

Single-centre 40-year results of redo operation for recurrent thymomas[☆]

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Abstract

Objective: Modes of treatment for recurrent thymoma remain controversial. The aim of this study is to analyse the early and long-term results of surgical intervention for this condition. **Methods:** Between 1972 and 2008, 43 out of 315 patients, who underwent resection with radical intent for thymoma, subsequently relapsed. Of these, 30 cases were deemed suitable for resection and operation, and were surgically treated. The remaining 13 were treated with radio- and/or chemotherapy (RT/CT). Overall outcomes for long-term survival up to 5 years (LTS) and disease-free survival (DFS) were analysed using standard statistics. **Results:** The average age of the relapsed patients was 54.7 ± 12.7 years. There were 21 males and 22 females. Forty out of the 43 had myasthenia gravis (MG). Fifteen cases concerned a single detected relapse lesion. Among the 43 patients, relapses were found in the following sites: pleura (25 cases), mediastinum (12), lung (five), liver and bone (one). The perioperative mortality was 0% and the morbidity was 27%. Twenty-two of the surgically treated patients had complete resection; their LTS was 77% and DFS was 71%. Those patients who underwent surgery had significantly better outcomes compared with patients treated with radio- and/or chemotherapy (LTS only 35%; hazard ratio (HR): 0.22; 95% confidence interval (CI): 0.08–0.59; $p = 0.001$). Complete repeated resection yielded much better outcomes than partial resection (LTS 91% vs 31%, $p < 0.001$), whereas incomplete resection was associated, as one might expect, with a poor prognosis (HR: 6.12; 95% CI: 1.18–31.55; $p = 0.031$). No evidence for an association with other clinical, surgical and pathological characteristics was found with regard to LTS or DFS. **Conclusions:** Surgical resection is recommended for the treatment of recurrent thymoma, provided that criteria for suitability for resection/operation are satisfactory at the time of diagnosis. Best survival outcomes are found to depend on the degree of completeness of the repeat resection.

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1. Introduction

Surgical resection represents the most effective therapeutic option in the treatment of patients with thymoma, greatly facilitating long-term survival (LTS) [1]. Unfortunately, the natural history of thymoma is unpredictable. Recurrences are found in 10–30% of patients initially treated with radical-intent resection; lesions may progress slowly, and can occur up to decades after the initial operation [2–5]. The most frequent site of recurrence is the mediastinum; pleural implants are often detected concurrently with these, whereas distant metastases are rare [1].

The strategy for managing recurrent thymoma is still a debated issue. Several authors have reported good LTS rates in patients who have undergone repeated operations [1,3,6], whereas others [7,8] still consider chemotherapy a better treatment choice, judging outcomes from their own series of patients. Sadly, it remains impossible to predict the fate of patients with recurrent thymomas. No surgical or pathological biomarker has yet been validated as an indicator or determinant of prognosis.

In this study, we examine the results of a 40-year single-centre experience in thymoma management [9] at the Department of Thoracic Surgery of the Catholic University of Rome. Our critical analysis is focussed on the series of patients, who developed disease recurrence after initial radical surgery. We discuss the frequency of recurrence; the interval between apparent disease-free state (DFS) to diagnosed recurrence; treatment modalities and patient outcomes (LTS and DFS), taking into consideration the clinical and pathological features of the thymoma at the time of first

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diagnosis; and the presence or absence of associated myasthenia gravis (MG).

2. Materials and methods

Before undertaking our data analysis, we obtained Institutional Review Board approval for research using data derived from standard clinical practice; this being an observational study, no additional interventions were required.

Between 1972 and 2008, a total of 340 patients diagnosed with thymoma were surgically treated with radical intent. A complete resection (CR) was found to be possible in 315 cases; of these, 43 (14%) developed tumour recurrence. These patients represent the subjects of the present analysis, as summarised in Fig. 1. We retrospectively mined clinical and pathological data, including gender, age, presence of MG, surgeons' notes on the initial and repeated operations, postoperative complications, pathological features, postoperative therapy, recurrence patterns and long-term follow-up (see Table 1). The staging of the original tumour was based on the Masaoka classification system [10], and subsequently assigned and reassigned by the same pathologist on the basis of a comprehensive review of available data. A similar procedure, intended to guarantee a homogeneous approach, was also employed to confirm the histological diagnosis. The morphological classification of the original and recurring thymomas was reassessed according to the World Health Organization (WHO) classification [11], and their states were compared to evaluate any histopathological shift to a class different from that assigned at the time of thymectomy. Those patients with initial histology of thymic carcinomas (WHO-C) were excluded from this study on the grounds of significantly different prognosis, much worse than for thymomas. The Masaoka staging assessment of the thymoma (at the time of initial diagnosis and first-step operation) was: two cases stage I, 10 stage II, 21 stage III and 10 stage IVa. Because the data under observation cover four decades, it could not be expected that postoperative treatment options would be entirely homogeneous; however, in the past three decades, adjuvant radiation therapy has been offered to

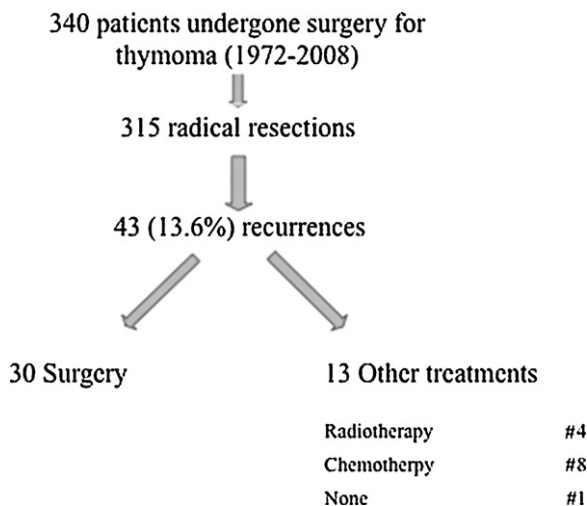


Fig. 1. CONSORT-type diagram of the study.

Table 1. Characteristics of patients: clinic-pathological features and patterns of relapse.

Feature	No. or mean	% or range
Gender		
Male	21	48%
Female	22	51%
Mean age (years) at thymectomy	47.9 ± 11.4	
Mean age (years) at recurrence	54.7 ± 12.7	
Mean follow-up (months) after recurrence	65.3 ± 48.1	50 (4–190)
Mean time (months) from thymectomy	92.7 ± 77.8	69 (8–390)
Comorbidity	17	40%
Myasthenia gravis	40	93%
Initial stage Masaoka		
I	2	5%
II	10	23%
III	21	49%
IV	10	23%
Initial WHO histological classification		
A	1	2%
AB	1	2%
B1	2	5%
B2	23	54%
B3	16	37%
Adjuvant therapy (after thymectomy)	33	77%
Site of recurrence		
Mediastinum	12	28%
Pleura	25	58%
Lung	5	12%
Other	1	2%
Relapse pattern		
Single lesions	15	35%
Multiple lesions	28	65%
Treatment		
Surgery	30	70%
Radiotherapy	4	19%
Chemotherapy	8	9%
None	1	2%
Resection (#30)		
Complete	22	73%
Incomplete	8	27%

patients with invasive thymoma (stage II, III and IV Masaoka). Radiation doses ranged between 38 and 44 Gy in fractions of 1.8–2 Gy over 4–5 weeks.

Treatment of the recurrent tumour varied according to its extent, the degree to which associated MG was controlled and the general condition of the patient. Obviously, the use of non-standardised data concerning a variety of treatment options represents an important limitation of this study, to be borne in mind when reflecting upon the clinical significance of the reported evidence. This difficulty appears unavoidable when analysing very long-term oncological series; despite this, we feel there are important lessons to be learnt from our analysis.

Thoracotomy was the access of choice in cases of pleural, pleuro-pulmonary or pulmonary recurrence, whereas repeat sternotomy was needed in those cases where the disease relapsed at the mediastinal level only. Short- and long-term results are reported in two groups, A and B: A refers to cases treated surgically; B to cases treated by chemo- and/or radiotherapy.

2.1. Statistical analysis

As data were normally distributed, these were analysed by the unpaired *t*-test; as well, the chi-square test and the Fisher's exact test were used where appropriate. The following variables were used for comparison between the

two groups of treatment: age; gender; co-morbidities; initial Masaoka-stage; initial WHO classification; presence/absence of MG; interval before recurrence; adjuvant therapy after thymectomy; and pattern of relapse (site and number of recurrences). Survival curves were obtained using the Kaplan–Meier method. The LTS (including non-cancer-related deaths) and the DFS were calculated by the Kaplan–Meier method and compared by the log-rank test.

The interval between thymectomy and recurrence (disease-free interval, DFI) was defined as the period from the first operation to the diagnosis of recurrence, and was reported as a continuous variable.

Follow-up in the LTS category was defined as the period between diagnosis of relapse and the last contact or death, while follow-up for DFS was calculated from treatment of recurrence to the second recurrence. All the variables showing a potential association with survival ($p < 0.10$) were entered into a multivariate analysis (Cox proportional hazard model) to identify independent prognostic factors. Results were considered significant if the p value was < 0.05 .

3. Results

The patients' gender and age, along with clinical and pathological characteristics at the moment of the thymectomy (after initial diagnosis), are shown in Table 1. It should be noted that 40 (93%) of the 43 patients were affected by MG (this datum is similar to our previously reported series of thymoma patients) [9]. In 2 of the 40 (5%) MG patients, the myasthenia occurred after initial thymectomy, respectively 36 months and 44 months after surgery. In one case, the clinical–neurological onset coincides with the relapse of the thymoma. In 33 cases (77%), adjuvant treatment was administered after the first operation. Specifically, radiotherapy was performed in 21 cases, chemotherapy in four cases and chemotherapy with concurrent radiotherapy in the remaining eight cases.

3.1. Recurrence patterns and repeat operations

The recurrences were revealed by a systematic neurological and oncological follow-up in 23 of the 43 cases. In eight cases, a clinical and neurological worsening gave first cause for concern, while in nine other cases, relapse was indicated by symptoms such as chest pain, dyspnoea and cough.

The recurrence rates from the entire population of resected thymomas were calculated according to initial Masaoka staging, WHO classification and MG distribution (Table 2).

The mean DFI was 92.7 ± 77.8 months. No differences were found in duration of DFI, according to the first Masaoka staging. On the contrary, patients who had a WHO class B3 after first resection showed a significantly shorter mean DFI when compared with patients with B2 and B1 disease (B3 mean 29.08 ± 7.3 months vs B2 mean 81.37 ± 16.96 months, $p = 0.002$; and B3 vs B1 mean 181.02 ± 128.0 months, $p = 0.007$). The use of adjuvant therapy had no effect on prolonging mean DFI, which remained approximately the same (93.0 ± 47.2 vs 92.6 ± 85.5 months, $p = 0.90$).

The relapse pattern (recurrence site and number of lesions) is described in Table 1. The most common sites of relapse were the mediastinum and the pleura; pulmonary

Table 2. The recurrence rates from the entire population of resected thymomas according to initial Masaoka staging, WHO classification and MG distribution.

	No. (%)	Relapses No. (%)	Recurrence rate
Stage Masaoka			
I	134 (43)	2 (5%)	1.5%
II	103 (33)	10 (23%)	9.7%
III	64 (20)	21 (49%)	32.8%
IV	14 (4)	10 (23%)	71.4%
WHO classification			
A	11 (4)	1 (2%)	9.1%
AB	31 (10)	1 (2%)	3.2%
B1	61 (19)	2 (5%)	3.3%
B2	185 (59)	23 (54%)	12.4%
B3	27 (9)	16 (37%)	59.2%
Myasthenia gravis			
Yes	275 (87%)	40 (93%)	14.5%
No	40 (13%)	3 (7%)	7.5%
Total	315	43	13.6%

metastases were found in five cases, whereas only one case of haematogenous widespread (liver and bone) metastasis occurred.

Repeated surgery was indicated and performed in 30 patients (70%; group A), while another treatment (group B) was performed in 13 patients (30%; radiotherapy and chemotherapy in four and eight patients, respectively). In one patient in particularly poor condition, no treatment was carried out.

During the administration of radiotherapy and chemotherapy, two cases of toxicity were detected (one of oesophageal toxicity (G2) and one of haematologic toxicity (G2)). All patients except one completed the planned adjuvant treatment. In two cases, MG was not suitably controlled by drugs, and, in one case, a patient died of respiratory failure 3 months after the start of chemotherapy.

Within group A, repeated resection was performed through a lateral thoracotomy in 25 patients, and median re-sternotomy in five. The pattern of relapse obviously influences the choice of the more adequate surgical access. Nevertheless, we prefer the thoracotomic surgical access, if technically feasible, because of the significant operative risk and postoperative morbidity related with the sternotomic procedure. The resection was complete (R0) in 22 cases (73%). In the remaining eight patients, the lack of completeness was already evident at the moment of surgery (R2), where a simple 'debulking' was achieved. Postoperative mortality was nil, whereas postoperative complications occurred in eight patients (27%). MG was present in all but one of these patients. The remaining 22 patients had no major complications, and the postoperative course was uneventful.

The WHO classification of the thymoma recurrences is reported in Table 3. Interestingly, a histological 'upgrading' shift was found in 18 cases (~60%) when the WHO status of the recurrence tumour was compared with the initial grading.

3.2. Survival

The mean follow-up duration was 65.3 ± 48.1 months. Overall 5-, 10- and 15-year survival for the whole population

Table 3. WHO classification at the time of thymectomy and at the time of recurrence: the ‘pathological shift’.

	WHO classification (at thymectomy) No. (%)	WHO classification (at recurrence) No. (%)	WHO upgrading
A	1 (2)	0	# 1 from A to C
AB	1 (2)	0	# 1 from AB to B3
B1	2 (5)	0	# 2 from B1 to B2
B2	23 (54)	10 (33)	# 9 from B2 to B3
B3	16 (37)	14 (47)	# 3 from B2 to C
C	0	6 (20)	# 3 from B3 to C
Total	43	30	#18 (60%)

was 64%, 51% and 43%, respectively. The percentages for 5- and 10-year DFS were 71% and 53%, respectively (Fig. 2).

Five-year survival (LTS) was significantly better when a repeated operation was performed (compared with chemo- and radiation therapy only): group A = 77% versus group B = 35%; $p = 0.001$ (Cox regression: hazard ratio (HR) = 0.22, 95% confidence interval (CI) = 0.08–0.59, $p = 0.001$, Fig. 3(A)). Survival analysis according to clinico-pathological variables (Table 4) showed that only the presence of multiple recurrences seemed to be slightly correlated with a worse prognosis ($p = 0.08$). Interestingly, histological WHO upgrading was not significantly correlated with a worse prognosis ($p = 0.40$).

Analysis of survival rates in group A demonstrated a significantly better 5-year LTS in patients undergoing a complete resection of the recurrent thymoma (91% vs 31%, $p < 0.001$), whereas a slightly worse prognosis was correlated with the presence of multiple relapse lesions: the 5- and 10-year LTS rates for patients with single and multiple

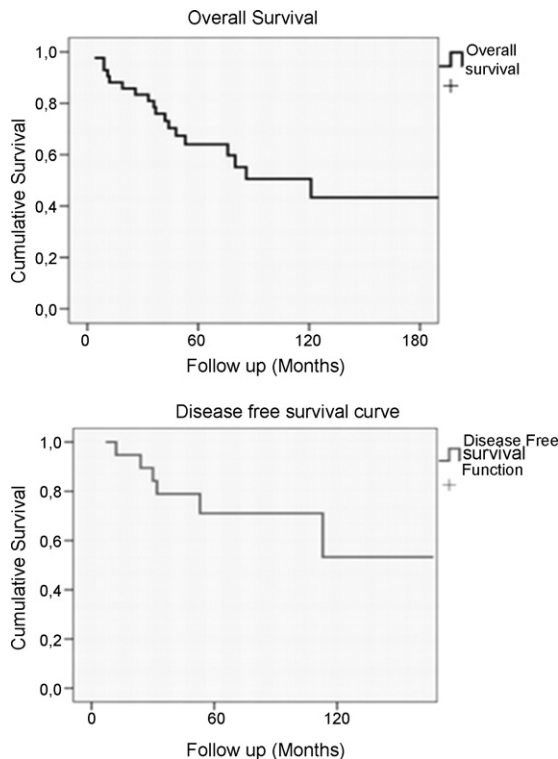


Fig. 2. Overall survival (LTS) and disease-free survival (DFS) in all population.

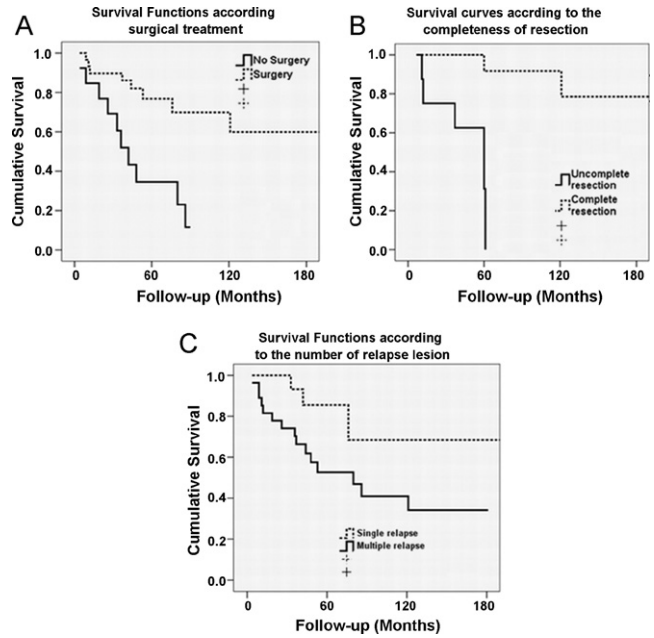


Fig. 3. Actuarial survival according to the treatment of the recurrence (surgery vs other treatment), completeness of the resection (complete vs incomplete) and the number of the relapse (single vs other multiple).

Table 4. Univariate analysis on long-term survival.

	HR	CI	p
Completeness of resection	0.064	0.008–0.461	<0.001
Surgery	0.223	0.084–0.589	0.001
Multiple relapses	0.327	0.094–1.135	0.08
Adjuvant	0.541	0.189–1.542	0.25
Site	1.455	0.73–2.902	0.29
WHO upgrading	1.882	0.433–8.16	0.40
Age	1.013	0.973–1.055	0.53
Comorbidities	1.341	0.511–3.521	0.55
Myasthenia gravis	0.796	0.101–6.286	0.83
Time from first recurrence	1.001	0.994–1.007	0.88
WHO class	0.951	0.488–1.853	0.88
Masaoka staging	1.018	0.557–1.864	0.95

recurrences were 100% versus 64% and 80% versus 53.3%, respectively ($p = 0.12$) (Fig. 3B and C).

3.3. Iterative surgery

Among the 22 patients, who underwent complete resection (R0), a second recurrence occurred in four cases (18%). A total of 11 repeated resections was performed. One patient is still alive and disease-free after the first repeated surgery, 21 years after the initial diagnosis [12].

4. Discussion

Information about the short-, medium- and long-term clinical outcome of patients with recurrent thymoma is necessarily limited by the small number of cases in the published series; a long- to very long follow-up period is required before one can achieve definitive conclusions. In fact, even after a thymoma has been completely resected, it

may produce a local recurrence only after a significant span of time (years, decades and even 30 years later). From our series, we can report a mean time of recurrence from the first operation of 92.68 months; this confirms previous findings by other authors [1,13]. The recurrence is often asymptomatic (in over 60% of the reported series) [13]; common clinical manifestations are the worsening of neurological MG symptoms and increased pulmonary functional impairment, if the pleural space is colonised by tumour implants. It is widely accepted that a long/very long follow-up is necessary for the detection of thymoma recurrences, even if the initial diagnosis is of an early-stage neoplasm. As for the potential predictive value of the different recurrence parameters observed and considered by us for the purpose of this analysis, we note that the relatively short DFI in WHO B3 tumours markedly separates this class from the B1 and B2 ones. This is in line with the data observed by Okumura and colleagues [14], where the DFI in patients with type B3 tumours was significantly inferior to the DFI in cases of tumoral types AB, B1 and B2. Interestingly, we have detected a very high rate of MG (~93%) in our series of recurrent thymoma; this finding could be easily explained considering the characteristics of the entire population, composed mostly by patients with MG (275 of 315 cases or 87%). This very huge percentage of MG patients is justified by the fact that our centre is a national landmark for the treatment of MG, as already previously reported [9].

No differences in outcome were found with respect to Masaoka staging and the administration patterns of adjuvant treatments. Thymomas are known to respond well to radiotherapy [15]; however, no surgical differences were found in patients treated with or without adjuvant therapy, as demonstrated in other series [16,17].

The role of surgery, and in particular its advantages with respect to chemo- and radiation therapy, is still a forum of open discussion. There is also no definitive consensus on the efficacy of debulking surgery.

A frequently encountered bias in almost all previous studies concerns the relatively restricted selection of patients for iterative surgery. The operation is generally reserved for those patients presenting a good clinical condition and whose recurrent tumour has been shown via imaging to be technically resectable. Up to the present day, the superiority of the surgical approach has not progressed much beyond scientific supposition.

Nevertheless, the majority of the studies, except that of Haniuda and colleagues [16], tends to support the hypothesis of better efficacy of the surgical approach. In Maggi's series, the effectiveness of iterative surgery in recurrent thymomas was demonstrated by a 5-year survival rate of 71% in 12 patients, who underwent repeated operations – definitely

better than the 41% achieved by those treated with radiation and chemotherapy during the same period. The difference, however, was not statistically significant in view of the small sample size. Okumura and colleagues [14] report similar results (10-year survival rates of 70% in surgical and 35% in non-surgical groups); our own results are in line with these (Table 5).

Another item worth discussing in this context is the indication for repeated surgery in those cases with pleural dissemination. Blumberg and colleagues [4] reported a significantly higher recurrence rate (80%) in stage IVa patients (as compared with earlier stages) after CR, suggesting some scepticism as to whether CR is justified after pleural dissemination has occurred. This report, however, remains isolated. In our study, we failed to find any significant stage-related difference in the survival rates of patients with pleural involvement. We therefore advocate a surgical re-operation, wherever this is deemed reasonably feasible on the basis of the imaging features.

This philosophy is supported by our low rate of incomplete resections at the time of repeat surgery. The sophistication of the imaging techniques could help in further reducing the rate of R2 re-operations, especially where a tumour recurrence is to be defined and discriminated from the effects of the previous surgical procedure. Data available on debulking surgery [1,13] including ours (LTS is lower in the debulking surgery group than in the non-surgical treatment one: 25% vs 35%, respectively), tend rather to indicate, though heterogeneously [14,18], that this procedure is not beneficial for the patient, and that it should be reserved to very selected cases, with alternative treatments being preferred for the others [16,19]. The completeness of resection at the time of repeated surgery remains as the most important determinant of LTS [1,6,19]. Moreover, it was this parameter that proved to be more important, as a prognostic determinant, than the pattern of diffusion (site and single vs multiple localisations, as reported occasionally (reference [17], this study)). To validate the pattern of diffusion as a prognostic determinant (and attribute a relative weight as compared with the completeness of resection), larger series are needed.

Pulmonary function could represent a factor of limitation in the indication of iterative surgery. Our group has an interest in multidisciplinary approaches, including pulmonary rehabilitation in oncological patients, in particular those with lung cancer in the postoperative setting [20]. Preliminary data on the perioperative pulmonary functionality of patients with thymoma and integrative rehabilitative strategies are currently being analysed (unpublished).

Finally, we would like to end with a brief discussion on the histological aspect. Reported results [14,21–23] are often

Table 5. Treatment of recurrent thymoma: other series.

	#	Surgery	Radicality	5-OS	10-OS	2 ^o Recurrence rate
Regnard (1997)	28	28	67%	51% (64% R0)	43% (53% R0)	35% (16% R0)
Ruffini (1997)	30	16	63%	48% (72% R0)	24% (72% R0)	n.d.
Haniuda (2001)	24	15	26%	37%	16%	n.d.
Okumura (2007)	67	22	82%	n.d.	70%	41%
Lucchi (2009)	20	20	65%	43%	26%	50%
Our series (2010)	43	30	73%	64% (91% R0)	51% (67% R0)	27% (18% R0)

contradictory; we did not find any significant difference in outcome by WHO class at the moment of first diagnosis and at recurrence. Heterogeneity is a common disadvantage when comparing the results of different series, including our own, and when attempting to match the relative values of the histological stage shift [23–25]. Some explanations made on the basis of pure morphology are given in the report by Ciccone and Rendina [23], suggesting that a mere fraction of the cortical component of the tumour may be responsible for eventual relapse; this suggestion, however, remains unconfirmed. It is our hope that a systems approach based on the oncogenetic features of thymoma will soon be available to help clarify these problems. Such an approach could contribute to the achievement of a better classification of tumours that correlates more strongly with clinical behaviour; this would undoubtedly aid in strategic treatment planning.

5. Conclusions

Surgery, where deemed reasonably feasible, is indicated in cases of recurrent thymoma. The completeness of resection, if performed, is the most powerful determinant of prognosis. Additional information, such as that which might derive from a systems approach, is needed to improve the tumour classification with the prospective of more efficient therapeutic strategies.

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Appendix A. Conference discussion

Dr M. Lucchi (Pisa, Italy): There are only a few papers about the treatment of thymoma relapse and they suffer from a limitation in the numbers in the series. All the series also suffer from an unavoidable bias concerning the selection of patients for surgical treatment and, indeed, to have a small series, you must have a huge experience for a long period. In this sense, I would like to congratulate the Catholic University of Rome for their remarkable experience.

I would like to highlight that 90% is really a huge percentage of myasthenic patients. It's probably a consequence of the patient referral, but I would like your comment on that. Also, I would like to ask you if you have any data regarding the neurological outcome following surgical treatment of thymoma recurrence?

Dr Margaritora: As you saw in the previous paper, in Italy we have some referral centres for myasthenia. Our centre is one of these and we are a tertiary care referral centre for myasthenia for central and southern Italy. So

this is the reason that the vast majority of our patients are myasthenic. The neurologists refer the patients to us.

Regarding the neurological follow-up, after the first operation, of these 43 patients, 29 experienced a partial or complete response of myasthenia symptoms, but in this group only 5 had a complete pharmacological remission. It's a low incidence, but it's common in this series.

At the time of the second relapse, in this group of 29 patients, only 8 also had a relapse of symptoms, and after the operation, the disease remained stable. So it is not an exciting response to myasthenia in this thymoma group, but this is not at variance with the literature.

Dr Lucchi: I have a concern about the inclusion of the initial stage IVA thymoma. In stage IVA thymoma, recurrence is not rare. I think it's quite natural. I would like to suggest excluding that kind of patient. Can you comment on that?

Dr Margaritora: Yes, you are right. You ask the question: Why do you include these patients? I can turn the question around: Why not? These 10 patients were not stage C, so nonthymic carcinoma, with small implants in the pleura, radically resected, and so I don't think that these selected cases could be a bias in this study, but from a theoretical point of view, you are right.

Dr Lucchi: The last question, I am a little bit surprised by the high percentage of upgrading, 60%, but particularly I'm surprised that you found 6 type C thymomas at recurrence. I am reminded what a very famous American pathologist told me 2 years ago, that if your pathologist does 3 sections, he will say B1, B2 tumour, and if he does 10 sections, he will say B3 or maybe also type C. So there is lot of heterogeneity inside the single thymoma, but from thymoma A or B to type C there is a lot of difference. Can you comment on that?

Dr Margaritora: From the beginning, all cases of thymoma in our institution have been reviewed by a single pathologist. I must trust him. I have no other elements to say why. The data on survival (I mean that the upgrading does not affect survival) is very strange, and I think that has to be validated by a multicentre study. With a 43-patient series, I don't think that we can make a conclusion.

Dr C. Choong (Melbourne, Australia): Obviously a lot of time has been put into this study and it is one of the largest series that we would have seen in the literature.

Firstly, I have a comment. Your paper is an important reminder to all of us that following up on these patients is very important in the long term because of the risk of recurrence. I have a simple question. What is your follow-up protocol in terms of doing X-ray every 6 months and a CT scan once a year? What is your suggestion?

Dr Margaritora: Well, after operation, the follow-up is performed on our patients by the neurologists, because you'll see that 90% have myasthenia. The neurologists follow-up these patients. For patients who had radiotherapy after operation, the follow-up is made by the oncologists. In general, we adopted a follow-up policy as for lung cancer, which is intensive for the first 5 years and then yearly with a CT scan.

Dr P. Van Schil (Antwerp, Belgium): Were there any patients who had recurrent symptoms as the first sign of recurrent thymoma?

Dr Margaritora: Yes, but it was at the same time, because you have to consider that when a patient has a worsening of symptoms, he goes to the neurologist, so at the same time we had the diagnosis. In all cases there was a very early diagnosis of recurrent disease.

Dr G. Leschber (Berlin, Germany): I want to continue with this discussion. You said that most of the patients who had a relapse are myasthenia gravis patients. These are the ones that are followed by your neurologists. On the other hand, you pointed out that a lot of these recurrences happen pretty late, years and years thereafter. So isn't it possible that a lot of patients actually have a small recurrence that we do not know of because after 5 years or so they are not followed anymore?

Dr Margaritora: Yes, it can happen in the nonmyasthenic patients, but the patient with myasthenia usually goes to the neurologist once a year.

Dr Leschber: No, I'm talking about the nonmyasthenia patients, but probably –

Dr Margaritora: Yes, but in this selected group we have only 3 nonmyasthenic patients.

Editorial comment

Recurrence of thymoma

Keywords: Thymoma; Thymic recurrence; Surgery

Despite the fact that recurrence of thymoma has been the object of a number of studies dating back to more than 20 years, the published series have provided conflicting results.

In fact, when viewing the impressive literature on thymomas, one cannot help noticing how virtually each study on thymoma suffers from the same methodological flaw: the lack of randomization. Thymomas are rare neoplasms with a tendency of a slow-growing progression and this implies that controlled randomized clinical trials are unlikely to be funded and supported because of the rarity of the disease, of the limited number of participating centers involved, and of the required long-term follow-up. In 2008, Davenport and Malthaner [1] published a systematic review of the literature to provide some evidence-based recommendations about the role of surgery in the management of thymomas. Among others, the authors tried to answer the question whether surgery is a useful treatment option in recurrent thymomas. The authors found six retrospective case series dealing with the role of surgery in the treatment of recurrence of thymoma. Since the completion of their literature search (June 2007), five

additional reports have been published. The conclusions of the authors and the more recent series indicate that re-resection of recurrent thymoma seems reasonable, although the data on which such a recommendation is based are methodologically weak. A further source of confusion arises when considering that non-surgical recurrence treatments (chemotherapy, radiotherapy, or a combination of both) resulted in reasonable intermediate-term survivals (35–65% 5-year survival rates) [2].

As a consequence, there is still confusion among centers dealing with thymic malignancies about optimal management in case of thymoma recurrence. A recent survey among the European Society of Thoracic Surgeons (ESTS) members [3] indicated that most centers agree that recurrence should be removed when resection is feasible; some centers reported to perform multiple subsequent resections in case of repeated recurrence; several centers pointed out that they proceed to resection only when complete resection may be anticipated.

Having said that, a major issue is how we may reduce the recurrence rates and improve survival rates in recurrent