Surgical treatment of stage III thymic tumors: a multi-institutional review from four Italian centers

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Abstract

Objective: Radical surgery is the cornerstone of treatment for thymic tumors, but a complete surgical resection in stage III is not always achievable; and recurrence of disease is not rare. We reviewed the results of four centers with large experience in multimodality treatment of stage III thymic tumors. Methods: Between 1980 and 2009, 249 patients (137 males: 112 females; median age 50 years) with stage III thymic tumors underwent surgery. Myasthenia gravis (MG) was present in 110 (44.2%) patients. A total of 94 (37.7%) patients received induction chemotherapy and 205 (82.7%) had adjuvant treatments. Results: Thirty-day mortality was 0.8%. A total of 203 (81.6%) had R0, 26 (10.4%) R1 and 20 (8%) R2 resection. World Health Organization (WHO) histotype was: A in 2.4%, AB in 15.3%, B1 in 16.5%, B2 in 31.3%, B3 in 22.1%, and thymic carcinoma in 12.4%. The R0 rate was lower in patients who received induction chemotherapy (p = 0.04), in B1—B2-thymic carcinoma histotypes (p = 0.05), and in patients without MG (p = 0.04). Overall 10-year survival rate was 64%; tumor-related and disease-free survival were 76% and 74%, respectively. At univariate analysis, R2 resection (p < 0.0001), recurrence of disease (p < 0.0001), absence of MG (p = 0.0009), thymic carcinoma (p = 0.002), age more than 50 years (p = 0.01), and vascular invasion (p < 0.0001) were predictors of poor survival. At multivariate analysis, type of resection (p < 0.0001), vascular involvement (p = 0.007), and recurrent disease (p < 0.0001) were independent predictors of prognosis. During follow-up, 43 (21.2%) patients developed recurrence. Patients with recurrence, who underwent redo surgery (n = 24), showed a similar survival to patients without recurrence. Conclusions: Multimodality treatment of stage III thymic tumors achieved good survival. Radical surgery, even at recurrence, seems to be the most important prognostic factor.

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1. Introduction

Thymomas represent the most common neoplasms of the anterior mediastinum; however, they are relatively rare accounting for approximately 0.2—1.5% of all malignancies [1]. Surgery is still considered the ‘gold standard’ in the treatment of early stages thymomas where a radical resection is always achievable. In Masaoka stage III tumors defined by the macroscopic invasion of neighboring structures (i.e., pericardium, great vessels, and lung), complete macroscopical resection is not always feasible; moreover, despite a radical surgical resection, local or distant relapses are commonly observed [2,3]. No common agreement exists yet on which is the best therapeutic strategy to adopt for stage III thymomas; but the high chemoradiosensitivity [4] of these tumors led most physicians, who face this disease, to use a multimodality strategy with various combinations of chemotherapy, surgery, and radiotherapy, with improved results compared with historical series [5,6]. In particular, the use of induction chemotherapy (IC) has been advocated in cases of tumors judged unresectable at preoperative work-up with the aim to reduce the mass and the surrounding infiltration and then potentially increase the resection rate and reduce the incidence of systemic relapses [7—9].

In this study, we retrospectively collected the series of stage III thymic tumors from four Italian institutions with well-known experience in treating thymic diseases. The aim was to evaluate long-term results and factors predicting survival and recurrence after multimodality treatment of thymic tumors.
2. Materials and methods

From 1980 to 2009, 249 patients with locally advanced thymic tumors (Masaoka stage III) underwent surgical resection at four Italian thoracic surgery divisions (University Hospital of Padova, University Hospital of Pisa, Catholic University of Rome, and Carlo Forlanini Hospital of Rome). Preoperative characteristics are reported in Table 1. Preoperative work-up included medical history and physical examination, complete biochemical profile, bronchoscopy, total body computed tomography (CT) scan in all patients, and chest magnetic resonance imaging (MRI) in selected patients with suspicion of vascular or chest-wall invasion. Since 1998, positron emission tomography (PET) scan (in 36 patients) and/or somatostatin receptor scintigraphy (Octreoscan, in 50 patients) have also been used for staging and follow-up. In those patients who were Octreoscan positive, a therapy with Octreotide LAR was started in cases of not operable recurrence.

The diagnosis of thymic tumor was reviewed and confirmed by pathologists according to the 2004 revision of the World Health Organization (WHO) classification [10]. Ninety-four (37.7%) out of 249 patients underwent IC. The main reason for adopting IC was the presence of a tumor that, at preoperative work-up, was not considered completely resectable due to the extensive invasion of the surrounding organs. Since 1989, the University Hospital of Pisa adopted the policy to treat with IC all patients (n = 46) with clinicoradiological diagnosis of stage III thymic tumors in the context of a prospective study. The other 155 (62.3%) patients underwent surgery directly. Three different chemotherapy regimens were adopted: 49 patients received the PEV scheme (cisplatin 75 mg m⁻² on day 1, etoposide 100 mg m⁻² on day 1, and etoposide 120 mg m⁻² on days 1, 3, and 5; three cycles repeated every 3 weeks); 27 patients received the ADOC scheme (cisplatin 50 mg m⁻² and doxorubicin 40 mg m⁻² on day 1, vincristine 0.6 mg m⁻² on day 3, and cyclophosphamide 700 mg m⁻² on day 4; three cycles repeated every 3 weeks); and 18 patients received the PAC scheme (cyclophosphamide 700 mg m⁻² on day 1; cisplatin 40 mg m⁻² on days 1–3, doxorubicin 40 mg m⁻² on days 1–3, and prednisone 100 mg m⁻²; three courses repeated every 3 weeks).

Response to chemotherapy was assessed following the WHO criteria: complete remission was considered as the complete disappearance of all tumor mass detectable by clinical and radiological means; partial remission was defined as 50% or greater reduction in the sum of the product of the largest diameter and its perpendicular of all measurable lesions; stable disease was defined as a regression of less than 50% of the mass with no new lesions appearing; and progressive disease was considered an increase of at least 25% in the size of measurable lesions or the development of new lesions. Surgical resection was reserved for patients with complete or partial remission or stable disease evaluated with CT scan after the third cycle of chemotherapy. A complete surgical resection (R0) was defined as a macroscopically radical resection and disease-free resection margins at histological evaluation, when feasible. R1 resection was considered a microscopic residual tumor evidenced at histological evaluation on section margins or a minimal macroscopic residual disease at the level of vital structures that the surgeon was unable to resect (e.g., residual tumor on great vessels such as the aorta) or did not resect for functional reasons (e.g., phrenic nerves). R2 resection was defined as a debulking with residual macroscopic disease of more than 10% but less than 50% of the original mass. Postoperative radiotherapy to the mediastinal or residual tumor areas was delivered at doses of 45 Gy for complete resection or 60 Gy for incomplete resection.

2.1. Statistical analysis

The relationships between categorical variables were evaluated by means of the chi-square test. Survival analysis was performed by the Kaplan–Meier method and was calculated from the date of surgery to the date of death or to the last follow-up (February 2010). Disease-free survival was determined in only those patients, who had undergone complete macroscopic resection, and was calculated from the date of surgery to the date of the first radiographic study demonstrating recurrent disease or the most recent study demonstrating absence of disease. The statistical difference between survival curves was determined using the log-rank test. Multivariate analysis by Cox proportional hazards model was used to investigate the relative importance of different prognostic factors. A p value less than 0.05 was considered statistically significant.

3. Results

IC was administered to 94 patients with the following histotypes: two (2.1%) type A, 16 (17%) type AB, 16 (17%) type B1, 24 (25.5%) type B2, 19 (20.2%) type B3, and 17 (18.7%) thymic carcinoma. Chemotherapy was well tolerated with no episodes of major toxicity. Six (6.4%) patients had a complete
clinico-pathological) disease remission, while 59 (62.8%) had a partial remission; in the other 29 (30.8%) cases, the disease was judged stable. A significantly higher rate of complete/partial remission was observed for histotypes A—AB—B1 in comparison with B2—B3-thymic carcinoma (82.3% vs 61.7%; \( p = 0.04 \)). No significant differences were observed in the response rate and R0 resection on the basis of the different chemotherapeutic schemes adopted. Surgical access for thymectomy was median sternotomy in 224 (89.9%) patients, sternotomy and thoracotomy in nine (3.6%), and thoracotomy in 16 (6.5%). Thymectomy was extended to surrounding structures as reported in Table 2. Perioperative mortality occurred in one (0.8%) patient. Macroscopically complete surgical resection (R0) was performed in 203 (81.6%) patients, R1 resection in 26 (10.4%), and R2 resection in 20 (8%). In R1 resection, a small residual disease was left at the level of the great vessels (\( n = 20 \), mainly the aorta), and/or the lung (\( n = 10 \)), and/or the phrenic nerve (\( n = 4 \)). The rate of complete macroscopic resection was significantly higher in patients, who underwent surgery directly in comparison with those who were treated primarily with IC (85.8% vs 74.5%; \( p = 0.04 \)); in patients with A—AB—B1 histotypes in comparison with those with B2—B3-thymic carcinoma (88.2% vs 78%; \( p = 0.05 \)); in patients with myasthenia gravis (MG) (87.3% vs 76.9%; \( p = 0.04 \)); and in patients with lung, pericardial, or phrenic nerve involvement in comparison with vascular invasion (83.1%, 89.7%, 92.6%, and 38.3%, respectively; \( p < 0.0001 \)).

Postoperatively, 205 (82.7%) patients received adjuvant treatments: 173 (69.8%) had radiotherapy alone, 24 (9.7%) chemoradiotherapy, and eight (3.2%) chemotherapy alone. Among 44 patients who did not receive adjuvant treatment, in 26 cases (most with only pericardial involvement) this was a policy of a single center (Carlo Forlanini Hospital of Rome), in 12 cases there was a contraindication (one post-pneumonectomy fistula, two respiratory failures in MG patients after phrenic nerve resection, two previous radiation treatments for breast cancer, four MG patients with exacerbation after surgery, and three poor performance status), and in six cases patients refused adjuvant treatment.

After a median follow-up of 60 months (range 2—350 months), 75 (30.1%) patients had died (28 without evidence of disease) and 174 (69.9%) were alive (21 with evidence of disease). Overall 5- and 10-year survival rates were 82% and 64%, respectively (Fig. 1). The 10-year tumor-related survival rate was 76%. Results of univariate analysis are reported in Table 3: R0—R1 resection versus R2 (Fig. 2), absence of...
recurrence of disease, MG, histology other than thymic carcinoma, age less than 50 years, and pericardial invasion were predictors of better survival. Vascular invasion predicted a worse survival both for the overall population (Fig. 3) and for the R0 population (10-year survival 46% vs 74%; \( p = 0.04 \)); IC was associated with lower survival when considering all patients, but this difference disappeared when the survival analysis was done only on R0 resections (10-year survival 62% for IC vs 71%; \( p = 0.95 \)). At multivariate analysis, radicality of resection (\( p < 0.0001 \)), vascular infiltration (\( p = 0.007 \)), and recurrence of disease (\( p < 0.0001 \)) were found as independent predictors of prognosis.

Out of 203 R0 patients, 43 (21.2%) recurred with a median time to relapse of 46 months (range 4—340 months). Relapses were intrathoracic in 27 (13.3%) cases, extrathoracic in 13 (6.4%), and both intra- and extrathoracic in three (1.5%) patients. The recurrence rate was significantly higher for histologic types B2—B3-thymic carcinoma in comparison with types A—AB—B1 (31.3% and 4%, respectively; \( p < 0.0001 \)). No difference in recurrence rate was found on the basis of the type of infiltration (28.6% for vascular invasion, 23.1% for lung invasion, and 22.6% for pericardial invasion); nevertheless, patients with vessels' invasion had a tendency to relapse distantly (66.6%), while intrathoracic metastases were most commonly seen in cases of lung (68%) and pericardial (76.2%) invasion (Table 4). Similarly, distant metastases were most common in B3 and thymic carcinoma histotypes compared with other histotypes (40.9% vs 19%; \( p = 0.11 \)), even if the difference was not significant. Surgical re-resection was accomplished in 24 (55.8%) patients with intrathoracic relapse, while the remaining 19 (44.2%) patients received chemotherapy alone (\( n = 16 \)) or chemoradiotherapy (\( n = 3 \)). Overall 10-year disease-free survival rate was 74% (Fig. 4). Patients with recurrence had a significant worse survival compared with those who did not relapse (10-year survival 47% vs 77%, respectively; \( p < 0.0001 \)). The surgical treatment of recurrence led to a significantly better survival in comparison with medical treatments (10-year survival rate from the first intervention: 75% vs 13%, respectively; \( p < 0.0001 \)).

### 4. Discussion

The therapeutic management of Masaoka's stage III thymic tumors, characterized by the invasion of intrathoracic
structures including major blood vessels, pericardium, heart, and lung, is still a matter of debate for clinicians. The most important concern is related to the difficulty to preoperatively assess surgical resectability by non-invasive radiological studies or invasive staging, resulting in a not negligible rate of incomplete resections [2,5]. The available studies report a rate of complete resection for advanced thymic tumors ranging between 60% and 89% [2,3,5,11,12]; our experience is similar, accounting for a total of 81.6% R0 resections. Factors which negatively affected the radicality of operation were the type of infiltration (vascular invasion was predictive of a lower rate of R0 resection), B1—B2-thymic carcinoma histology, IC, and the absence of MG. Several factors have been found to predict the prognosis in thymic tumors; but completeness of surgical resection has been widely identified as the most important predictor of outcome [2,3,12,13], being the debulking operation associated with a poor prognosis, comparable to a simple biopsy [2—12]. Our series confirms that a radical surgical resection is of paramount importance to guarantee long-term survival; however, those patients who received an R1 resection showed a similar survival, signifying that a small residual disease left in the surgical area can be successfully 'cleaned' by adjuvant treatments. Our actual indications for non-radical resections are to use adjuvant radiotherapy for those patients, who received IC, and to use chemoradiotherapy for those who underwent directly to surgery.

Thymic tumors are chemo- and radiosensitive; thus, a multidisciplinary treatment that integrates surgery with chemo- and radiotherapy has been advocated for advanced stages with the aim to improve both local and distal control of the disease and prolong survival.

After the first encouraging reports in the early 1990s [7,8], IC for advanced stages' thymic tumors has been adopted by several centers [5,6,9,11,12]. The aim was to improve surgical resectability by shrinking the mass and down-staging the tumor and, as for other tumors, to prevent local and systemic recurrences. The chemotherapies schemes are various, but all have been demonstrated to be effective with a response rate higher than 50% and a variable rate of complete remission [4]. In our experience, a complete response to IC was observed in 6.4% and a partial response in 62.8% with an overall response rate of 69.2%. Venuta et al. [5] reported an extraordinary rate of 87% R0 resections after IC, which led to a significant advantage in term of long-term survival. We reached a 74.5% rate of R0 resection, significantly lower than that of the group of surgery without IC (85.8%), but this is justified if we consider that the IC group comprised, in most part, patients with tumors judged not suitable for radical surgery at the preoperative evaluation. However, in the setting of a multidisciplinary treatment for thymic tumors, if we consider also those patients who underwent R1 resection, the IC group obtained an overall 83% of R0 + R1 resections. Differently from other studies [5,7,11] in which a survival advantage was demonstrated in patients receiving IC, we found a worse survival in the IC group. This finding is explained by the higher rate of incomplete resection in the IC group; in fact, upon analysis of only the R0 patients, the survival rate was similar to that of the surgery group.

MG occurs in 20—30% of patients with thymoma [14]. In the past, several studies have reported that the presence of MG in thymoma patients is an indicator of poor prognosis because of increasing risk for surgery and a higher perioperative mortality [15,16]. However, in more recent reports, MG symptoms did not affect the outcome or were even found to be associated with a favorable survival in case of thymoma [17—19]. The reduction of perioperative mortality is attributable to the improvements of the medical and anesthesiological management of MG patients; nevertheless, it is controversial whether a favorable prognosis for thymoma with MG is due to the earlier diagnosis of the thymoma with less advanced stage, or to the tumor behavior of thymoma with MG [18,19]. In our analysis, MG was present in a high percentage (44.2%) of patients with thymoma; but this is due to the fact that the centers involved in this study are also referral centers for the treatment of MG. We found that MG was associated with a significantly better survival at univariate analysis and was almost significant at multivariate analysis (p = 0.06), confirming that, independently from an early diagnosis, in stage III thymic tumors the behavior seems less aggressive.

Okumura et al. [20] reported that vascular infiltration is a negative prognostic factor in thymomas, and a similar finding was reported by Tseng et al. [21] for thymic carcinoma. Also, in our series, the invasion of major vessels was associated with a worse prognosis both in overall patients and R0 patients. This suggests that the reason for poor survival in this group of patients is related not only to the great difficulty in obtaining an R0 resection, but also to the specific modality of resection. In fact, similar to the experience of Utsumi et al. [22], in our population, despite the fact that the type of infiltration did not affect the recurrence rate, tumors with vascular invasion showed mainly systemic recurrences, which were not suitable for a redo-resection and were associated with a negative prognosis. On the other hand, a preferential intrathoracic (pleural) recurrence was observed for patients with tumors invading the lung or pericardium; this finding supports the theory of Haniuda et al. [23] that the pleural and pericardial invasion (p and c factors) are significant risk factors for intrathoracic recurrence.

Recurrences in thymic tumor are frequent (ranging from 10% and 60%) in Masaoka’s stage III of thymic tumors [23—25], with a most common pleural localization. In our series, the recurrence rate was fairly low (21.3%) with 62.8% of relapses at exclusive intrathoracic localization. As reported by other authors [23—25], a surgical approach (when a macroscopic radical resection is feasible) is indicated also in cases of intrathoracic recurrences being associated with a significant survival advantage. In our survival analysis, recurrent disease was an independent negative predictor; nevertheless, the group of patients who underwent a redo-resection showed a survival similar to that of patients without recurrence and was significantly better in comparison with patients who received medical treatments.

5. Conclusions

In conclusion, the multimodality treatment of Masaoka’s stage III thymic tumors provided high survival rates and low recurrence rates. Completeness of resection, type of infiltration, and recurrence were the most important prognostic factors.
References


Appendix A. Conference discussion

Dr P. Van Schil (Antwerp, Belgium): I would like to start the discussion regarding the response to chemotherapy. What criteria do you use to have a correct evaluation of response in stage III thymic tumors after induction chemotherapy?

Dr Marulli: We use the WHO criteria based on radiological findings.

Dr Van Schil: What could be more important is, for example, some regression of the tumor, when you have vascular invasion at the level of the superior vena cava. It’s probably more important than the size or the volume of the tumor itself. Do you agree with that?

Dr Marulli: That’s right, and this is the reason why we had 20 patients with R2 resection. Sometimes it’s very difficult to evaluate the possibility of resection of the tumor or not when there is vascular invasion.

Dr Van Schil: If I am correct, you only used induction chemotherapy?

Dr Marulli: Yes.

Dr Van Schil: Would you consider giving some patients chemoradiation, as our oncologists sometimes do?

Dr Marulli: No. All of the patients had induction chemotherapy that usually leads to less fibrosis than radiotherapy, with an easier intervention.

Dr C. Chong (Melbourne, Australia): My question is regarding your subgroup of patients who had induction chemotheraphy. We are assuming that this is the subgroup of patients who would have locally advanced, invasive thymoma, that sort of typical thymoma you showed on the CT scan where it’s invading or surrounding the aorta and pulmonary artery. Now, my question to you and the floor is whether you think that in this subgroup of patients there is a role for not offering them surgery? Some surgeons and multidisciplinary teams would suggest that this is a very locally invasive thymoma and perhaps there is no role for surgery, because, as you know, it is very likely that you will not be able to get a complete resection, of course assuming you have restaged them after the chemoradiation therapy or multimodality therapy. There are two groups of surgeons. One group will say, ‘Yes, we should go in and take them all out, debulk them aggressively,’ but there is another group of surgeons who say, ‘Well, look, we should stop and do not any more harm given that you would worsen the quality of life by aggressive surgery and with potential morbidity and mortality.’ I think, if I’m correct, your data probably may support that, in that they do poorly and you have got a lot of patients who have incomplete resection anyway after surgery. What are your thoughts and the thoughts of the audience?

Dr Marulli: Obviously this is only a surgical series and therefore there is a bias in the data, being all patients operated on. We have a lot of patients in whom we did chemotherapy with induction intent but they did not receive surgical treatment. Those patients who had surgical resection were patients in whom we thought that it was possible to do at least a maximal resection. If you look at resection in those patients who had minimal residual disease on the aorta or, for example, on the phrenic nerve, on the superior vena cava sometimes, on the lung, these patients had a good survival rate. So it is possible to do a good debulking or at least a very big resection. For us, this is a good indication. But obviously in my institution we had at least 20% of these kind of patients who did not receive surgical resection. But if it is possible, you have to do the surgery.

Dr Chong: So what you are saying is that if the restaging shows that potentially you could have a complete resection, you would go for it. I think most of us would agree, but then what about those who have thymoma invading into the pulmonary artery and the ascending aorta, would your group be operating on those patients, or would you be saying, ‘Look, we’ll treat this with other modalities’?

Dr Marulli: Usually for us, aortic and the main pulmonary artery invasion is a contraindication for surgery. Dr Chong: That’s right.

Dr Van Schil: Yes, I agree with you. There are even some papers from surgeons performing an extrapleural pneumonectomy in cases where you have a pleural spread limited to one side; in fact, an operation for mesothelioma, but that is probably beyond the limits.
Dr Choong: I think as surgeons, we have to be wise and correctly and carefully select our patients and do no harm to the patients really.

Dr K. Athanassiadi (Athens, Greece): I probably missed it, but in cases of induction chemotherapy, in what way are you doing the histology: needle biopsy under CT guidance or are you doing a small Chamberlain incision?

Dr Marulli: Sixty percent of cases had a fine-needle biopsy, the other cases usually a mediastinotomy, and a few cases a VATS. I don’t remember the exact rate.

Dr P. Van Schil (Antwerp, Belgium): When you referred to medical treatment, could you explain exactly what it means?

Dr Marulli: All patients had chemotherapy. Some of the patients with mediastinal involvement had chemo and radiotherapy.

Dr Van Schil: And in cases of recurrent disease, which will be discussed in the next paper, how do you decide on whether to operate the patient or not? Is it only on radiological criteria?

Dr Marulli: Yes, radiological. We also do Octreoscan and PET scan, but usually it’s a clinico-radiological evaluation.

Dr Van Schil: Is there any contribution from PET scanning?

Dr Marulli: No. The Octreoscan is better than a PET scan.

Dr K. Chen (Beijing, China): If you have patients with R1 and R2 resections, how do you evaluate these patients? Which treatment do you decide on? Do you give the induction chemotherapy to some patients but keep the stable or the minor response? For these patients do you choose radiation only or radiation plus chemotherapy?

Dr Marulli: As I said, since 1989 the Pisa group mainly started with induction chemotherapy independent of the preoperative judgment of resectability or not. Most of these patients who were in the stable group were judged already resectable before the radiological study. For R1 and R2 groups usually radiation treatment was the preferred modality.