifocal calcification were suggestive.

The most common operative approach was median sternotomy, used

in 79% of cases. This is the preferred approach, no matter how small or limited the thymoma, and a complete thymectomy should always be performed if possible. Simple enucleation may result in recurrence, since remaining thymic tissue is a potential site for later development of additional thymoma.[5] Median sternotomy is well tolerated, and the tumour can be carefully evaluated for invasion and therefore correctly staged. For these reasons, unilateral thoracotomy and cervical incision are generally not appropriate.

Although certain studies have shown that histologic classification correlates with clinical behaviour, reproducibility of these results has been inconsistent, with relatively equal numbers of studies being unable to demonstrate clinicopathologic correlation.[9,13–15,19,23–26] Confounding the situation further are the apparent high rates of observer variation when tumours are classified according to certain histologic schemes.[15] In this series, the clinical staging (Masaoka) and the completeness of resection were most predictive of outcome, and histopathology was less predicitve. We conclude that a histopathologic classification system that is reproducible and can provide reliable prognostic information for patients with thymoma remains elusive.

Competing interests: None declared.

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