Prognostic factors in thymic epithelial neoplasms

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Abstract

Objectives: The primary thymic epithelial neoplasms (PTENs) are uncommon tumours with a broad spectrum of both biological and morphological features. The aim of this study is to analyse the prognostic factors that influence survival.

Methods: Forty-four patients with a complete follow-up were analysed. Nine patients (20.5%) were asymptomatic, the most common symptoms in the rest being myasthenia gravis and dyspnoea. All the patients underwent surgery, 30 cases (68.2%) receiving total thymectomy and the rest a partial resection or biopsy. Marino–Müller's histological classification showed the mixed type to be the most common (52.3%). Clinical staging was done according to the Masaoka classification, which gave the most common stage as stage III (34.1%).

Results: Twelve patients died during a mean follow-up of 8.2 ± 3.5 years. The accumulated survival rate was 77% at 5 years and 60% at 10 years. Analysis of the survival curves shows significant differences (P < 0.05) when considering surgical technique, clinical staging and histological subtype. The multivariate analysis shows the only parameters with prognostic significance in PTENs to be clinical staging and histological type (P < 0.001).

Conclusions: The most important prognostic factors in PTENs are Masaoka’s clinical staging and Marino–Müller’s histological subtype.

Keywords: Thymic epithelial neoplasms; Thymoma; Epidermoid carcinoma; Lympho-epithelial carcinoma; Surgery; Radiotherapy

1. Introduction

Primary thymic epithelial neoplasms (PTENs) are uncommon tumours with a broad spectrum of both biological and morphological features. This rareness and heterogeneity have favoured the appearance of numerous subclassifications for these tumours without there being to date a consensus on their nomenclature [1]. One characteristic of these neoplasms is the high frequency with which they are associated with auto-immune diseases known as 'parathyroid syndromes', including myasthenia gravis (MG), cytopenia and hypogammaglobulinaemia [1–2].

The evolution shown by these patients varies greatly, and the factors involved in this evolution are controversial [1–2]. Various clinical and histological classifications and staging systems have been devised, each seeking the best prognostic correlation of these neoplasms. The usefulness of these classifications has not been confirmed universally, and some authors even claim that the subdivision of thymomas from a histological point of view is insubstantial for prognosis [2].

The aim of this study is to identify the clinical, therapeutic and histological variables that have prognostic value in PTENs.

2. Patients and methods

Between January 1980 and December 1999, 51 patients underwent surgery in our department with a definitive diagnosis of thymic epithelial neoplasia. Seven (14%) were rejected due to a lack of follow-up data; the study was conducted on the remaining 44 (86%).

The mean age of the patients was 57 ± 14 years (range 15–77), and 70% were females (31 cases). The preoperative study included complete clinical history, simple chest radiology and computed axial tomography (CT).

Nine patients (21%) were asymptomatic and included initially in the study due to the casual finding of a mediastinal mass in a chest radiography. The most common symptoms in the remaining cases were MG in 19 cases (43%), dyspnoea in 11 (25%), thoracic pain in seven (16%), coughing and dysphagia in three (6.8%) and superior vena cava syndrome in one (2.3%). The severity of the 19 patients with MG was assessed with Osseman’s classification [3] (Table 1). In no case did we find association with any other immunological disease.
All the patients were followed-up in the thoracic surgery outpatients’ department; the MG cases were seen also in the neurology outpatients’ department.

The variables analysed were age, sex, presence of MG, surgical technique employed, Marino–Müller histological type and Masaoka staging.

The Kaplan–Meier method (survival curves) and Cox regression model (multivariate analysis) were used for statistical analysis. Statistically significant differences were considered when $P < 0.05$.

3. Results

All 44 patients underwent surgery, 29 (66%) receiving a total vertical sternotomy, 13 (30%) a postero-lateral thoracotomy, and two (4.5%) a mediastinoscopy. The surgical technique was total thymectomy in 30 cases (68%), partial tumour resection (23%) in ten and biopsy only in four patients (9%).

No mortality was recorded intraoperatively, but one patient died on the third post-operative day due to cardiac insufficiency secondary to a ventricular fibrillation. Post-operative morbidity was 39% (17 patients), 11 cases corresponding to pneumonia or atelectasis (25%), three cases to surgical wound infection (6.8%), two cases to unilateral paralysis of the phrenic nerve (4.5%) and one patient to congestive cardiac insufficiency (2.3%).

Adjuvant treatment was given to 21 patients (48%), corresponding to Masaoka grades III and IV, and consisted of radiotherapy. This therapy was applied in various sessions, at a dose total of between 100 and 50 Gy, depending on the spread of the tumour. Chemotherapy was administered to only one patient (lympho-epithelial carcinoma).

Follow-up averaged 8.2 ± 3.5 years. Twelve patients (27%) died from evolution of the PTEN, deaths related to

### Table 1
Osserman’s clinical classification [3] for MG

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>No. of cases</th>
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<tbody>
<tr>
<td>I</td>
<td>Ocular involvement</td>
<td>3</td>
</tr>
<tr>
<td>IIa</td>
<td>Generalised involvement</td>
<td>2</td>
</tr>
<tr>
<td>IIb</td>
<td>Generalised and bulbar involvement</td>
<td>13</td>
</tr>
<tr>
<td>III</td>
<td>Acute respiratory involvement</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>Late respiratory involvement</td>
<td>0</td>
</tr>
</tbody>
</table>

Simple chest radiology disclosed a localised mediastinal mass in 41 patients (93%) and two patients with associated pleural effusion (4.5%). CT revealed localised tumours at the thymus in all cases, which were of a solid nature in 19 cases (43%) and of a solid-cystic nature in 25 (57%). It also indicated local spread and in 20 patients (45%) revealed the involvement of neighbouring structures (pleura, pericardium, etc.).

Diagnostic conformation was by fine-needle aspiration (FNA) biopsy in seven cases (16%), mediastinoscopy and biopsy in six (14%) and open surgery in the rest.

For the histological study, all the sections were fixed and stained with haematoxylin–eosin and reviewed by the same pathologist. The Marino–Müller classification [4] was used for histological typing (Table 2), the mixed type being the most common (23 cases; 52%).

Clinical staging was done using Masaoka’s classification [11] (Table 3), stage III being the most common (15 cases; 34%).

The surgical technique is classified into three categories: (1) total thymectomy (total resection of tumour); (2) partial tumour resection (the resection is realised in patients with affectation of pericardium and large vessels, and the maximum tumoral tissue is resected with minimal residual tumour burden around vital structures affected); and (3) biopsy (simple biopsy and partial debulking).

### Table 2
Comparison of the main histological classifications of thymic epithelial tumours (our cases are indicated using the Marino–Müller classification)

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>Benign thymoma (encapsulated)</td>
<td>Thymoma: well-differentiated PTENs</td>
<td>A</td>
<td>Extreme low-grade</td>
<td>Medullary thymoma</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic predomiance</td>
<td>AB</td>
<td>B1</td>
<td>Low-grade</td>
<td>Mixed thymoma</td>
<td>23</td>
</tr>
<tr>
<td>Mixed</td>
<td>Malignant thymoma-Invasive I</td>
<td>Atypical thymoma: moderately differentiated PTENs</td>
<td></td>
<td></td>
<td>Organoid thymoma or cortical predomance</td>
<td>1</td>
</tr>
<tr>
<td>predomiance</td>
<td>No cytological evidence of atypia</td>
<td>B2</td>
<td>B</td>
<td></td>
<td>Cortical thymoma</td>
<td>11</td>
</tr>
<tr>
<td>Spindle cell</td>
<td>Malignant thymoma-Invasive II</td>
<td>Thymic carcinoma: poorly differentiated PTENs</td>
<td>B3</td>
<td>Intermediate-grade</td>
<td>Well-differentiated thymic carcinoma</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Predominance</td>
<td></td>
<td></td>
<td></td>
<td>Epidermoid carcinoma</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Malignant thymoma-Invasive II</td>
<td></td>
<td></td>
<td></td>
<td>Non-keratinised epidermoid carcinoma</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cytological evidence of atypia</td>
<td></td>
<td></td>
<td></td>
<td>Lympho-epithelial-like carcinoma</td>
<td>1</td>
</tr>
</tbody>
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Table 3
PTEN classification systems: Masaoka, GETT and Suster and Moran (distribution of our cases is shown using Masaoka’s system)

<table>
<thead>
<tr>
<th>Stages</th>
<th>Description</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masaoka’s staging [11]</td>
<td>Stage I: Totally encapsulated tumour, without invasion of the capsule</td>
<td>10</td>
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<tr>
<td></td>
<td>Stage II: 1. Macroscopic invasion of surrounding fatty tissue, mediastinal pleura or both</td>
<td>13</td>
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<tr>
<td></td>
<td>Stage III: Macroscopic invasion of neighbouring organs such as pericardium, large vessels or lung</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Stage IV: IVa: pleural or pericardial spread</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>IVb: haematogenous or lymphatic metastases</td>
<td></td>
</tr>
<tr>
<td>Gett staging (Groupe d’Etudes des Tumeurs Thymiques) [12]</td>
<td>Stage I: IA: totally resected encapsulated tumour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IB: totally resected, macroscopically encapsulated tumour but with suspicion of mediastinal adhesion and potential capsular invasion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage II: Totally resected invasive tumour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage III: IIIA: subtotally resected invasive tumour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIIB: biopsied invasive tumour</td>
<td></td>
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<tr>
<td></td>
<td>Stage IV: IVA: supraclavicular metastasis or distant pleural implants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVB: distant metastases</td>
<td></td>
</tr>
<tr>
<td>Suster and Moran staging [8]</td>
<td>Stage I: Encapsulated tumours confined to the thymus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage II: Locally invasive tumours or tumours with pleural or pericardial implants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stage III: Tumours with haematogenous or lymphatic metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIIa: intrathoracic metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IIIb: extrathoracic metastases</td>
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</tr>
</tbody>
</table>

Fig. 1. Survival rate of thymic epithelial neoplasms according to time of evolution.
the disease itself. The accumulated survival rate was 77% at 5 years (30 patients at risk at 5 years), 69% at 7 years (25 patients at risk at 7 years) and 60% at 10 years (18 patients at risk at 10 years) Fig. 1. There are currently two patients, with a follow-up of 9 and 7 years, respectively, who present with local recurrence; the rest of the living patients are disease-free.

Analysis of the survival curves shows no significant differences when individually considering age, sex or presence of MG. Conversely, surgical technique ($P = 0.0091$), clinical staging ($P = 0.0001$) and histological subtype according to Marino–Müller’s classification ($P = 0.0003$) do show statistically significant differences Figs. 2–4. The multivariate analysis showed that the only parameters with prognostic significance in thymic epithelial neoplasms are Masaoka’s clinical staging and Marino–Müller’s histological type.

4. Discussion

PTENs are singular tumours characterised by the fact that they comprise forms with different biological behaviours. As for clinical manifestation, approximately one-third of the patients are asymptomatic, another third present with local symptoms and the rest start with paraneoplastic syndromes, especially MG [13]. There is currently controversy over the effect of MG on the survival of patients with thymoma. Our results, unlike those of other authors, indicate that MG does not influence prognosis; it may even confer a survival advantage, but this may be due to the preponderance of early stage tumours discovered incidentally in myasthenic patients [14]. We did not find any clinical variable with prognostic influence.

Simple chest radiography is the first imaging technique that should be performed, which usually reveals a mass at the superior mediastinum. The problem with such a finding is making a correct differential diagnosis, as here, besides the thymus, we find the large vessels, lymph nodes and lymphatic vessels, fatty tissue and the thyroid. The most common neoplastic lesions here are thymoma, lymphoma, thyroid and parathyroid tumours and germ cell neoplasms. Furthermore, several benign diseases should be borne in mind when making a differential diagnosis, such as thymic hyperplasia, retrosternal goitre, cysts (pericardial, thymic, bronchial and oesophageal), lymphadenitis and vascular aneurisms. Less frequently they correspond to metastatic tumours. CT is one of the diagnostic tests that best defines the characteristics of the tumours and their relationship to neighbouring structures [13]. The nuclear magnetic reso-

![Fig. 2. Survival rate of thymic epithelial neoplasms according to type of surgery ($P = 0.0091$).](https://academic.oup.com/ejcts/article-abstract/21/2/307/412495)
NMR is now being used to assess the thymus, and initial results have proved better than with CT, although more studies are needed to confirm these results [15]. Nuclear medicine imaging techniques do not usually provide more information than the above techniques [13]. As it is difficult with imaging techniques to make a differential diagnosis between thymoma, lymphoma and germ cell tumours, FNA is usually done [13]. In the event of thymomas of a lymphoid predominance we should consider the possibility of lymphoma, whereas with those of an epithelial predominance we should consider differentiation with a papillary thyroid carcinoma [16]. The size of the biopsy is important, bearing in mind the large number of diagnostic errors with FNA in these patients.

Immunohistochemical studies have recently been acknowledged as useful for differential diagnosis [17]. Immunoreactivity for cytokeratins is a feature that differentiates thymomas from lymphomas. Also, simultaneous focal positivity of T and B markers (CD45-RO, CD20) rules out monoclonal proliferation and therefore a diagnosis of lymphoma [17]. There are also markers that are highly indicative of thymic carcinoma, such as CK 18, epithelial membrane antigen (EMA) or CD5, although their absence cannot exclude the diagnosis. As for prognostic implication, detection of p53 or bcl2 antigen may be related to poorer survival rates in the series published [18], although more studies are needed to confirm these initial results.

Traditionally, PTENs have been classified histologically into four categories based on the lymphocyte/epithelial cell index and on the type of epithelial cells [5–6]. In 1978, Levine and Rosai [7] carried out a clinicopathological classification to obtain a better prognostic evaluation, differentiating benign thymomas from category I malignant (without cytological atypias) and category II malignant (with cytological atypias) thymomas. In 1985, a histological classification was proposed by Marino and Müller-Hermelink [4] based principally on the morphological similarity of neoplastic epithelial cells to the normal subtypes of thymic epithelial cells, which is still the most commonly used classification. In their last attempt to provide a consensus on these neoplasms, the World Health Organisation proposed a coded nomenclature using letters (A–C) and numbers [1–3] depending on prognostic severity [9]. All the same, there are still new reclassifications, notably Yoneda’s [10], which classifies them into four grades of increasing malignancy, each with a prognostic value. Table 2 shows a correlation between the six currently most used classifications [4–10]; we also show the distribution of our cases using Marino–Müller’s classifi-

Fig. 3. Survival rate of thymic epithelial neoplasms according to Marino–Müller’s histological type ($P = 0.0003$).
cation. The prognostic value of the different histological classifications of these neoplasms is possibly the most controversial point. The main reason for this alteration in classification is the current impossibility of predicting clearly the biological behaviour of these lesions from the morphological findings [19]. PTENs should conceptually be considered a continuous and progressive spectrum of lesions without a clear dividing line between them. The Marino–Müller classification shows a very good prognostic prediction in our series.

Just as there are numerous classifications there are also various clinical staging systems for these tumours. The three most important are those of Masaoka [11], the GETT [12] and Suster–Moran [8]. However, the most used and accepted system is still Masaoka’s, which shows clear prognostic implications as confirmed by our results [20]. Although this clinical staging system is useful, it is not when the thymic epithelial tumour corresponds to the spectrum of a thymic carcinoma [19], something which in our series cannot be evaluated in isolation since most of the tumours are thymomas.

Surgery is the first-line treatment in patients with thymic pathology [21], although the technique varies according to the stage of the disease. In 1996, Regnard et al. [22] presented a series of 307 patients with thymoma and analysed the prognostic factors and long-term results after resection, and they concluded that the sole significant prognostic factor was completeness of resection. In our series, the type of surgery Fig. 2 is an initial prognostic factor, however, in multivariate analysis it is not significant ($P > 0.05$). This result in the statistical analysis by surgery has been well associated with tumour clinical stage. In this way, the patients with partial thymectomy or biopsy have a tumour with a clinical stage III or IV, and so in the multivariate analysis the stage acquires the statistical force of the surgical resection.

In stage I patients (encapsulated and non-invasive), surgical removal leads to a cure in more than 90% of cases at 5 years [13]; in our series it was 100%. In this stage I, only surgery cures 100% of patients, so we think that no other adjuvant treatment is indicated in this group. In patients with invasive tumours (stages II and III) we recommend resection, even if it is palliative, and the use of post-surgical adjuvant treatments. Our patients with stage II were not administered adjuvant treatment, neither radiotherapy nor chemotherapy, however, this stage has mortality, so we recommend radiotherapy in this group. Radiotherapy is the treatment of choice for stage IV and is used as an adjuvant in stages II and III to reduce local recurrences [13,23,24].

Chemotherapy is less used in thymic tumours, although
doxorubicin and cisplatin seem to be effective [13,25] in advanced stages and carcinomas, although results are scarce and disparate. Approximately, one-third of patients with invasive thymoma and all stage IV disease will be potential candidates for systemic therapy. Numerous small series and case reports have demonstrated varying results with single agent and combination chemotherapy in patients with advanced disease [13,25,26]. In 1998, Shin et al. [27] presented a series of 13 patients with unresectable malignant thymoma who underwent a multidisciplinary aggressive treatment (induction chemotherapy, surgical resection and post-operative radio-chemotherapy); 73% of the patients were disease-free at 7 years. These data are encouraging, although they need to be confirmed by others with a greater number of cases.

After analysing our data, we find that the main prognostic factors determining the survival rate of these patients are Masaoka’s clinical staging and histological subtype [1,24]. However, as these neoplasms represent a single spectrum of progressive malignancy as the stage increases it is difficult to tell one histological subtype or clinical stage from the one immediately next to it, which is why new classifications continue to appear, both histological and clinical, in an attempt to delimit them as best as possible.

References