Does adjuvant radiation therapy improve disease-free survival in completely resected Masaoka stage II thymoma?§,§§

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Objective: To determine whether or not patients with completely resected Masaoka stage II thymoma benefit from postoperative radiotherapy (RT). Methods: We retrospectively review the case records and compared the long-term outcomes of patients affected by Masaoka stage II thymoma treated by resection alone with same stage thymoma patients submitted to resection and RT. Surgical specimens were reviewed to confirm pathological stage, negative resection margins and histological subtype. Results: Between 1988 and 2000, we performed 197 resections for thymoma; 58 patients resulted to be affected by completely resected tumours with microscopic transcapsular invasion (stage IIA, n = 25) or macroscopic invasion into the surrounding fatty tissue with or without adhesion to the mediastinal pleura (stage IIb, n = 33). Thirty-two patients underwent only complete surgical resection (14 stage IIA and 18 stage IIb); 26 patients underwent complete resection and subsequent mediastinal RT (11 stage IIA and 15 stage IIb). RT dosages were 45—54 grays (Gy), in 25—30 fractions. Histological subtypes were similarly represented in both groups. Median follow-up was 91 months (range 9—170). Five intrathoracic recurrences occurred: three radiated patients (2 stage IIb — 1 AB and 1 B2 thymoma; 1 stage IIA B1 thymoma) and two not-radiated patients (1 stage IIA AB thymoma and 1 stage IIb B1 thymoma). Disease-free survival rate at 5- and 10-year were 94% and 87%, respectively. Log-rank test showed no difference in Kaplan—Meier survival curves (p = 0.432) between radiated and not-radiated patients. Conclusions: These data support the concept that radical surgical resection alone should be considered a sufficient treatment for stage II thymoma.

1. Introduction

Thymoma is an epithelial tumour arising from the thymus gland, which is frequently encapsulated. Because of its sporadic occurrence, indolent natural history and high mortality due to unrelated causes, thymoma is a difficult condition to study. Even today, despite advances in operative management, radiotherapy and chemotherapy during the past three decades, the 5-year overall survival rate for thymoma is approximately 60%. Recently, many papers have confirmed Masaoka staging, World Health Organisation (WHO) histological classification and completeness of surgical resection factors influencing prognosis, even if the last one remains the most important one and so is considered the cornerstone of thymoma therapy [1—4].

Whereas surgery alone is considered curative for stage I thymoma, and results in 5-year and 10-year overall survival rates of over 100% and 100%, respectively [3], current therapeutic indication for stage II thymoma are still controversial. Controversies are dependent from the concept that a transcapsular invasion could not be completely managed by surgical removal. During the past decades, following this consideration, adjuvant radiation therapy was advocated in hope to reduce the incidence of local relapse. The criteria for administering adjuvant radiation to patients with stage II thymoma remain controversial too. Current indications range from postoperative radiation for all thymoma patients [5,6], to postoperative radiation for only patients with large tumours (>5 cm in great diameter) or with radiographic evidence of
invasiveness [7]. Because of the absence of a large consensus, in the current practice radiation therapy is recommended for the majority of stage II thymoma patients. It may be that patients in whom radiotherapy is not indicated will receive it, subjecting them to the morbidity related to this therapeutic modality. The aim of this study was to investigate whether or not the utilisation of adjuvant radiation therapy confers an advantage by reducing the frequency of local relapse or by influencing the long-term survival in patients undergoing operation for stage II thymoma.

2. Material and methods

The surgical logs, clinical records and pathology files at the University of Torino and at the University ‘A. Avogadro’ of Novara were retrospectively reviewed between 1988 and 2000.

2.1. Patient population and evaluation methods

Between January 1988 and December 2000, 197 patients underwent thymoma resection at the University of Torino and of Eastern Piedmont. Hospital and office medical records were reviewed to extract information including demographic and clinical characteristics (age, gender), clinical presentation (myasthenia gravis, other autoimmune related diseases, local symptoms and incidental findings), preoperative studies (CT-scan or MRI of the chest), surgical approach (median sternotomy, thoracotomy, transcervical thymectomy), post-operative course and complication, pathologic report. Patients’ follow-up was obtained by review of hospital and office records, telephone interviews with patients or physicians.

2.2. Clinical and pathologic revision

Operative notes were reviewed to determine if there was or not an intraoperative suspicion of local invasion, gross tumour extension and adhesion to adjacent structures and completeness of surgical resection. Pathology charts were obtained for each patient. Slides of 58 consecutive patients believed to be affected by stage II thymoma were available and reviewed by a single pathologist (DN). There was a complete agreement between the pathological records and the revision on margin status, histological subtype and degree of transcapsular or adjacent structures invasion. Thymomas were retrospectively classified into the five WHO histological classification subtype [8]. Surgical notes and pathology were reviewed by a single surgeon (GM) and pathologist (DN), and patients were than staged using the modified Masaoka classification system [4].

2.3. Adjuvant radiation therapy

The decision to refer patients for adjuvant radiation therapy was based on the surgeon’s subjective assessment of the risk of recurrence considering the great diameter of the neoplasm (>4 cm), previous open biopsies, close resection margins (stripping of the phrenic nerve). Treatment regimens for patients undergoing radiotherapy (RT) were reviewed for total doses, fractionation and short- and long-term complication.

2.4. Follow-up

Complete follow-up was obtained for 56 patients and 2 were lost at long-term follow-up (1 submitted to surgery alone and 1 to surgery and RT). Patients were followed-up with computed tomographic scan every 6 months until death or lost at follow-up. Survival was calculated from the date of operation. Treatment-related deaths (operative or post-operative, or radiation related) were considered as death from thymoma. Time to relapse (disease-free survival), time until death from thymoma (disease-specific survival) and time until death from other causes (overall survival) were registered for all patients. Disease-specific survival was censored if patients died from non-thymoma-related causes. In this series of patients, the mean follow-up was 91 months and ranged from 9 to 171. Patients at risk at 5- and 10-year were 43 and 16, respectively.

2.5. Statistical analyses

Variables such as histological subtype, Masaoka stage, treatment and morbidity were analysed with respect to relapse and survival. The Student’s t-test (no categorical data) and the Fisher’s exact test (categorical data) were used to compare the mean value of the variables of the groups studied as appropriate. A p-value less than 0.05 was considered significant. The Kaplan—Meier method was used to estimate the time to relapse or death. Log-rank test was used to compare survival between groups.

3. Results

Between January 1988 and December 2000, 197 patients underwent surgical resection for thymoma. Fifty-eight patients believed to be affected by stage II thymoma were operated for thymoma resection as surgery alone (18) and surgery and RT (40). Median age was 39 years (range 18–69).

Table 1 Characteristics of 58 stage II thymoma patients undergoing surgery or surgery and radiation therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgery (n = 32)</th>
<th>Surgery and RT (n = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>17</td>
<td>13</td>
<td>0.849</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years) ± SD</td>
<td>52.11 ± 10.94</td>
<td>50.2 ± 15.58</td>
<td>0.582</td>
</tr>
<tr>
<td>Compliant presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local symptoms</td>
<td>5</td>
<td>3</td>
<td>0.955</td>
</tr>
<tr>
<td>MG</td>
<td>12</td>
<td>11</td>
<td>0.729</td>
</tr>
<tr>
<td>OAI</td>
<td>2</td>
<td>1</td>
<td>0.796</td>
</tr>
<tr>
<td>None</td>
<td>16</td>
<td>9</td>
<td>0.518</td>
</tr>
<tr>
<td>Masaoka stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>14</td>
<td>11</td>
<td>0.908</td>
</tr>
<tr>
<td>IIB</td>
<td>18</td>
<td>15</td>
<td>0.850</td>
</tr>
<tr>
<td>Pleural adhesions</td>
<td>8</td>
<td>11</td>
<td>0.265</td>
</tr>
<tr>
<td>Mean tumour diameter (mm) ± SD</td>
<td>39.4 ± 18.1</td>
<td>42.3 ± 16.8</td>
<td>0.534</td>
</tr>
</tbody>
</table>

RT, radiation therapy; MG, myasthenia gravis; OAI, other autoimmune disease; SD, standard deviation.
patients were surgically and pathologically staged as Masaoka stage II. Clinical characteristics are shown in Table 1. Tumours were classified by using the WHO histological classification system. Twenty-five of 58 (43.1%) patients demonstrated a transcapsular microscopic invasion (stage IIA) and 33 of 58 (56.9%) a pleural or pericardial adhesion or fatty tissue invasion (stage IIB).

Fifty patients (86.2%) underwent an enlarged total thymectomy (surgical resection of the thymoma ‘en bloc’ with the entire thymus gland, mediastinal fatty tissue and pericardium or mediastinal pleura in case of tumour adhesions to these structures) through a total median sternotomy. In eight cases (all intrathymic thymomas of great diameter less than 2 cm), thymectomy with thymomectomy and resection of the mediastinal fatty tissue was carried out through a cervicotomy associated with splitting of the sternal manubrium. There was no postoperative mortality. Postoperative morbidity included one atrial fibrillation in day 3 treated with medical therapy. No one among myasthenic patients had acute recrudescence or myasthenic crisis during the postoperative period.

Thirty-two patients received only surgical complete resection of their disease. Twenty-six patients were submitted to postoperative radiation therapy. Of the 25 stage IIA and 33 stage IIB patients, similar number received surgery with and without RT (11/25—44% and 15/33—45.4%, respectively). Histological subtypes of radiated and non-radiated patients are illustrated in Table 2.

Radiotherapy was administered with a 6 MV linear accelerator. The treatment volume at our Hospital for postoperative RT was the whole mediastinal field with or without boost including the primary tumour bed, with the upper margin at the thoracic inlet and the lower margin at the diaphragmatic crurae. Patients were treated with anteroposterior opposed fields with the spinal cord dose limited to 45 grays (Gy) in all patients. Two anterior, wedged portals or off-cord, oblique, opposed portals were used to boost the anterior mediastinum to higher doses. The total dose to the primary tumour was 45—54 Gy (median 50 Gy). Daily fraction sizes of 1.8—2.0 Gy 5 days per week were used the most. No other adjuvant therapies were used during the initial treatment.

The median follow-up time after surgery or surgery and RT was 91 months (range 9—170); one patients of each group was lost at follow up. Three patients out of 26 (11.5%) submitted to postoperative RT had treatment-related complications: two radiation pneumonias requiring steroids and one pericarditis with good recovery after conservative treatment. Four patients died of other causes: no one had signs of thymoma recurrence at time of death. Disease-free survival rate at 5- and 10-year were 94% and 87%, respectively. Among 31 patients treated with surgery alone, 2 (6.45%) had tumour recurrence. These patients, affected by stage IIA AB thymoma and stage IIB B1 thymoma manifested a mediastinal recurrence and drop metastases to the diaphragm and parietal pleura after 8.4 and 4.3 years, respectively. Both were submitted to surgical resection of their disease and subsequent chemotherapy; the first is alive and disease free after 2.5 years and the second died for unrelated causes 3.4 years after the re-operation. Among 25 patients treated with surgery and RT, 3 (12%) suffered from tumour relapse. One patient affected by stage IIA B1 thymoma had mediastinal relapse 6.8 years after surgery: he was submitted to re-operation and adjuvant chemotherapy; he is still alive with not operable recurrent disease 4.5 years after the second step therapy. Two patients affected by stage IIB AB and B2 thymoma experienced pleural recurrence after 4.7 and 1.7 years: both were submitted to re-operation and adjuvant chemotherapy, the first died for other causes after 4.2 years and the second died of tumour relapse after 3.6 years.

In particular, all pleural recurrences occurred in stage IIB thymoma with pleural adhesions (1/8, 12.5% not radiated and 2/11, 18.2% radiated patients, respectively). There was no statistical difference ($p = 0.432$, log-rank test) between stage II thymoma patients undergoing surgery alone ($n = 31$) and those undergoing surgery and radiation therapy ($n = 25$). Patients at-risk at 5-years follow-up (surgery alone: 23, surgery and radiation: 20). Patients at-risk at 10-years follow-up (surgery alone: 9, surgery and radiation: 8).

4. Discussion

It is well accepted that factors influencing prognosis in thymoma are completeness of the surgical resection, Masaoka stage and WHO histological classification, in particular the former seems to be the most important one. The prognostic significance of these factors has been largely demonstrated in some recent series in the international literature [1—3,9—11]. Conversely, the utility of adjuvant radiation therapy in invasive stage II thymoma is still controversial. Although completely
resected, about 10% stage II thymoma manifest local or pleural recurrence even after many years [1–3]. This observation, associated to the demonstrated relative high sensibility of thymoma to radiation therapy sustains the favour of many thoracic surgeons to postoperative radiation therapy for even completely resected stage II thymoma patients. Some recommendations advocate radiation therapy for all patients with stage II thymoma, but the consistency of such recommendation is not clear [12]. Whereas the true indication of radiation therapy for stage II thymomas is still controversial, late local morbidity associated to mediastinal and lung irradiation are well-known (cardiac morbidity such as valve fibrosis, pericarditis with pericardial effusions, increased frequency of coronary artery disease; radiation pneumonia and chronic pulmonary fibrosis; oesophageal strictures, dismotility and malignancies; mediastinal fibrous and haematopoietic malignancies) [13–16]. The evaluation of the real impact of RT on long-term survival of completed resected stage II thymoma patients is difficult by the relative indolent natural history of these tumours: great accuracy must be taken in follow-up data elaboration because a large number of patients die of unrelated causes. The use of overall survival data in the past literature have falsely lowered long-term survival of thymoma patients; because of the long natural history of the disease, physicians should refer to disease-free prognosis and disease-related death such as in this series.

During the past decades, some authors have advocated postoperative radiation therapy [17–19], whereas few studies have argued against it [7,20]. Curran et al. [18] reported about 19 patients undergoing complete resection for stage II thymoma. One patient received postoperative RT without long-term recurrence. Six patients out of 18 submitted to surgery only experienced recurrence: the authors stated that resection without RT is not acceptable. Statistical analysis was not feasible because of the presence of only one patient in the harm of surgery and RT. Nakahara et al. [6] in 1988 reported 29% (2 of 7) recurrence rate for patients with stage II thymoma submitted to surgery only, whereas 8% (2 of 25) patients have disease relapse after surgery and RT. Ogawa et al. [19] presented 61 Masaoka stage II patients undergoing postoperative mediastinal RT. Six thymomas recurred despite RT (two mediastinal and four pleural). They concluded that mediastinal RT probably prevents local recurrence, but cannot avoid pleural relapse. Blumberg et al. [7] reported about 30 patients submitted to surgery and RT (n = 17) or to surgery alone (n = 13): the recurrence and survival rates were similar for the two groups.

In some cases, the association of RT to surgery for the treatment of stage II thymomas seems to negatively affect long-term survival. Quintanilla-Martinez et al. [21] in 1994 presented 32 stage II patients submitted to surgery. Seven of them received postoperative RT. Recurrence rates were 28% and 8% for patients undergoing surgery and RT and surgery alone, respectively (difference was not significant). In a previous study with a different focus, one of the authors referred about the lower recurrent rate in a cohort of patients submitted to surgery compared with patients submitted to surgery and RT (the difference was significant p = 0.02); the effect of postoperative RT seemed potentially harmful [20]. The great part of the mentioned literature does not perform disease-free or disease-specific survival analysis for stage II thymoma, but demonstrated only the absence of impact on survival in all thymoma patients.

More recently, two papers focused on the value of postoperative RT in stage II completely resected thymomas. Mangi et al. [22] updated their 27-year experience and presented 49 completely resected stage II patients. Thirty-five patients were submitted to surgery alone, whereas 14 patients underwent surgery and RT. The addition of adjuvant RT did not affect long-term disease control. Disease-specific survival for stage II thymoma patients was 100% with and without RT (p = 0.87).

Singhal et al. [23] reported about two groups of patients with stage II thymomas submitted to radical surgery (n = 20) and to radical surgery and RT (n = 20). Recurrence rate was 5% in the group of surgery and RT and null in the group of surgery alone; no differences in long-term disease-free survival were recorded (p = 0.72).

Our experience adds to those recent reports suggesting that complete resection alone seems to be a sufficient management for stage II thymoma. Appropriateness of adjuvant therapy with reference to the histological type of the tumour was not easily investigated because of the restricted number of cases for each subtype of thymoma. Stage IIA disease manifested mediastinal whereas stage IIB thymoma manifested primarily pleural recurrence. This fact agree with previous reports that stated the most common failure of thymoma treatment is pleural recurrences and it is well known that mediastinal radiation does not prevent pleural recurrences. Conversely, the great part of patients with recurrent thymoma during an accurate follow-up may benefit of second surgery and adjuvant chemotherapy with good control of their disease for a relative long period. In the future, it should be more indicative to consider adjuvant chemotherapy in stage IIB thymoma, particularly regarding to those histological subtypes demonstrated to be more aggressive.

Concluding, thymoma is confirmed to be a tumour with an indolent natural history and low recurrence rate even if locally invasive as in stage II of Masaoka classification. Mediastinal irradiation does not seem to affect local control in stage IIA and cannot prevent pleural recurrences, which are the more frequent relapsing mode of stage IIB resected thymoma. When recurrent during an accurate follow-up, because of its moderately aggressive behaviour, thymoma frequently can benefit of second step surgery and adjuvant therapies with good long-term response.

References


Appendix A. Conference discussion

Dr A. End (Vienna, Austria): Just to clarify, was this a single or a multi-institutional study?

Dr Rena: This was a two-institutional study.

Dr. M. Dusmet (London, United Kingdom): You have just two quick comments. First of all, I’d like to invite you to please, please, please stop presenting this paper to surgeons. We’re convinced. Present your paper to the oncologists so that we can convince our oncology colleagues to stop irradiating these patients, because I find it impossible to convince our radiation oncologists that, at best, they are doing no harm to these patients, and I think that you’ve demonstrated that even that is probably not the case. So please try to convince our radiation oncologists instead of surgeons, because they are the ones that need convincing, not us. And perhaps, Paul, you could use your influence with the EORTC to set up a randomised trial so that we can finally have the kind of evidence that oncologists cannot refuse so that we can finally stop irradiating completely resected thymoma patients.

Dr M. Zielinski (Zakopane, Poland): Did you find any correlation between the recurrence and the histological type of thymoma according to WHO or the Muller–Hermelink classification?

Dr Rena: The question is absolutely important, but there are five subtypes distributed in a small series and it’s not very easy to study a correlation between histological subtypes and the recurrences. The only thing I can say is that we have recurrences in type A, B1 and B2.

Dr P. Van Schil (Antwerp, Belgium): Would you comment on the type of incision used. Was it the same in all patients with thymoma and could it influence the results?

Dr Rena: We used total median sternotomy in 50 patients and 8 cervicotomy and upper partial sternotomy. In these 8 cases, upper partial sternotomy was used because the thymoma was very small on the preoperative CT scan of the chest.

Dr Van Schil: Was your rate of recurrence influenced by the type of incision?

Dr Rena: We have not investigated whether there is a pattern, but, if I remember, only one patient had recurrence in this population, so about 12%.

Dr T. Stokes (Szeged, Hungary): I think the two groups are not comparable. You indicated adjuvant radiotherapy if the tumour was greater than 5 cm and the resection margins were very close. I think the radicality of operation is not similar in the two groups.

Dr. Rena: Radiation therapy was administered on the basis of a subjective assessment of risk of recurrence. Yes, this is not a prospective randomised trial. The only message that I would give is that thymoma is a tumour with an intermediate behaviour, and so probably sometimes with strict follow-up, detection of early recurrence may benefit for surgery of second or third steps.