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Surgical treatment of recurrent thymoma: is it worthwhile?†

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Abstract

OBJECTIVES: Radical resection of thymoma is the most important predictor of survival; despite a complete resection, 10–30% of patients develop a recurrence. The surgical treatment of thymic relapses is an accepted therapeutic approach; however, no clear data are available yet regarding the indication for surgery and the long-term prognosis of this subset of patients. The aim of our work was to review the data of a group of recurrent thymomas treated by surgery, comparing it with non-surgical therapy, and analysing the outcome and the prognostic factors.

METHODS: Between 1980 and 2010, 880 patients with thymoma underwent complete macroscopical resection and were followed up for recurrence. Masaoka stage IVa and type C thymic tumours were excluded from the study. A total of 82 (9.3%) patients developed a recurrence, and 52 (63.4%) were reoperated. The other 21 patients, originally operated outside, underwent surgical resection of recurrence. Finally, 73 patients were operated on for recurrent thymoma and 30 received medical treatment. This entire cohort represents the subject of the study.

RESULTS: There were 57 (55.3%) males and 46 (44.7%) females. The median time to relapse was 50 months. Sixty-three (61.2%) recurrences were regional, 17 (16.5%) local, 14 (13.6%) distant, 6 (5.8%) regional and distant, and 3 (2.9%) local, regional and distant. No operative mortality was observed. In 50 (68.5%) patients, a macroscopic complete resection was accomplished. The 5- and 10-year overall survival rates from recurrence were 63 and 37%, respectively. Complete surgical resection was associated with a significant better survival when compared with incomplete surgical resection and non-surgical treatment ($P < 0.0001$). A significant poorer prognosis was observed for multiple versus single relapses ($P < 0.0001$), Masaoka stage III primary tumour versus Masaoka stage I–II primary tumour ($P = 0.02$), distant versus loco-regional relapses ($P = 0.05$) and B3 histotype versus other ($P = 0.02$). On multivariate analysis, completeness of resection, number of metastases, Masaoka stage of primary tumour and site of relapse were identified as the only independent predictors of prognosis.

CONCLUSION: Reoperation for recurrent thymoma is effective and safe, achieving a prolonged survival. Complete macroscopic resection and single recurrence are associated with better prognosis.

Keywords: Thymoma • Thymic recurrence • Surgical treatment • Prognostic factors • Survival

INTRODUCTION

Thymomas are the most common neoplasms of the anterior mediastinum. Surgical resection, when possible, is the mainstay of treatment and assures a good long-term prognosis. Unfortunately, in 10–30% of patients, recurrence of the tumour may occur in a variable range of time, from few months to several years after the first operation [1–6]. The most common site of tumour relapse from thymoma is the thoracic cavity, most of all in the form of single or multiple pleural implants probably due to the seeding of the pleural cavity during dissection of the tumour or spillage from the surface of the invaded capsule. Less frequently, the relapse is located in the anterior mediastinum as a result of incomplete resection or contamination of the field in case of invasion of the capsule or neighbouring organs. Distant metastases are rare in thymoma, but typical of thymic carcinomas. The management of thymoma recurrence is still unclear. Various authors [1–5, 7–11] emphasized the efficacy of surgical re-resection to prolong the survival of these patients; other authors [6, 12] found no differences in the results obtained through surgery and chemo- or radiotherapy. However, a significant bias was present in almost all

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studies, related to the selection criteria used for these patients, particularly when considering relapses from Masaoka stage IV, from thymic carcinoma or from incomplete resection of primary thymoma. Additionally, the comparison of patients treated by surgery or chemoradiotherapy is often inappropriate due to the different extension (single or multiple relapses), location of the disease (local versus distant metastases) and performance status of the patients. We reviewed the data of a group of recurrent thymomas treated by surgical and non-surgical approaches, analysing the outcome and the prognostic factors.

MATERIALS AND METHODS

Data were retrospectively collected from four Italian centres (Thoracic Surgery University of Padova, Thoracic Surgery University of Pisa, Thoracic Surgery Catholic University of Rome and Thoracic Surgery Carlo Forlanini Hospital of Rome) with large experience regarding the surgical treatment of thymomas. Information was shared and a common database was built up. The local ethical committee approved the study. Following the indications of the International Thymic Malignancies Interest Group (ITMIG), recurrences were classified as: local [disease appearing in the bed of the thymus (i.e. the anterior mediastinum) or tissues immediately contiguous with the normal thymus or with the thymoma], regional (intrathoracic tumour that is not immediately contiguous with the thymus gland or the previous thymic neoplasm) or distant (disease outside the thorax or the lower neck and intraparenchymal pulmonary nodules) [13]. We excluded from the study the patients with type C thymic carcinoma due to the particular aggressiveness of this subtype compared with the other subtypes of thymoma; in this manner, we avoided a possible bias related to the inclusion of a group of patients with very poor prognosis and high risk of recurrence. We also excluded patients with Masaoka stage IVa and IVb thymomas, as it was virtually impossible in these cases to achieve a microscopically radical resection, and therefore when the disease 'relapses', it is difficult to differentiate a recurrence from a progression. Another exclusion criterion was an incomplete resection of thymoma. Between 1980 and 2010, 880 patients with thymoma underwent complete macroscopical resection at our centres and were followed up for recurrence. The follow-up included a clinical evaluation (including a neurological evaluation in myasthenia gravis patients) and a chest and abdomen CT scan every year. Eighty-two (9.3%) patients developed a recurrence, and 52 (63.4%) were reoperated. Furthermore, 21 patients previously operated elsewhere underwent surgical resection of recurrence in one of the above-mentioned centres. The main reasons of exclusion from surgery were as follows: (i) diffuse intrathoracic and/or distant metastases and (ii) technical inoperability at the preoperative assessment (most of all for a very diffuse intrathoracic disease or mediastinal recurrence with diffuse invasion of the great vessels or the heart). Finally, 73 patients were operated on for recurrent thymoma and 30 received medical treatments; this cohort of 103 patients represents the subject of the study. Primary thymomas and recurrences were classified according to WHO criteria [14] as type A (medullary and spindle cell), type AB (mixed) and types B1–3 (cortical). Staging of the primary tumour was determined following the modified Masaoka's classification. Single pleural relapses were resected by limited pleural resection; in case of multiple relapses, a partial or total pleurectomy was done. Regarding the policy for the use of adjuvant treatments, it was tailored to each patient based on the following criteria: completeness of resection, previous use of chemo- and/or radiotherapy as well as location and extent of residual disease. Clinical and demographic characteristics of the study population are summarized in Table 1. Of 103 patients, 57 (55.3%) were males and 46 (44.7%) females with a median age of 46 years (range 24–72). Myasthenia gravis was associated with thymoma recurrence in 63 (61.2%) patients. The median time to relapse was 50 months and the most common site of relapse was regional (pleural cavity; 61.2%).

Statistical analysis

Data are expressed as absolute numbers, percentage, mean or median values. Survival curves were calculated with the Kaplan–Meier method, and the log-rank test was applied for univariate analysis of factors predicting survival. In the multivariate analysis, the variables predicting death at simple analysis were entered in the Cox proportional hazard regression model. Forward stepwise selection was applied to identify the best effects. The effects meeting the 0.1 significance level of Wald's statistic, testing the null hypothesis that the corresponding effect is null, entered and stayed in the model. Statistical analysis was performed with Statistica, stat soft, setting the significance level at 0.05.

RESULTS

Surgical treatment

Before surgery, 19 (26%) patients underwent induction chemotherapy and 3 (4.1%) chemoradiotherapy. The surgical approach for resection was thoracotomy in 52 (71.2%) patients, median sternotomy in 13 (17.8%), video-assisted thoracoscopic surgery in

Table 1: Demographic and clinical characteristics of the study population (*N* = 103)

Gender	
Male	57 (55.3%)
Female	46 (44.7%)
Median age [years, (range)]	46 (24–72)
Myasthenia gravis	63 (61.2%)
Median time to relapse [months, (range)]	50 (10–301)
Masaoka stage of primary tumour	
Stage I	11 (10.7%)
Stage II	34 (33%)
Stage III	58 (56.3%)
WHO histology of primary tumour	
Type AB	8 (7.8%)
Type B1	9 (8.7%)
Type B2	38 (36.9%)
Type B3	48 (46.6%)
Site	
Local	17 (16.5%)
Regional	63 (61.2%)
Distant	14 (13.6%)
Regional and distant	6 (5.8%)
Local, regional and distant	3 (2.9%)
Number	
Single	52 (50.5%)
Multiple	51 (49.5%)

Data are presented as number (%) or median (interquartile range) as appropriate.

3 (4.2%), laparotomy in 2 (2.7%), laparotomy plus thoracotomy in 2 (2.7%) and sternotomy plus thoracotomy in 1 (1.4%) patient. A complete macroscopic resection was achieved in 50 (68.5%) patients, whereas the resection was judged incomplete in 23 (31.5%) patients. Sixteen (21.9%) patients received more than one operation. No intra- and perioperative mortality occurred; postoperative complications occurred in 9 (12.3%) patients. Adjuvant chemotherapy was administered to 20 (27.4%) patients; adjuvant radiotherapy was delivered to 9 (12.3%) patients, whereas adjuvant chemoradiotherapy was done in 5 (6.8%) patients.

Non-surgical treatments

Thirty (29.1%) patients were considered not suitable for surgery for a diffuse intrathoracic and/or distant disease ($n = 27$) or for a local recurrence judged technically inoperable at the preoperative assessment ($n = 3$). Among this group of patients, 23 received definitive chemotherapy, 3 chemoradiotherapy and 4 had only radiotherapy.

Survival and prognostic factors

The median follow-up was 50 months (range 12–190 months). At the last follow-up, 54 (52.4%) patients were alive [17 (16.5%) with recurrence], 48 (46.6%) were dead [35 (33.9%) due to recurrence] and 1 (1%) was lost. Overall survival rates at 5 and 10 years from recurrence were 63 and 37%, respectively (Fig. 1). Table 2 resumes the statistical analysis on prognostic factors. On univariate analysis, we found no significant impact on survival by gender, disease-free interval, myasthenia gravis and adjuvant treatment. Complete surgical resection was associated with a significant better survival when compared with incomplete surgical resection and non-surgical treatment ($P < 0.0001$; Fig. 2A). A significant poorer prognosis was observed for multiple versus single relapses ($P < 0.0001$; Fig. 2B), Masaoka stage III primary tumour versus Masaoka stage I–II primary tumour ($P = 0.02$; Fig. 2C), distant versus loco-regional relapses ($P = 0.05$) and B3 histotype versus other ($P = 0.02$). On multivariate analysis, completeness of resection, number of metastases, Masaoka stage of primary tumour and site of relapse were identified as the only independent predictors of prognosis.

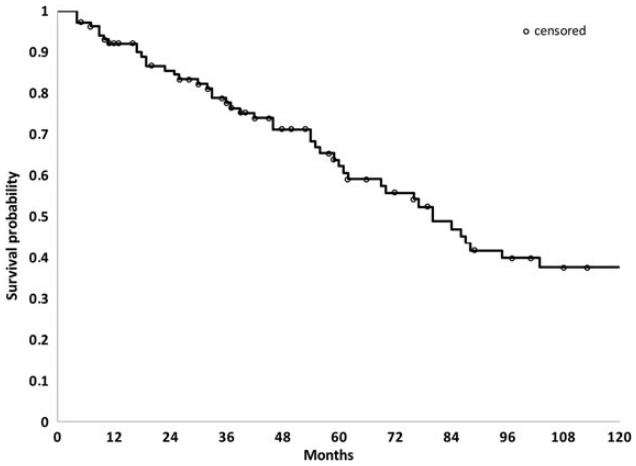

Figure 1: Overall survival from recurrence.

DISCUSSION

Radical surgical resection represents the most effective therapeutic option in the treatment of patients with thymoma, assuring a long-term survival in a high percentage of patients, particularly in early stages [15, 16]. Despite that, the natural history of thymoma is unpredictable and a recurrence may be diagnosed in patients initially treated with radical-intent resection. The recurrence rate has been recently reported as ranging from 8 to 30% of operated patients [1–12]; recurrent lesions may progress slowly, and can occur up to decades after the initial operation [1–3]. Our recurrence rate of 9.3% and a time to relapse of 50 months for all radically resected thymomas are also consistent with previous reports [5, 17, 18]. The probability of recurrence seems to be related to the initial Masaoka stage of the disease [16, 19], as well as to the WHO histology [11], with an increased relapse rate for Masaoka stage III and types B2–3 primary tumours. The pattern of recurrence of radically resected thymic tumours includes local or regional (pleural or pericardial implants) recurrences and distant metastases. The most common site of relapse in almost all of the reported series on recurrent thymoma is the pleural space, ranging from 46 to 80% of all recurrences [2, 3, 17, 20]. Our experience was comparable with exclusive pleural recurrence observed in 61.2% of cases. Treatment for recurrence may not be easy and the optimal strategy for managing these patients is still a matter of debate. Although several series of recurrent thymic tumours have been published, no consensus on treatment has been established. Thymoma is a rare disease and recurrences are even rarer, and therefore no randomized trials on different therapeutic approaches are available in the literature. The main data on the results of treatment of recurrent thymomas emerge from a few retrospective series [1–12] with small numbers of patients (the larger one includes 43 patients). These studies include patients with heterogeneous degrees of severity, variable patterns of recurrence, different types of therapeutic approach and various selection criteria (regarding the presence of primary Masaoka stage IVa, type C thymic carcinoma, recurrence on patients with incomplete resection and technical resectability). Treatment options for recurrent disease include surgical resection, chemotherapy, radiotherapy, a combination of medical and surgical approach or even observation. Surgical resection of recurrence from thymoma has been advocated as the most effective treatment by several authors, based on improved survival compared with non-operatively managed patients [2–5, 9, 10]. However, these tumours are sensitive to radiation therapy and chemotherapy, and other authors found no significant difference in survival between operative and non-operative management, discouraging surgical treatment due to excessive perioperative morbidity [6, 12]. In 2008, Davenport and Malthaner [21] published a systematic review targeted to provide some evidence-based recommendations about the role of surgery in the management of primary and recurrent thymomas. The conclusions of the authors regarding recurrent thymoma treatment were that surgical resection of relapses seems reasonable, although the data on which such a recommendation is based were methodologically weak and based only on reports coming from six retrospective series. A recent meta-analysis published by Hamaji *et al.* [20], considering 11 studies, led to the same conclusions, underlining that the best results are obtained when a complete resection is anticipated by preoperative radiological assessment or is obtained during surgery. Nevertheless, the majority of the studies, except that of Haniuda *et al.* [6], tends to support the hypothesis of better efficacy of the surgical approach. It is without doubt, however, that most of the studies concerning surgery for recurrent

Table 2: Statistical analysis (univariate and multivariate analyses)

Parameter	*P*-value*	*P*-value**	Hazard ratio	95% Hazard ratio confidence limits
Gender (female : male)	0.38	–	–	–
Myasthenia gravis (no : yes)	0.50	–	–	–
Treatment (CSR : ISR : NST)	<0.0001	–	–	–
ISR[a]	–	0.01	3.00	1.25–7.16
NST[a]	–	<0.0001	7.65	3.07–19.10
Histology WHO (B3 versus other)	0.02	0.88	1.06	0.51–2.18
Site (local : regional : distant)	0.05	–	–	–
Local[b]	–	0.57	1.40	0.43–4.54
Regional[b]	–	0.04	0.47	0.23–0.95
Number (multiple : single)	0.0001	0.002	3.79	1.62–8.91
Masaoka stage (III : I/II)	0.02	0.04	1.40	1.02–1.93
Adjuvant therapy (no : yes)	0.87	–	–	–
Disease-free interval (≤60 : >60 months)	0.47	–	–	–

CSR: complete surgical resection; ISR: incomplete surgical resection; NST: non-surgical treatment.
[a]CSR was the reference parameter for comparison.
[b]Distant recurrence was the reference parameter for comparison.
*Significance level obtained by the log-rank test.
**Significance level obtained by the Cox proportional hazard test.

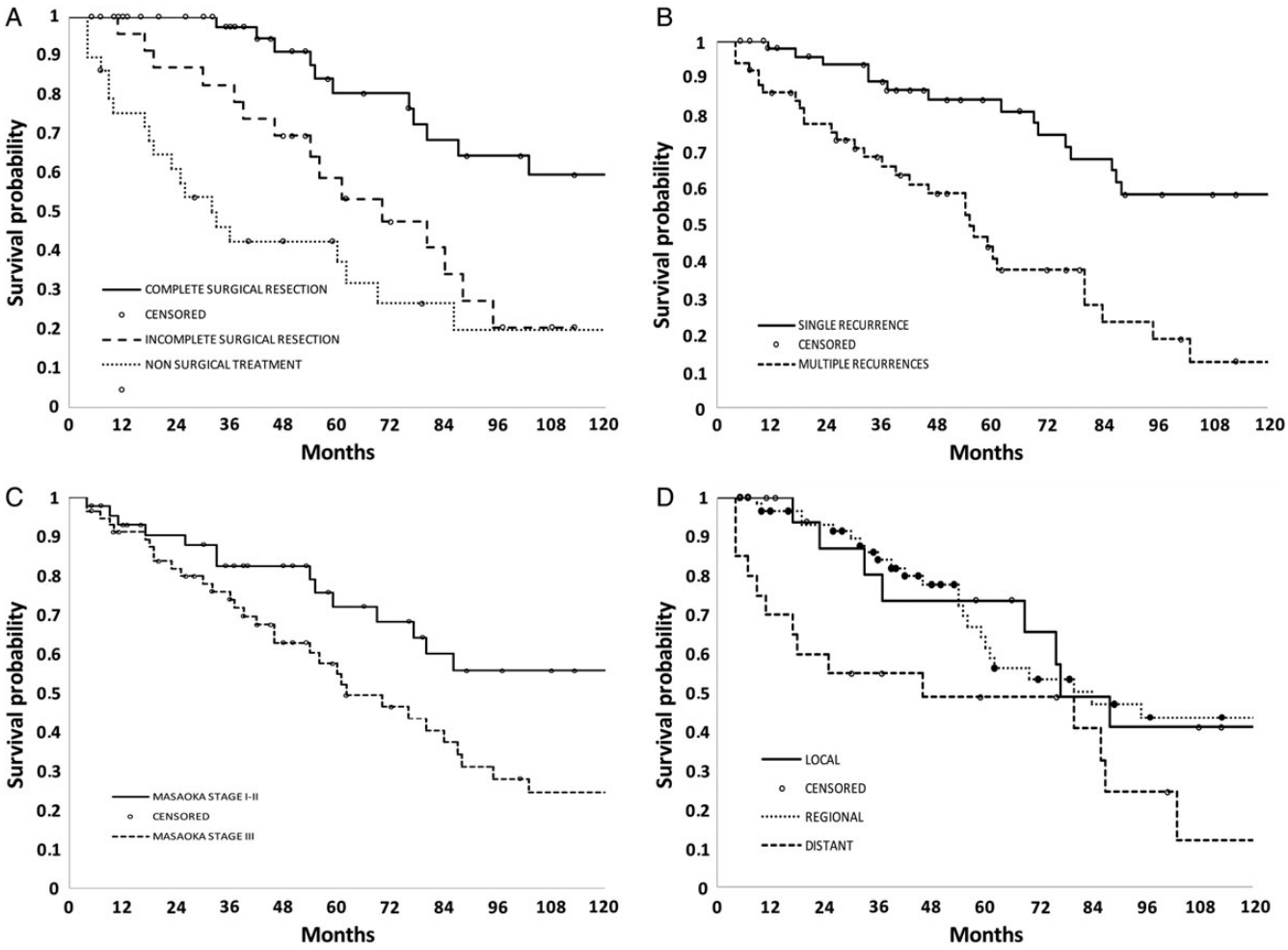

Figure 2: Survival based on (**A**) the type of treatment, (**B**) the number of lesions, (**C**) Masaoka stage of the primary tumour and (**D**) site of recurrence.

thymoma suffer from an inherent selection bias: surgery is reserved for patients with limited disease and better performance status, with an anticipated survival advantage in the surgical group. A survey among members of the European Society of Thoracic Surgeons (ESTS) [22], published in 2011, reported a general agreement regarding the preference (91%) for surgical approach to recurrence when resection is feasible. Some centres reported performing multiple subsequent resections in case of repeated recurrence, and many centres added in their comments that a correct patient selection is crucial and that they proceed to resection only when complete resection may be anticipated. The average rates of 5- and 10-year overall survival after recurrence are 70.9 ± 16.2% (range 40–85.7%) and 49.6 ± 27.4%, respectively, for surgical series. Our results are similar, with 5- and 10-year overall survival rates of 63 and 37%, respectively, for the entire cohort of patients, and 80 and 60% for patients receiving a complete surgical resection. No mortality occurred and complications were reported in 12.3% of operated patients.

Completeness of resection has been found as the most important prognostic factor in both primary thymoma and recurrence [1, 2, 4, 16]. In our experience, such as in most of other studies [2, 3, 5, 9, 20], a radical resection was strongly associated with a better long-term survival and was found as an independent prognostic factor. A macroscopic radical resection of recurrence is reported in a range between 45 and 91% (average: 67.2 ± 20.4%) [20], and in our series, the complete resection rate reached 68.5%. The pattern of relapse and the number of lesions predict the completeness of resection: multiple lesions and mediastinal recurrences with invasion of vessels are the most common cause of failure in redo operations. Single recurrences, independently from the site, also have a favourable prognosis in our and other studies [8, 10]. This may reflect a lower tumor aggressiveness and could be the result of a high probability to achieve a radical resection in this subset of patients. No differences in outcome were found in our experience with respect to myasthenia gravis, disease-free interval and administration of adjuvant treatments. Thymomas are known to respond well to chemo- and radiotherapy; however, no differences were found in patients treated with or without adjuvant therapy, as demonstrated in other series [6, 10]. Masaoka stage I–II of the primary tumour was associated with a better prognosis in statistical analysis, suggesting a less aggressive behaviour of the recurrence. Data available on debulking surgery [2, 3], including ours, tend rather to indicate that this procedure is not highly beneficial for the patient, and that it should be reserved to very selected cases, with alternative treatments being preferred for the others [6]. Based on this evidence, many efforts have been oriented in the last years in the direction of improving the radical resection rate by a better selection of patients or aggressive operations, particularly for multiple pleural relapses. Some authors have described the use of extended resections, from pleurectomy/decortications to extrapleural pneumonectomy, integrated in some cases by induction chemotherapy or intraoperative hyperthermic pleural cavity irrigation or chemoperfusion, both for Masaoka stage IVa or diffuse pleural relapses. The results of these studies are controversial and often poor [23–25]. Another debated issue in this context is the role and the indication for iterative surgery in those cases with new recurrent lesions. The rate of re-recurrence is high also in radical resection (27–50%), and chemotherapy is considered as a candidate of modality for these patients. However, in selected patients with resectable lesions, some authors reported good results with redo resection. Also, in our study, we have not denied patients a redo operation in case of re-recurrence, with 21.9% of patients who were operated more than one time.

In conclusion, surgery for recurrent thymoma is effective and safe, leading to good long-term survival rates. Complete macroscopical resection and single recurrence are associated with better outcome. The role of integrated treatments, particularly when a radical resection is not achievable, needs to be defined.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

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Dr P. Rajesh *(Birmingham, UK):* You had 82 patients in your series, and you operated on a substantial number of them. Tell me what precluded you from not operating on some of these patients.

Dr Marulli: When we looked at the patients that were not operated, usually they were patients with very diffuse distant metastases. Additionally, we had about 10% of patients who were considered since their preoperative assessment deemed them not technically operable, most of all for a very diffuse intrathoracic disease or mediastinal recurrence with diffuse invasion of the vessels or the heart. These were the main reasons of exclusion from surgery of these patients.

Dr Rajesh: Did you follow up this group of patients to see what the natural history was of the disease?

Dr Marulli: Yes. We followed these patients, and the prognosis was very poor. However, in contrast to other studies, we didn't compare this group of patients with the group of surgical patients because they are very different patients. They are patients with a predicted poor prognosis because of a diffuse disease.

So in our opinion, it is not useful to compare this group of patients, despite chemo or radiotherapy is very useful for this kind of patient.

Dr Rajesh: My second question is in the 73 patients you reoperated, you showed that 50 of these patients you had macroscopic complete resection. The other 23, what sort of adjuvant treatment did they receive? Because you talked about ITMIG trying to collect data to make sure that there is consistency in the way we treat these patients with chemotherapy, radiotherapy, or a combination of both. What was your experience with these patients?

Dr Marulli: In our experience, in the entire cohort of patients, more than 40% of patients had adjuvant treatment. The adjuvant treatment was in 30% of cases only chemotherapy, and in other cases mainly a combination of chemoradiotherapy.

The problem of the choice of the type of adjuvant therapy was related to the previous therapies that these patients had. For example, for Stage III patients, probably most of these patients had previous radiotherapy on the mediastinum. So in cases of a local recurrence, it was difficult to do a chemoradiotherapy. These patients were treated only with chemotherapy.

The majority of the patients who had chemotherapy were patients with diffuse pleural relapses, where we were not so sure of a complete resection.