**Introduction**

Thymoma is an uncommon, anterior mediastinal neoplasm arising from thymic epithelial cells and lymphocytes, characterized by a remarkable morphological heterogeneity and variable clinical behavior (1-3). Prognostic factors in the diagnosis and treatment of thymic tumours are difficult to define, since they are slow growing tumours, and their nature is often impossible to determine (4). Although they are generally encapsulated and well differentiated, these tumours may behave in a locally aggressive fashion and may metastasize outside the thoracic cavity. The degree of encapsulation and invasion of adjacent tissues and the association with specific auto-immune diseases, particularly MG, represent the most important prognostic factors in these patients (5-7). The incidence of thymomas in patients with myasthenia gravis (MG) was defined as 9-28% (8-9), and MG was detected in 25-59% of patients with thymoma (9-10). Since the association between thymoma and MG was first recognized in 1901 by Weigert, it has been frequently reported that MG may influence the operative mortality and lead to poor remission rates due to the poor prognosis of the MG. In contrast to these reports, some authors showed that the prognosis was better in patients with MG, which enables early detection of the myasthenic thymoma, which can be treated with complete excision.

Thymomas are most appropriately treated by complete resection, resulting in a 96% 10-year survival (11). In thymoma patients with MG, mortality is related to myasthenic crisis, whereas tumoral invasion was the major factor causing death in non-myasthenic patients. In this study, we describe our experience with the surgical treatment of thymoma.

**Material and methods**

Between 1980 and 2002, 73 patients with thymoma underwent operation. Twenty-four (32.9%) patients were female and 49 (67.1%) were male. Ages ranged from 26 to 64 years and the mean age was 46 ± 3.5 years.

Diagnosis of thymoma was established with a routine chest roentgenogram in five asymptomatic patients. The most common symptoms were symptoms related to MG, chest pain, and dyspnea. Cough and shortness of breath were present in four, dysphagia in two and vena cava superior syndrome due to the extent of the tumour in one. Associated diseases were MG in 59 patients (80.8%), scleroderma in 2, pure red cell aplasia in 1, hypogammaglobulinaemia in 2, dermatomyositis in 1, and lepra in 1.

Thymectomy was performed through a median sternotomy (partial or complete sternotomy depending on the extent of the tumour) in 71 patients. In two patients without myasthenia, heterotopic thymoma was
diagnosed at the time of an explorative thoracotomy for an intrathoracic tumour. Complete resection of the thymoma and thymic tissue, including whole anterior mediastinal lipid tissues, was carried out in 67 (91.8%) patients. Two patients with and three without MG underwent incomplete resection, and in one a biopsy alone was performed. Four patients with stage III underwent partial pericardectomy and wedge resection of the left lung. Incomplete resection was performed in 2 patients operated via thoracotomy. Both of these patients had non-myastenic thymomas. In these patients complete resection was impossible due to gross lung and tracheal metastases.

Extubation was accomplished in the operating room for patients who had no bulbar and/or respiratory involvement and in the intensive care unit for the remaining patients who required ventilatory assistance. Sixty-two (94.6%) patients were extubated in the first 24 hours. Eleven (5.4%) patients required mechanical ventilatory support for a period ranging between a week and 3 months.

The tumours were classified into five stages, according to the clinical stage (the criteria have been described by Masaoka and associates) (12): macroscopically encapsulated tumours and microscopically non-capsular invasion (stage I), macroscopic invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion into the capsule (stage II), microscopic invasion of surrounding tissues such as lungs, pericardium, aorta and superior vena cava (stage III), metastasis to thoracic cavity (stage IVa) and distant tissues (stage IVb). The distribution of stage and association with MG is shown in Table I.

We used the histological classification system that was proposed by Bernatz and associates (1). This classification is based on morphological grounds, according to the cell type of the tumour as epithelial, lymphocytic, or lympho-epithelial according to the ratio of lymphocytes to epithelial cells, and undifferentiated malignant types.

Radiation therapy was used as an adjunct to surgical treatment in 74.4% of all patients with invasive thymoma. Postoperative chemotherapy was performed in patients with invasive thymoma in which an incomplete resection was performed. Cyclosporine-A and Azothioprine were administered as chemotherapeutic agents in addition to prednisone.

The survival rate was studied using the Kaplan-Meier method. Log-rank test was used to compare survival curves. The statistical significance of the clinical factors was evaluated by the \( \chi^2 \) test, Fischer exact test. \( P \) value of less than 0.05 was considered significant.

**Results**

There was no intra-operative mortality, but 7 patients died postoperatively. Three patients died of tumoral invasion. They had incomplete resection or open biopsy only because resection was impossible due to tumoral invasion of the trachea and the lung. The histopathological evaluation revealed the presence of malign thymoma. Two patients died of respiratory failure after 12-day and 23-day intubation periods respectively. From the patients with myasthenic thymoma two patients died of myasthenic crisis. These patients were in the 2nd stage. One of them also had pure red cell aplasia and died 5 years after the operation.

Comparison of surgical procedures and survival rates revealed a 97.6 % survival rate for 5 years in patients with complete resection and 34.3 % in patients with incomplete resection (Fig. 1). Table 2 demonstrates the relationship between prognosis and the stage of the tumour. Although high survival rates (100%) were achieved in patients with stage 1, survival rates for 2nd and 3rd stages were 92.8% and 80%, respectively. There were no statistically significant differences in the survival rates in function of the histological type in patients undergoing complete resection (\( P > 0.05 \) Kaplan-Meier method).

The effect of MG on the prognosis was evaluated and it was clearly demonstrated that myasthenic symptoms led to the diagnosis in the 1st and 2nd stage in 83% of myasthenic patients versus 50% for non-myasthenic patients (Table I). This difference was significant (\( P < 0.05 \) Fisher Exact Test). The survival rate for myasthenic patients was 94.7% and for non-myasthenic patients 77.7% at 10 years (Fig. 2). The survival rates in patients with myasthenic symptoms were higher than in patients with non-myasthenic symptoms, but there were no statistically significant differences (\( P > 0.05 \)). After complete resection, there were only three recurrences. The distribution of the histopathologic types is shown in Table II.

Sex (\( P > 0.05 \)) and age (\( P > 0.05 \)) did not significantly affect survival.

**Comment**

Thymomas, defined as anterior mediastinal neoplasms, are histologically well-differentiated tumours in more
Actuarial survival curves based on surgical procedure. Comparison of surgical procedures and survival rates for 5 years in patients with complete resection and incomplete resection revealed a higher survival rate for 5 years in patients with complete resection than in patients with incomplete resection ($p < 0.05$).

Actuarial survival curves based on patients’ characteristics. The survival rates in patients with myasthenic symptoms were higher than in patients with non-myasthenic symptoms, but there were no statistically significant differences ($p > 0.05$).

### Table II

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Stage</th>
<th>Histology</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Complete resection</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>100</td>
<td>96.4</td>
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</tbody>
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than 95% of cases and their malignant variant is rare (5). The most important prognostic determinant of these tumours is the gross finding at surgery and the unique clinical association, most notably, with myasthenia gravis and haematological abnormalities (13, 14). In addition, their relatively indolent course and their potential for local recurrence rather than metastasis have been noted in several studies (15). Thymomas are accepted as benign lesions when no microscopic or macroscopic invasions are present, but capsular invasions are regarded as the indications of malignancy and accepted as malign lesions. A third category of thymomas includes a histology of undifferentiated malign epithelial cells. Their prognoses are poor and they are called thymic carcinomas.

Following histological findings, the degree of tumoral invasion to adjacent tissues is defined as the most important factor affecting prognosis. In addition, the association of other auto-immune diseases, techniques of surgical approach, the use of chemotherapy and/or radiotherapy are important prognostic factors. The presence of MG is one of the most important factors affecting prognosis. A number of studies report a relationship between the presence of MG with a worse prognosis (16, 17), while other studies state that patients with MG have a survival advantage (15, 18-21). Some authors conclude that the better prognosis in patients with MG is because of early symptoms. Our study also demonstrates that higher survival rates were achieved in patients with MG because of early diagnosis of myasthenic thymomas.

The frequency of association with MG is different in individual series. Although patients with thymoma and MG may have increased operative mortality due to the possible occurrence of myasthenic crisis, advances in
anaesthesia, respiratory support techniques and medical treatment regimens has recently led to a decrease in perioperative mortality and morbidity. Wilkins and Castleman (8) reported high mortality rates (18/37) caused by myasthenic crisis and high frequency of association with MG (1). In our series, the proportion of patients with MG is high (80.8%) and low mortality rates (2/59) related to myasthenic crisis were achieved. The high survival rates achieved in our series is attributed to a higher proportion of patients with stage II and stage I disease. The association with MG in those particular patients led to earlier detection of the tumour, which is small and can be completely resected. In addition it is shown that recurrence of thymoma is higher in those without than in those with MG (7, 20). As a result, with improved intensive medical care, MG no longer appears to have a deleterious effect on the clinical outcome.

Regarding histologic evaluation, significant high mortality and low survival rates were obtained in malignant thymomas. Maggi and associates (18) demonstrated in their series with 241 patients that the histological type has no influence on prognosis except in the case of malignant thymomas. However, there are also articles reporting lower survival rates in epithelial types.

Since the long-term prognosis is certainly related to the completeness of resection, controversy persists over the optimal operative approach. According to surgical-anatomic studies, thymic tissue is widely distributed in the neck and anterior mediastinum and microscopic foci of thymic tissue might be present in pericapsular mediastinal fat (10, 22). For this reason, complete thymectomy, including the extensive resection of surrounding tissues, necessitates a median sternotomy with wide exploration of both pleural cavities in patients with invasive thymoma to decrease the risk of recurrence. Inadequate removal of thymic and perithymic tissue can be a potential cause of the development of a thymoma. Therefore, transcervical thymectomy described by Cooper (23) should be avoided as well as unilateral thoracotomies. Controversy exists concerning the results of maximal thymectomy and complete thymectomy. Jaretzki et al. (22) defined maximal thymectomy and recommended combined transcervical-transsternal en bloc resection of the thymus and all mediastinal tissues. This approach allows excellent visualization and complete resection of the thymus, including the cervical extensions and perithymic tissue with all the anterior mediastinal lipid tissues and soft tissues from phrenic nerve to phrenic nerve. Some authors propose that tumoral recurrence might be prevented with maximal thymectomy (10, 24). However, in studies on complete thymectomy, no statistical difference was noticed between maximal thymectomy and complete thymectomy (18-20). Nonetheless, in some studies subtotal resection was demonstrated as ensuring better survival in some patients than in patients who underwent a biopsy alone (17, 20).

Although the malignancy of thymoma has been attributed to the invasiveness of the tumour to the surrounding tissues, uncommon recurrence (1.5%) or dissemination has been reported in patients with non-invasive thymomas (20, 25). Controversy exists in these particular cases as to whether radiation therapy (RT) and/or chemotherapy should be performed, since recurrence of non-invasive thymomas after postoperative RT has been shown (18). However, Nakahara and associates (20) have recommended postoperative radiotherapy in all patients with thymoma, since survival rates and remission rates increase after postoperative radiotherapy and because of a propensity for recurrence and malignancy, even in patients with stage I disease. They concluded that regardless of the histologic type, if the tumour is removed completely and postoperative radiotherapy is administered, even in invasive thymoma the prognosis over the long term is comparable with that of non-invasive or minimally invasive thymomas (20). The role of pre-operative RT is currently less certain, although some authors reported good results with radiotherapy alone (12). We believe that successful treatment of a thymoma depends on complete surgical resection of the tumour including co-existing thymic and perithymic tissue. There is no indication for postoperative RT for patients with stage I tumours. We have applied RT for invasive thymoma even if resection was complete, since it improves local control and survival. Because of the well-documented propensity for late recurrence and because recurrence of thymomas has been reported as late as 32 years after the initial operation, patients with thymoma need life-long follow-up (26).

The survival rates in our series were higher than in other reported series. This is because of the presence of MG in a high proportion of our patients, which led to earlier tumour detection. These patients had significantly smaller tumours, which led to complete resection and improved survival outcome.

References


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