Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa)∗

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Abstract

Objective: We sought to evaluate factors influencing long-term survival of patients with locally advanced thymoma/thymic carcinoma (Masaoka stages III and IVa) treated by immediate surgery or induction therapy plus surgery. Methods: From January 1991 to April 2007, we surgically treated 61 patients with locally advanced thymoma/thymic carcinoma (Masaoka stages III and IVa). Staging included total body computed tomography (CT) scan in all patients, and chest magnetic resonance imaging (MRI) in 27 selected patients. All patients had histological confirmation before surgery. Thirty-one patients (group A) underwent induction chemotherapy followed by surgery. Thirty patients (group B) underwent immediate surgery. Thirty-four patients (group A: 13; group B: 17) received postoperative radiation therapy. Results: No intraoperative mortality was reported. World Health Organization (WHO) histological classification included 19 AB, four B1, seven B2 and 13 B3 thymomas and 18 thymic carcinomas. Thirty-four patients were Masaoka stage III (group A: 18; group B: 16) and 27 patients were stage IVa (group A: 13; group B: 14). After a median follow-up of 77 months, six patients of group A and seven patients of group B died of disease. The overall 10-year survival rate was 50.6%. The 10-year survival rate was 57.9% in group A and 38.1% in group B (p = 0.02). Multivariate analysis showed complete resection (p = 0.02), Masaoka stage (III vs IVa) (p = 0.02), induction chemotherapy (group A vs group B) (p = 0.003) and histological WHO subtype (AB vs B1, B2 and B3) (p = 0.01) to be statistically significant independent predictors of survival. Sex, age and adjuvant radiation therapy showed no statistically significant difference. Conclusions: Complete resection, Masaoka stage, induction chemotherapy and histological WHO classification showed to be independent predictors of survival in locally advanced thymoma/thymic carcinoma.

Keywords: Thymoma; Thymic carcinoma; Induction therapy; Surgery

1. Introduction

Thymomas are neoplasms arising from the epithelial cells of the thymus. Due to the low incidence of this neoplasm and to the morphologic and clinical heterogeneity, there is still much debate regarding the histological classification, the predictors of malignancy and the optimal pre- and post-operative treatment [1].

The Masaoka staging system [2], which takes into account the anatomic extent of the involvement, is the most widely used clinical classification system. Histological typing was established for the first time in 1994 by the World Health Organization (WHO) [3] and reviewed in 2004 [4]. According to this classification, thymomas are classified as Type A or B according to their epithelial cell morphology. Type B thymomas are further subdivided into B1 to B3 according to the atypia of epithelial cells and the extent of lymphocyte infiltration. The co-existence of both Types A and B was designated Type AB. The revision made in 2004 eliminated the term Type C thymoma and defined thymic carcinoma as an independent entity. In the present series, neuroendocrine tumours are not included among thymic carcinoma [5].

All thymomas should be considered potentially malignant and total thymectomy (rather than thymomectomy) should be considered the surgical procedure of choice [6,7]. There is no debate regarding the need for surgery for Masaoka stages I and II [8]; in locally advanced thymomas (Masaoka stages III and IVa) radical resection is not always feasible when there is widespread tumour growth to the entire thorax; thus, some authors have put forward a case for induction therapy [9–11].

We sought to evaluate factors influencing the long-term survival of patients with locally advanced thymoma/thymic carcinoma (Masaoka stages III and IVa) treated by immediate surgery or induction therapy plus surgery.
2. Materials and methods

From January 1991 to April 2007, we surgically treated 61 patients with locally advanced thymoma/thymic carcinoma (Masaoka stages III and IVa). Staging included total body computed tomography (CT) scan in all patients, and chest magnetic resonance imaging (MRI) in 27 selected patients. Since 2005 most of the patients (11 patients) underwent 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG-PET-CT) scan. All patients had histological confirmation before surgery by means of anterior mediastinotomy.

Thirty-one patients (group A) underwent induction chemotherapy followed by surgery. Thirty patients (group B) underwent immediate surgery. No patient of our series had superior vena cava syndrome. Patient characteristics are shown in Table 1. Written informed consent was obtained from all patients.

All patients were selected on the basis of the following criteria of eligibility: (1) clinical and radiological stage of tumour as locally advanced thymoma (corresponding to stages III—IVa of Masaoka staging system); (2) stage IVa thymoma/thymic carcinoma with only isolated pleural or pericardial metastases; (3) Karnofsky performance scale index between 70% and 100%; (4) a leucocyte count greater than 4000 cells mm$^{-3}$, a platelet count greater than 100 000 cells mm$^{-3}$, haemoglobin count greater than 10 g dl$^{-1}$ and normal renal and hepatic functions. Patients with recurrent thymoma and/or previous chemotherapy or radiation therapy for any other malignancies were not being included in this study.

All 61 patients had preoperative history and physical examination, complete blood count, liver function tests (ALT, ast, alp, bili t/d and gamma-glutamyl transpeptidase (GGT)), renal function tests (blood urea nitrogen (BUN) and cr), electrocardiogram (echocardiogram was done when indicated), pulmonary function tests and blood gas determination, routine chest radiographic examination; and conventional (or spiral) chest, abdomen and brain CT scans were preoperatively accomplished. In 27 patients it was necessary to resort to MRI to assess the extent of mediastinal involvement. Four patients underwent 18-FDG-PET scan. Patients in whom a radical resection was not thought to be possible from a surgical point of view underwent induction chemotherapy according to the following regimen: cyclophosphamide (700 mg m$^{-2}$ on day 1; continuous infusion of cisplatin (40 mg m$^{-2}$ day$^{-1}$) on days 1–3, doxorubicin (40 mg m$^{-2}$ day$^{-1}$) on days 1–3 and prednisone (100 mg m$^{-2}$). This cycle was repeated three times at 3–4-week intervals. Response to neo-adjuvant treatments was assessed in accordance with the WHO criteria. Complete remission (CR) was referred to complete disappearance of all clinical and radiological evidence of disease; partial response (PR) referred to 50% or greater reduction in the sum of the product of the largest diameter and its perpendicular of all measurable lesions and progressive disease referred to increase of at least 25% in the size of measurable lesions or the development of new lesions. Out of 41 patients who underwent neo-adjuvant therapy, 31 patients (75.6%) of group A, with at least a minimal response to induction therapy, underwent surgery (24 males, seven females, mean age: 45.7 ± 12.5 years; range: 14—72 years). Thirty patients (group B; 20 males, 10 females, mean age 48.1 ± 12.7 years; range: 22—77 years) underwent immediate surgery. Patients with incomplete resection as well as those whose histopathological findings resulted in non-microscopic radical resection and/or tumour-free margin <1 cm, patients with stage IVa and patients deemed at risk of local recurrence according to multidisciplinary meeting conclusions, underwent adjuvant mediastinal radiation therapy (50 Gy) delivered in 5 weeks with five fractions per week to the residual tumour areas (Fig. 1). In stage IVa patients, thoracic radiation fields included the site of pleural involvement as well.

3. Surgery

All 61 patients underwent surgery through midline sternotomy; a total thymectomy was performed in addition to en bloc removal of involved pericardium, pleura, lung,
phrenic nerve, innominate vein or superior vena cava when the tumour was invasive. If radical resection was deemed infeasible, the surgeon clipped the area of close margins or residual disease to assist the radiation oncologist in treatment planning. Radicality of resection was defined as macroscopical removal of whole tumour with tumour-free margin >1 cm.

4. Statistics

All patients assigned in this retrospective study of prospectively collected data were followed up to date and were included in the analysis. Duration of survival or time to recurrence was calculated from the date of entry in the protocol until the date of death or the last follow-up. Statistical differences in patients’ data were calculated by the chi-square test and the unpaired t-test, respectively, in categorical or numerical variables. Survival was calculated by the Kaplan—Meier method. Log-rank test was used to perform univariate analysis. Multivariate analysis was performed by the Cox proportional hazard model. The covariables analysed were age (older or younger than 40 years), sex, induction chemotherapy, radical resection, adjuvant radiotherapy, Masaoka stage and 2004 WHO histological system. Nevertheless, only the statistically significant variables were considered in the final Cox-regression analysis. Results were considered significant if the p value was less than 0.05. All calculations were performed with the NCSS (Number Cruncher Statistical System, Kaysville, UT, USA) 2004 statistical software.

5. Results

There were no significant differences between the two groups in age, sex, histological and staging distribution (Table 1). Preoperative histological examination was in line with the pathological examination of the surgical specimen. All 41 patients completed the treatment regimen with no major complications and were restaged; 31 patients (75.6%) with at least a minimal response to induction therapy are shown in Table 2. No 30-day (operative) mortality was reported. The mean hospital stay was 8 days (range: 5—11 days). Nine patients had major non-lethal complications (one pulmonary embolism, one postoperative bleeding, two pulmonary infections and five wound infections), which resolved with conservative treatment. One patient experienced adult respiratory distress syndrome after surgical resection and required prolonged hospitalisation. Beyond radical thymectomy, some patients needed right upper lobectomy (three patients), wedge lung resections (nine patients), pericardial resections (15 patients), pleural resections (eight patients), wedge superior vena cava resection (three patients), resection of left brachiocephalic vein (six patients) and resection of phrenic nerve (21 patients), among others.

Table 2
Response to induction chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>Complete regression</th>
<th>Decrease at least &gt;50%</th>
<th>Decrease &lt;50%</th>
<th>Total</th>
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<tr>
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<td>≤40</td>
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<td>6</td>
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<td>8</td>
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<tr>
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<tr>
<td>III</td>
<td>1</td>
<td>11</td>
<td>6</td>
<td>18</td>
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<td>IVa</td>
<td>1</td>
<td>5</td>
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<td>13</td>
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<td></td>
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<tr>
<td>AB</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>8</td>
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<tr>
<td>B1</td>
<td>—</td>
<td>2</td>
<td>1</td>
<td>3</td>
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<tr>
<td>B2</td>
<td>—</td>
<td>1</td>
<td>3</td>
<td>4</td>
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<tr>
<td>B3</td>
<td>—</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td></td>
<td>—</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2</td>
<td>16</td>
<td>13</td>
<td>31</td>
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Thirty-four patients, including nine with R1 resection (five patients because of a microscopic residual disease and four because of a tumour-free margin less than 1 cm), underwent postoperative radiotherapy. Six recurrences occurred. Reoperations (four cases) were performed through re-do sternotomy.

5.1. Survival analysis

As of December 2008, the median follow-up time for all patients was 77 months (range: 10—138 months). Six patients of group A and seven patients of group B died of disease. The overall 10-year survival rate was 50.6%. The univariate analysis showed the 10-year survival rate, respectively, of 57.9% in group A and 38.1% in group B (p = 0.03); 59.8% in stage III and 28.2% in stage IVA (p = 0.02); 48.8% in R0 resection and 36.5% in R1 resection (p = 0.04). According to histological classification, the 10-year overall survival for subtypes AB, B1, B2, B3 and thymic carcinoma was 63.8%, 100%, 0%, 85.7% and 54.1%, respectively (p = 0.3). The small number of patients in groups B1 and B2 did not allow any statistical analysis to be made. Multivariate analysis showed the following variables to be statistically significant independent predictors of survival: complete resection (p = 0.02), Masaoka stage (stage III vs stage IV; p = 0.02), induction chemotherapy (group A vs group B; p = 0.003) and histological WHO subtype AB (AB vs B1 plus B2 plus B3; p = 0.01). Patients receiving radiotherapy had a 42.5% 10-year survival rate versus 61.6% in patients who did not (p = 0.7). Sex, age and adjuvant radiation therapy showed no statistically significant difference and they did not feature in the final analysis (Table 3).

6. Discussion

It is generally agreed that margin-free surgical resection alone is the best treatment for Masaoka stage I thymoma [12]. In completely resected Masaoka stage II thymoma, some authors currently favour postoperative radiotherapy, though the most recent studies have not reported benefit from the use of radiotherapy [12]. In locally advanced thymomas (Masaoka stages III and IVA), the percentage of non-radical operations is higher and the overall 5-year survival is not very satisfactory [13]. The need for induction therapy has been postulated as early as 1985 by Giaccone et al. [14] and later on by Macchiarini et al. [9] in 1991 in the light of the evidence that the major cause of initial treatment failure in thymoma is local recurrence. As in other solid tumours, the goals of induction therapy are the following: (1) downstage the primary tumour and thereby facilitate and enhance its surgical clearance; (2) obtain early and increased systemic control; (3) prevent dissemination of local tumour cells during the operation; (4) reduce the emergence of drug-resistant clones; and (5) assess the activity and toxicity of a drug or drug combination [9]. Nevertheless, to date few prospective reports on this topic have been published [9,10,15]. Due to the small number of patients enrolled in such studies, and the lack of randomised studies, the results are not conclusive and, consequently, the decision making for immediate surgery or induction therapy plus surgery in patients with invasive thymoma/thymic carcinoma is still a matter of clinical judgement and individual bias.

18-FDG-PET examination reflects glucose metabolism in a tumour and is believed to serve as an indicator of tumour malignancy. 18-FDG-PET accumulation in thymic epithelial tumours significantly correlated with the WHO classification. These findings suggest that 18-FDG-PET scan may be helpful in assessing the grade of malignancy in thymic epithelial tumours and in differential diagnosis according to the WHO classification. In our series 11 patients only underwent 18-FDG-PET scan, but we recommend 18-FDG-PET scan in all patients with a suspicious thymic tumour [16].

All 61 patients enrolled in the present study were clinically staged as invasive thymomas/thymic carcinoma according to Masaoka classification, which represents the best staging criteria. Patients underwent histological confirmation through anterior mediastinotomy [7,17]. Following histological confirmation, patients judged to be operable underwent surgery only (group B) and patients judged to be inoperable were treated with induction therapy (group A). No patient underwent adjuvant chemotherapy. The response to induction chemotherapy in our series was as high as 75.6% (31 out of 41 treated patients): probably the underpowered sample size gives an explanation of such an unexpected result. A bias of the present study is the lack of an independent control, there being the same group of surgeons and oncologists in charge either for the preliminary evaluation or for the post-induction restaging.

In our series, multivariate analysis showed complete resection (p = 0.02), Masaoka stage III (p = 0.02), induction chemotherapy (p = 0.003) and histological WHO subtype AB (p = 0.01) to be statistically significant independent predictors of survival. Sex, age and adjuvant radiation therapy showed no statistically significant difference and they did not feature in the final Cox-regression analysis. A benefit in survival with induction chemotherapy plus postoperative radiation was also reported in stage III thymoma by Venuta et al. [15] (prospective but not a randomised study of 45 thymic tumours) and Macchiarini et al. [9] (prospective but not randomised study of seven patients). Rea et al. [10] conducted a multimodality trial (chemotherapy with or without postoperative radiation) in 16 patients with stages III and IVA thymoma: in five patients no residual disease was found in the surgical specimen. Kim et al. [11] from the M.D. Anderson Cancer Center reported a phase II study of a multidisciplinary treatment with induction chemotherapy, followed by surgery, radiotherapy and consolidation chemotherapy for 22 patients with stages III—IV thymoma: the overall 5-year survival rate was 95% at 5 years. Lucchi et al. [18] presented a comparison between different multimodality treatments in stages III and IVA thymomas comparing 36 patients undergoing neo-adjuvant versus 20 undergoing

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<tr>
<th>Parameters</th>
<th>HR; 95%CI</th>
<th>p value</th>
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<tbody>
<tr>
<td>Complete resection</td>
<td>0.18; 0.04—0.78</td>
<td>0.02</td>
</tr>
<tr>
<td>Masaoka stage III</td>
<td>0.22; 0.05—0.81</td>
<td>0.02</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>0.09; 0.01—0.46</td>
<td>0.003</td>
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<tr>
<td>Histological WHO (AB)</td>
<td>0.11; 0.02—0.66</td>
<td>0.01</td>
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surgery only. They showed neo-adjuvant treatment to be effective both at down-staging and increasing resectability and also to be a statistically significant prognostic factor in stage III tumours (p < 0.05). In 18 patients in stage IVa, Wright [19] from the Memorial Sloan Kettering Cancer Center, New York, presented the results of an aggressive treatment including preoperative chemotherapy, radical surgery (with four concomitant extrapleural pneumonectomies) and postoperative hemithoracic radiation. They achieved an impressive 78% 5-year survival and a 65% 10-year survival. Huang et al. [20] from the Massachusetts General Hospital treated 10 patients with thymic tumours staged III and IVa with induction chemoradiotherapy, surgery and adjuvant chemotherapy. They achieved a 69% 5-year survival with 2 R1 resections.

Similar to Regnard et al. [21] and Lardinois et al. [22], we found no survival benefit related to the use of adjuvant radiotherapy (10-year survival rate: 42.5% vs 61.6% for patients receiving radiotherapy and those who did not), although it has been reported as a potentially useful modality of treatment for locally advanced thymoma [23]. It should be stressed that, in the present study, radiotherapy was mainly employed in patients with R1 resections and in patients with stage IVa, a group of patients with advanced disease. This could be one of the reasons for postoperative radiotherapy not emerging as an independent prognostic factor.

In our series, 27 patients (13 in group A and 14 in group B) had Masaoka stage IA neoplasms. All cases had isolated pleural or pericardial nodules, being multiple disseminations to be excluded from surgery. In all patients the approach was resection of visible nodules. We do not believe extrapleural pneumonectomy (EPP) to be a feasible operation for advanced thymoma even if there are some reports from the literature favouring this approach in young and healthy patients [19,24].

In conclusion, complete resection, Masaoka stage, induction chemoradiotherapy and histological WHO classification showed to be independent predictors of survival in locally advanced thymoma/thymic carcinoma. Preoperative staging of a thymoma is a difficult task and such problem represents the bias of the present study. Furthermore, because of the rarity of the neoplasm, multicentric prospective randomised trials with larger number of patients are needed for conclusive assessment of predictors of survival in locally invasive thymomas/thymic carcinoma.

References