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ORIGINAL ARTICLE

The major prognostic factors of thymomas: about a Tunisian study of 100 cases

M. MLIKA[1], M.S. BOUDAYA[2], S. LAABIDI[3], Y. ZAIMI[2], H. SMADHI[2], A. MARGHLI[2], F. EL MEZNI[1], T. KILANI[2]
[1] Department of Pathology, Abderrahman Mami Hospital, [2] Department of Thoracic Surgery, AbderrahmanMami Hospital,
[3] Department of Carcinology, Abderrahman Mami Hospital, Faculté de Médecine. Université Tunis El Manar

Key words

Thymoma • Prognosis • Surgery • Pathology • Masaoka classification

Summary

Aim. Thymomas are characterised by their rarity, histologic variability and peculiar patterns of recurrence. Herein, we present the experience of a single institution and aim to highlight the major prognostic factors of these tumours.
Materials and methods. We present a retrospective study on 100 thymomas diagnosed between 1994 and 2011. Statistical analyses were performed using version 18.0 SPSS. The Kaplan Meier method was used to estimate survival, and survival curves were compared using the Log-Rank test. A $p < 0.05$ was considered statistically significant.
Results. 50 men and 50 women underwent surgical resection for thymoma. Radiologic findings highlighted a diagnosis of thymoma in 51% of cases. The thymomas were classified as stage I in 25 cases, stage II in 47 cases, stage III in 25 cases and stage IV in 3 cases. According to the WHO classification, tumours were classified as type A in 14 cases, type AB in 24 cases, type B1 in 17 cases, type B2 in 20 cases, type B3 in 8 cases, B1/B2 in 8 cases and B2/B3 in 9 cases. The mean survival of patients was 136 months. Age, sex, tumour size, WHO classification and Masaoka stage were evaluated as prognostic factors. Univariate analysis showed that the major prognostic factors were WHO classification ($p = 0.019$) and Masaoka Stage ($p = 0.0001$).
Conclusion. Our results place emphasis on the prognostic value of WHO classification and Masaoka stage in thymomas; in addition, the necessity of improving reproducibility of microscopic classification to avoid discrepancies among prognostic groups is highlighted.

Introduction

The term 'thymoma' has been used to describe a large variety of tumours of the thymus. Today, it is employed only for epithelial tumours, and not for mesenchymal, germ cell, lymphomatous and neuroendocrine tumours. Thymomas are rare and account for less than 1% of all adult cancers. The association of two components defines thymomas: an epithelial one and an immature one composed of immature lymphocytes. The former is tumoural and responsible for the aggressive potential of these lesions so that they are considered malignant even if there are no microscopic features of invasion because of their propensity to recur and metastasise. We report a Tunisian study on 100 thymomas and aim to highlight the key role played by surgical resection and assessment of the main prognostic factors.

Materials and methods

Between 1994 and 2011, 100 patients underwent surgical resection for thymoma at the Department of Thoracic Surgery. All thymomas were diagnosed in the Department of Pathology at the same hospital. Clinical records, radiologic features and follow-up information were retrieved from the Department of Thoracic Surgery, and all slides were reviewed in the Department of Pathology. Staging of tumours was based on Masaoka's classification and histologic classification was based on the World Health Organization classification (WHO) updated in 2004. Mortality was defined as death during surgery, or during the 30 first days after intervention. For the follow-up period, the date of point chosen was 31 December 2012. The patients were considered lost to follow-up if they were not seen after discharge.

Correspondence
Mona Mlika, Department of Pathology. Abderrahman Mami Hospital - Tel. +216 98538862 - Fax: +216 71710780 - E-mail: mlika.zorgati.mona@hotmail.com

Statistical methods

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, IL). A Student's t test was used to compare means. The Kaplan Meier method was used to estimate survival, and survival curves were compared using the Log-Rank test. A p value < 0.05 was considered statistically significant.

Results

Clinical characteristics: 50 men and 50 women were included in the study. The mean age of patients was 51.3 years (range 50 to 59). The delay between the onset of symptoms and surgical resection varied from 1 month to 120 months with a mean of 9 months and a median of 4 months; 47% of tumours were resected within 12 months following the onset of symptoms. Thoracic symptoms including chest pain, cough, expectoration, or dyspnoea were reported in 62% of cases. Myasthenia gravis was reported in 26 patients; it was assessed using an electromyogram in 11 patients (42%) and highlighted the diagnosis in 8 patients showing a block of the neuro-muscular junction. The level of anti-acetylcholine receptors was assessed in 4 patients and was increased in 3 patients reaching 0.2 nmol/l. Prostigmin was used in 2 patients and demonstrated reversibility of symptoms in both. The tumour was discovered incidentally in 12 patients.

Radiologic findings: Chest-x-ray was performed in all patients and showed a mediastinal mass in 89% of cases, tracheal deviation in 13% of cases, diaphragmatic ascension in 5.5% of cases and was normal in 11% of cases.

CT was performed in all patients and showed a mediastinal mass with a mean size of 8.6 cm with extremes varying from 2.5 to 16 cm. Radiologic findings highlighted a diagnosis of thymoma in 51% of cases. In 22% of cases, diagnosis was suspected based on radiologic findings. The latter were challenging in 27 patients and did not allow diagnosis.

CT scan allowed staging of tumours and showed local or regional extension in 13% of cases (Fig. 1). Infiltration of the pleura or pericardium was observed in 6 patients (46%). Extension to the lung was observed in 5 cases (38%) and infiltration of the mediastinal vessels was observed in 2 patients (15%). In one patient, CT showed a adrenal gland infiltration. The 100 thymomas were classified as stage I in 25 cases, stage II in 26 cases, stage IIb in 21 cases, stage III in 25 cases, stage IVa in 2 cases and stage IVb in 1 case.

Microscopic findings: Definitive diagnosis was based on histologic examination in all patients. Diagnosis included a trans-parietal biopsy in 18 patients. The results were concordant with the results on the surgical specimen in 11 cases. In the remaining 7 cases, the results were not concordant because of the lack of sufficient biopsy material. In the other cases, surgical resection was performed and the mean size of the tumour was 8.7 cm (range 2 to 19 cm; median 8.5 cm). According to the WHO classification, thymomas were classified as type A in 14 cases, type AB in 24 cases, type B1 in 17 cases, type B2 in 20 cases, type B3 in 8 cases, B1/B2 in 8 cases and B2/B3 in 9 cases (Fig. 2).

Relationship between Masaoka and WHO classification: Type A thymomas were diagnosed in early stages in 86% of cases (5 stage I, 4 stage IIa, 3 stage IIb); 14% were discovered in stage III and no case with stage IV was seen. Type AB thymomas were mainly non-invasive accounting for 87% of cases (7 stage I, 5 stage IIa, 8 stage IIb), 4 stage III and 1 stage IVa. B1 thymomas were in stage I and II in 70% of cases (7 stage I, 3 stage IIa, 2 stage IIb and 5 stage III). B2 thymomas were classified into stages I or II in 50% of cases (2 stage I, 5 stage IIa, 3 stage IIb), 8 stage III and 2 stage IV. No B3

Fig. 1. CT scan showing a right sided homogeneous and well limited mass corresponding to a typical stage I thymoma.

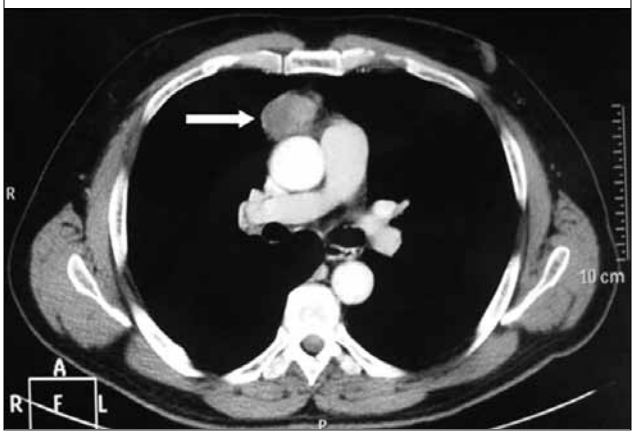
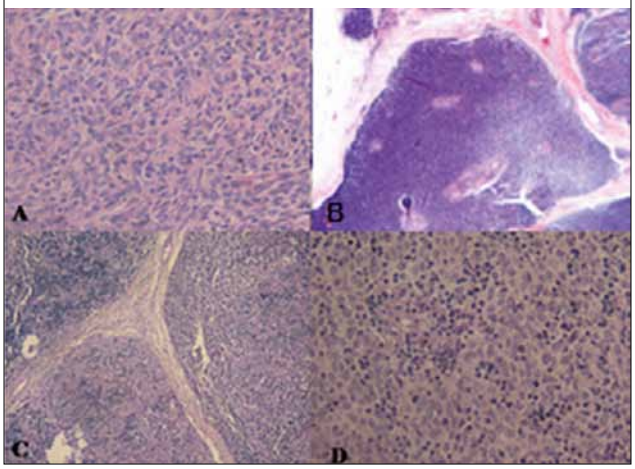


Fig. 2. A. Microscopic findings showing a type A thymoma characterised by spindle cells with rare lymphocytes. B. Microscopic findings of type B1 thymoma characterised by an organoid architecture with the presence of rare epithelial cells admixed with an abundant inflammatory infiltrate. C. Microscopic findings of a B2 thymoma with numerous epithelial cells with vesicular nuclei within some lymphocytes. D. Microscopic findings showing a B3 thymoma with syncytial epithelial cells.



thymoma was classified in stage I. Five cases were classified in stage IIa and 3 cases were classified in stage III.

Treatment modalities: 14 patients received neo-adjuvant chemotherapy based on platinum with etoposide or gemcitabine with a mean of 4 courses (range 2 to 9). These patients presented a decrease of the tumoural volume reaching 50%, thus enabling surgical resection. Radiochemotherapy was performed in 2 patients. Surgical resection was performed in all patients through sternotomy in 69.1%, postero-lateral thoracotomy in 18.5%, video-assisted thoracoscopic surgery (VATS) in 11.2% and mediastinotomy in 1.2% of cases. Surgical resection was performed in stages I, IIa or IIb and 9 stage III thymomas. The surgical procedure consisted in total thymectomy enlarged to the mediastinal fat in 66% of patients and tumourectomy in 33% of patients. Dissection of adjacent structures was performed in 45% of patients excising the pericardium, phrenic nerve, lung and tracheo-cephalic venous trunk. According to histological findings, the surgical resection was classified as R0 in 97% of patients. Adjuvant chemotherapy was used in 16 patients.

Follow-up: 28 patients died, 17 were lost to follow-up and 57 patients are still alive. Five patients presented local recurrence or metastasis during follow-up. Two patients presented local recurrences and were initially classified in stage II of Masaoka's classification. The recurrences appeared after 3 years. Three patients were classified in stage II and presented pulmonary and pleural recurrences. Only one of these patients had an initial tumourectomy. The mean survival of patients was 136 months (95% CI 114-158). The 1-year, 3-year and 5-year survival rates were respectively estimated at 89%, 78% and 67%.

Prognostic factors: Age, sex, tumour size, WHO classification and Masaoka stage were evaluated as prognostic factors; survival curves are shown in Figures 3 and 4.

Fig. 3. A. Survival curves according to age show no significant difference between patients aged > 51 years and < 51 years (p = 0.9). B. Survival curves according to sex show no significant difference between men and women (p = 0.7). C. The survival curves according to the presence or absence of myasthenia gravis show no significant difference (p = 0.53). D. Survival curves according to WHO classification showing a significant difference between types A, B1, AB and B2, B3 thymomas (p = 0.0019).

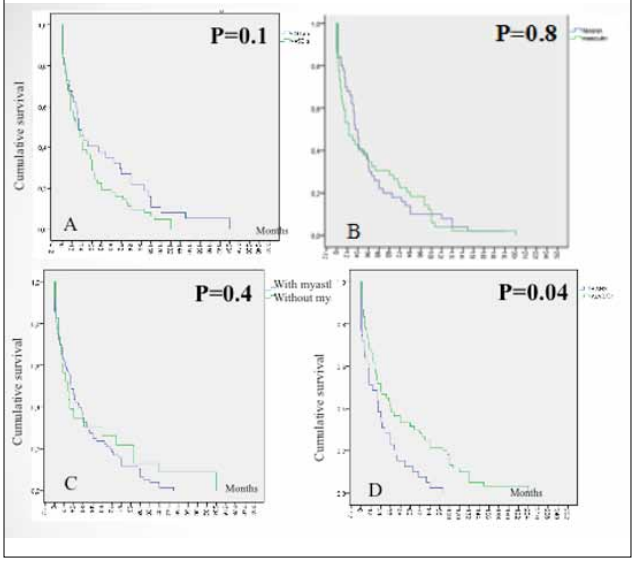
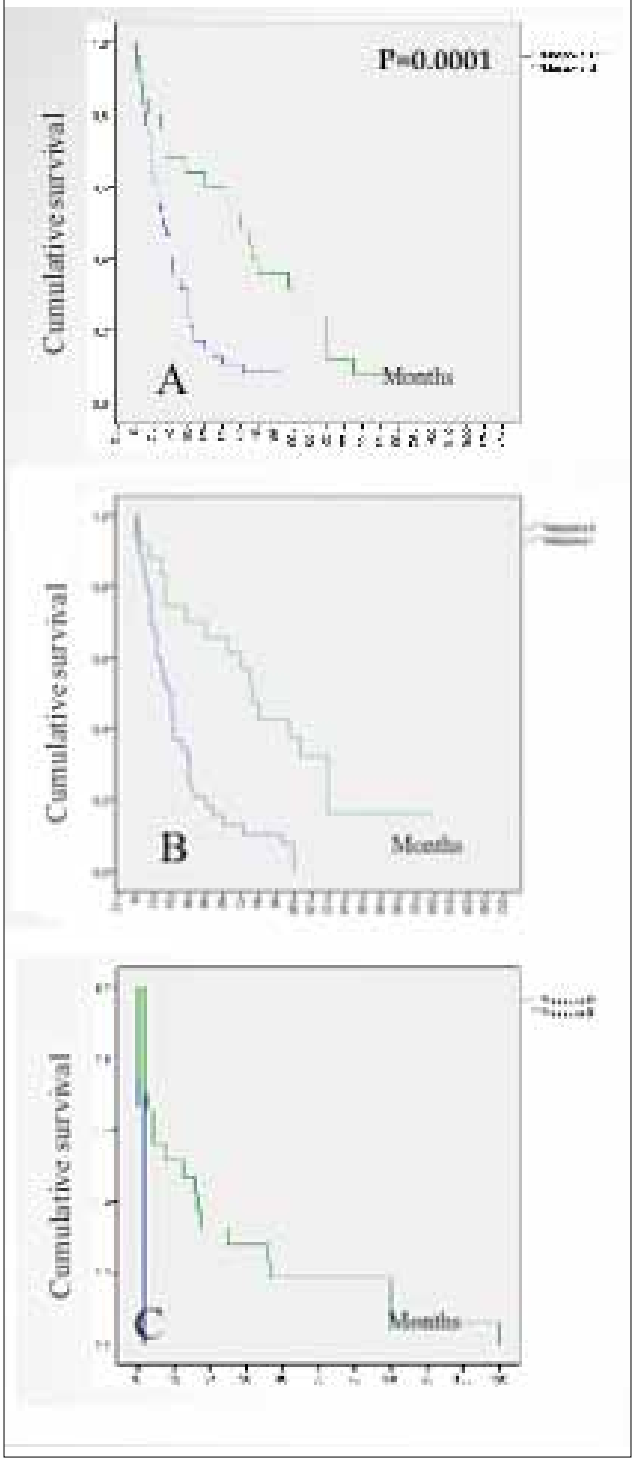


Fig. 4. A. Survival curves according to stage show a significant difference between stages I and II vs. stages III and IV (p = 0.0001). B. Survival curves according to stage show a significant difference between stages I and II (p = 0.001). C. Survival curves according to stage show no significant difference between stages III and IV (p = 0.66).



- **Age:** The mean age of patients was 51 years. There was no statistical difference in survival between patients aged < 51 years and > 51 years (p = 0.9).
- **Sex:** There was no significant statistical difference in survival considering gender (p = 0.7).
- **Myasthenia gravis:** There was no difference in survival between patients with myasthenia compared to those without myasthenia (p = 0.53).
- **Tumour size:** There was no difference between survival according to tumour size (p = 0.81).
- **WHO classification:** There was a significant difference between group A, AB and B1 thymomas and groups B1/B2, B2, B2/B3 and B3 thymomas (p = 0.019). The 1-year, 3-year and 5-year survival rates were 87%, 75% and 72% in the first group and 67%, 58% and 40% in the second group.
- **Masaoka stage:** Better survival was observed in stages I and II (p = 0.0001). The 1-year, 3-year and 5-year survival rates estimated at 86%, 79% and 74% in non-invasive thymomas and 51%, 42% and 33% in invasive thymomas. In the group of non-invasive thymomas, there was a significant difference between stage I and II (p<0.01). The 1-year, 3-year and 5-year survival rates reached 95% in stage I and 81%, 68% and 55%, respectively, in stage II. In invasive thymomas, the survival of patients with stage III tumours was higher than those with stage IV, although this difference did not reach statistical significance (p = 0.66).

Univariate analysis showed that the major prognostic factors were WHO classification and Masaoka Stage.

Discussion

About the present study examined 100 Tunisian patients who underwent surgical resection for thymomas between 1994 and 2011. The mean age of patients was 51 years. In the literature, the mean age of patients is between 40 and 60 years [1 2]. The sex ratio of our patients was 1 in contrast to the literature where a female predominance was seen in the majority of studies [1 2]. The diagnosis of these tumours is challenging because of the lack of specific symptoms. In the literature, approximately one-third of patients are non-symptomatic [1 3], but in only 13% of our patients, and only 9% of patients presented general signs. Myasthenia gravis is observed in 30-50% of patients in the literature [3-5], and in 26% of the present series. Electromyogram plays a key role in diagnosis and helps in diagnosis in 95% of cases [6]. Anti-acetylcholine antibodies are present in 85-90% of patients with myasthenia [7 8]. The course of auto-immune diseases is independent of the evolution of the thymoma [7]. Radiologic findings are mandatory not only to assess the diagnosis, but also to evaluate the extension of disease. Chest-x-ray is performed in most of patients, but it is not always able to localise the tumour. CT plays a key role in both diagnosis and staging of tumours [7]. In specific cases, it shows a thymic homogeneous and lobulated mass. The tumour is homogeneously enhanced unless there is necrosis or haemorrhage. The mean size of the tumour in our study was 8.6 cm, similar to what reported in the literature with a size between 5 and 10 cm. Many radiologic signs may indicate the invasive potential of the tumour. In fact, Marom et al. showed in their study in 99 patients that these signs include a size greater to 7 cm, lobulated boundaries and infiltration of mediastinal fat. In our study, CT showed signs of invasion in 14 patients, while MRI did not seem to play a major role. This is due to the lack of a typical aspect that distinguishes the tumour from muscles and adjacent mediastinal fat [8]. Nevertheless, it seems to be useful in assessing possible cardial or pericardial extension [7]. Positive diagnosis is based on histological findings. Transparietal biopsy and the surgical specimen represent the primary means of diagnosis, and may be CT guided or surgical. Its sensitivity reaches 77% in published studies. In our study, it was performed in 18 patients and had a sensitivity of 61%, and false negative cases were due to the lack of sufficient material. Histological diagnosis is based on the last WHO classification updated in 2004 [10] that recognizes two main categories of thymomas depending on whether neoplastic cells and their nuclei have a spindle/oval or round/polygonal appearance. They are classified into type A and type B thymomas. The former has uniformly bland nuclei, while the latter presents several degrees of nuclear atypia and number of lymphocytes and are classified into three subcategories: B1, B2 and B3 thymomas. Thymomas with a mixture of type A and B1-like (rarely B2-like) features are defined as AB thymomas. A third category of thymic epithelial tumour, namely thymic carcinoma, was also introduced. Rare histotypes including metaplastic, micronodular, sclerosing, microscopic and anaplastic thymoma have also been included. This classification has been shown to be prognostic [11]. In our study, we reported a statistically significant difference in survival between group of A, AB and B1 thymomas and the group of B2, B1/B2, B3 and B2/B3 thymomas. However, similar results have not been previously reported. In fact, a Chinese study of 200 cases observed that types A, AB, B1, B2 and B3 display increasingly poor prognosis [12]. Rieker and colleagues observed that type AB and B1 tumours showed the most favourable outcome [13] whereas, types A and B2 behaved much worse and essentially showed overlapping survival curves. These discrepancies in prognostic groups may be explained by the lack of reproducibility of the WHO classification [13 14]. In fact, in a study of 129 thymic tumours, Zucali et al. reported moderate agreement of the WHO classification highlighting the necessity to improve the accuracy in the allocation of these neoplasms. This lack of reproducibility may be related to the different prognostic groups reported in the literature [15]. Surgical resection represents the mainstay of treatment. Radical thymectomy or enlarged thymectomy are recommended and justified by the multifocal potential of these tumours and their tendency to recur [16]. Surgical procedures may be classified as minimally-invasive by VATS and video-thoracoscopy and invasive

by sternotomy and right postero-lateral thoracotomy. Although the fact that invasive procedures have generally been accepted as the gold standard for resection of thymomas [17], many authors advocate the role of VATS and even robotic-assisted thoracoscopic surgery in almost all Masaoka stage I tumours [18] because they are associated with less operative trauma, shorter hospital stays, preserved pulmonary function and superior cosmetic results [19 20]. In our study, sternotomy was the most commonly used procedure (67%) and was associated with infectious complications in only 4 cases. Minimally invasive procedures are mainly performed in localised tumours with no invasion of adjacent structures. In our study, VATS was performed in 9 patients with stage I tumours in 3 patients, stage II in 5 patients and stage III in 1 patien No complications were observed after minimally invasive procedures. Our results put emphasis on the availability of minimally-invasive techniques even in stage III tumours, although one cases was not indicated for this technique. The major role of radiation therapy is to prevent further recurrences, while the role of chemotherapy is mainly in neo-adjuvant therapy and based on cis-platinum. Postoperative radiation is recommended for incompletely resected stage III tumours [21]. The prognostic factors vary among different studies. Herein, the main prognostic factors were Masaoka staging and WHO classification. In other studies, age, sex, neurologic symptoms and size of the tumour have been reported to be prognostic factors [22-25].

Conclusions

In this study, we present the experience of a single Tunisian institution on 100 surgically resected thymomas. Our results highlight the prognostic value of the Masaoka stage and WHO classification of tumours. Moreover, discrepancies in histologic prognostic groups found in the literature places emphasis on the necessity of improving the reproducibility of the WHO classification.

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