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Prognostic factors after treatment for iterative thymoma recurrences: A multicentric experience*

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ABSTRACT

Objectives: Thymomas are rare neoplasms with a low recurrence rate, which are preferably surgically treated. Iterative thymoma surgery has not been well investigated yet. Study aim is to analyse prognostic factors after iterative recurrence treatment.

Methods: Clinical, pathological and surgical findings of 155 patients, treated for thymoma recurrence in three high-volume centres from 01/01/1990 to 1/07/2017, were retrospectively reviewed. Recurrence patterns/treatment types (surgery or chemotherapy, radiotherapy or combined) were correlated to overall (OS) and disease free survival (DFS).

Results: Myasthenia Gravis was present in 135 (87%) patients. Surgery was performed in 135/155 (87%) patients with 109 (80.7%) complete resections. Sixty (55%)patients experienced a second recurrence surgically treated in 31/60 (52%) cases with 18 (58%) complete resections. Eleven (61%) patients experienced a third recurrence and nine underwent complete resection. Myastenia Gravis (HR: 0.45; 95% CI: 0.20-0.98, p = 0.046), DFS after the initial thymectomy > 36 months (HR: 0.9; 95% CI: 0.96-0.99, p = 0.006) and complete second recurrence resection (HR: 1.45; 95% CI 2.07–10.01, p = 0.010) resulted as independent favorable prognostic survival factor. Despite patient selection bias, rewarding long-term survivals was predictable after iterative thymoma surgery (5 and 10 years survival of 79.6% and 64.6%) while a poor prognosis was observed after CT/RT (5 and 10 years OS of 56.7% and 21.5%), Masaoka stage and DFS > 36 months were risk factor for iterative recurrences.

Conclusions: Myasthenia Gravis and long DFS after thymectomy are favorable survival factors for multiple thymoma recurrences. Iterative surgical treatment is a viable therapeutic option associated to long-term survival if technically and clinically feasible.

1. Introduction

Thymomas are rare neoplasms occurring in the anterior mediastinum, with an annual incidence of about 1–3 cases per million [1] and a usually clinical indolent behavior. The prognosis of treated patients is almost favorable, with a 10-year overall survival of 70–90%

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in stages I-II, 46–88% in stage III and 24–70% in stage IV according to Masaoka-Koga staging system [2–6]. Recurrences are quite uncommon, occurring in about 10–15% of patients after radical resection, sometimes even more than a decade after thymectomy [7,8]. The mediastinum and pleura are frequently involved, while extrathoracic localizations are quite rare [9].

Although thymomas recurrences are considered a systemic disease, surgical treatment is recommended for "clinically fit" patients and in case of technical feasibility, considering the indolent behavior of the tumor [10,11]. Re-do surgery compared with other treatment approaches, such as chemo- /radiotherapy (CT/RT) or other local ablation therapies, demonstrated survival advantages [12], even if prospective randomized clinical trials are currently unavailable.

Scientific literature investigates mostly surgical (early/long term) outcomes after first recurrence but the role of iterative recurrence surgery, (second, third etc recurrences after radical surgical attempts) has not been well investigated yet [13–15]. This restriction is mainly related to iterative recurrence rarity - because thymoma has a low incidence and consequently an even lower recurrence incidence - but also to technical difficulties to perform re-do surgery. Moreover, a discrete knowledge regarding the risk factors for recurrence after thymectomy with complete resection exists [16,17] while risk factors for a further disease relapse after first thymoma recurrence treatment are not been investigated till now.

The aims of this study are:

1) to report long-term results after treatment for first thymoma recurrence;
2) to identify the risk factors for a further relapse after re-do surgery
3) to describe the long-term results of patients who underwent iterative surgery for recurrences

2. Methods

Clinical and pathological records of patients treated for recurrent thymoma from 1/1/1990 to 1/7/2017 in 3 high volume centers were collected and retrospectively reviewed.

The Promoting Center selected other institutions based on volumes, experience in managing thymoma recurrences and treatment strategy/guideline adoption to assure treatment homogeneity between centers. Despite some discordance between the different tumour boards, the overall "treatment policy" was essentially similar.

Thymomas were classified using the Masaoka-Koga staging classification [2], but also with the 8th edition of the Tumor Node Metastases staging system for thymic neoplasm [18]. WHO classification system for thymic epithelial tumours [19] was used to group patients classified with type A, AB and B1 histology in a subgroup labelled "low grade" patients; B2 and B3 were considered as "high grade" patients. In case of mixed histology, thymoma was categorized according to the highest histologic type (example: B2-B3 thymomas were categorized as B3). A pathological revision of all specimens was conducted by dedicated pathologist in each involved centre. Thymic carcinomas were excluded from the analysis, because biologically and prognostic different from thymomas. We analysed the localization quantity (single vs multiple recurrences based on the number of relapse foci detected), histology (also considering the change in histology from a lower grade to an higher one), resection completeness, disease free survival (DFS) after thymectomy, organ involvement using the *ITMIG(International Thymic Malignancy Interest Group)* definitions for local, regional and distant recurrence as reported just below [20]:

- "- local recurrence: disease presenting in the bed of the thymus or tissue immediately contiguous with the resected thymoma,
- - regional recurrence: intrathoracic disease not immediately contiguous with the thymus or the previously resected thymoma
- distant recurrence: extrathoracic recurrence and intra-parenchymal pulmonary nodules".

We performed preoperatively Computed Tomography scan with contrast and magnetic resonance, if needed [11,21] to validate reoccurrences. In the last 10 years, 18-fluorodesossyglucose positron emission tomography was used to confirm in some patients the presence of suspected reoccurrence. Thymoma recurrences were considered as such after careful radiological evaluation [11,20] while pathological pre-treatment confirmation was obtained in all doubtful cases.

2.1. Surgery, postsurgical treatment and follow-up

The surgical approach in all centers consisted of complete thymoma, entire thymus gland and surrounding fat resection in all cases [4,7]. The resection was extended, with the aim to obtain a macroscopic complete resection, in case of surrounding organ infiltration or uncertainties.

Regarding the recurrence treatment indication, a multidisciplinary tumour board, involving at least a thoracic surgeon, radiologist, oncologist and radiotherapist, decided on a case-by-case basis the treatment approach, recommending surgery if the outcome would result in a radical resection.

Although it is extremely difficult to retrospectively reconstruct the decision-making process and considering few unavoidable discrepancies between the different tumour boards, the overall policy of treatment was essentially similar and basically based on two main factors: the baseline performance status of the patient (ECOG score) and the resectability of the recurrence. The latter was judged by an expert thoracic surgeon taking into account the localization and the number of recurrence(s). Thus, a cancer-directed surgery was proposed only in patients with radiologically resectable disease (radical intent) judged fit for surgery as a first treatment or following neoadjuvant chemotherapy.

Moreover, in presence of MG, a dedicated and expert neurologist managed the neurological disorder and evaluated, in association with the surgeon, the proper timing for surgical treatment. Recurrence surgery was also conducted with the aim to achieve a macroscopic complete resection, even in case of distant recurrences or diffuse pleural involvement (total pleurectomy). In selected cases, hyperthermic intrathoracic chemotherapy (HITHOC) was associated with complete pleurectomy. A good pulmonary performance was mandatory in case of lung resection.

The surgical access was decided based on recurrence localization. Thoracotomy was mainly performed in case of intrathoracic recurrence and redo-sternotomy in case of mediastinal recurrence. After adhesions lysis, a carefully examination of all pleural cavity and of the mediastinum was conducted. After blunt dissection, an en bloc resection with the aim to obtain 1 cm of macroscopically free margin was performed. In case of parenchymal or other organ resection, carefully palpation was conducted for other metastases identifications. If resection of diaphragm, pericardium, great vessels or chest wall was performed, reconstruction using prosthesis was done. In case of incomplete resection, residual tumor was signaled leaving titanium clips for helping complementary treatments.

The medical oncologist or the radiotherapist decided the postsurgical treatment approach, combined or single CT or RT, based on recurrence characteristics, patient clinical conditions and previous treatment incidences (induction or adjuvant treatments for the initial thymoma).

CT regimens changed along the study period, following always the most recent guidelines available [11,12,21]. Cisplatin-based combination regimens and fractionated RT (55–66) were compatible with eventual previous treatments in non-surgical patients.

"Iterative recurrences" refer to patients with one or more relapse after the first recurrence treatment.

All hospitals conducted the follow-up after thymectomy following a substantially similar policy. In case of early stage thymomas (Masaoka-

Koga stage I-II) a clinical evaluation and a thoracic Computed Tomography scan was performed after surgery every 3–6 months for two years, which was extended to annual evaluation for 5 years and biennial follow-up for other 5 years. Instead, stage III/IV thymomas, clinical evaluation and thoracic Computed Tomography scan scan was carried out every 3–6 months for 2 years and after annually for 10 years at least. Patients affected by MG undergone also a neurological surveillance (clinical evaluation and lab tests), and Computed Tomography scan was anticipated in case of clinical worsening of symptoms.

2.2. Statistical analysis

Descriptive statistics were used to describe the participants included in the study. Continuous variables were defined as mean, standard deviation or as median, interquartile range, where appropriate. Categorical variables were defined as absolute and relative percentages. Variables considered in the statistical analysis were age, sex, comorbidities, Myasthenia Gravis (MG), integrated treatment such as induction or adjuvant RT or CT. OS was calculated using the interval between the first recurrence treatment and the last follow-up or death for all causes, if not differently specified. DFS was calculated beginning from time of surgery to the occurrence of any recurrence. Patients were classified disease free if follow-up clinical evaluation and Computed Tomography scan resulted negative. The Kaplan-Meier method was used to calculate survival rates and to plot survival curves. The prognostic variable significance of the OS and DFS was estimated using the Cox's proportional hazards model, after testing the proportional hazard assumption using Schoenfeld residuals. All tests were two-sided. Statistical significance was set at $p < 0.05$. A multivariate Cox hazard model was developed using stepwise regression (forward selection), selecting significant variables upon univariable analysis, to identify independent outcome predictors. Enter limit and remove limit were $p = 0.10$ and $p = 0.15$, respectively. All statistical analyses were performed using Stata software (StataCorp.2015.Stata Statistical Software: Release14. College Station, TX:StataCorpLP).

3. Results

During the study period a total of 160 patients were treated for thymoma recurrence among the different centers.

Five patients with macroscopic residual of disease after thymectomy were excluded from the analysis, thus the final analysis was conducted on a total of 155 patients treated for recurrent disease after radical thymectomy. Of the 155 patients, 135 (87%) underwent surgical treatment, obtaining a complete resection in 109 (80.7%) cases. Sixty (55%) patients experienced a second recurrence that was surgically treated in 31/60 (52%) cases, achieving R0-resection in 18 (58%) cases. Tables 1 and 2 reports clinical and pathological patient characteristics. A third recurrence occurred in 11 (61%) patients, surgically treated with complete resection in 9 (82%) patients (supplemental figure). Considering all iterative surgical procedures, post-operative mortality was nil while 90 days mortality occurred in only one patient after second recurrence surgery.

Regarding the 1 st recurrence, we observed distant relapse in 23 (14%) patients according to ITMIG classification, which were 10 pulmonary, 5 diaphragmatic and 8 liver/peritoneum recurrences. In all cases surgery was performed expect for one patient with multiple pulmonary recurrences, where R0-resection was not feasible.

Among 20 patients considered as not suitable for a second surgical treatment (first recurrence resection), 19 underwent complete thymoma resection. All of them had intrathoracic-loco-regional disease, which was classified as multiple in 15 cases and single in 5 cases. Surgery was not considered, because of high incomplete resection risk. The 15 multiple localizations patients received CT. The 4 single localization patients received RT/CT and one patient radiofrequency ablation.

Table 1
Population Characteristics.

Variable	
Patients	155
Sex	
Male	85 (54.8%)
Female	70 (45.2%)
Age	45 (± 12,7)Mean
Myasthenia Gravis	107 (69%)
Induction Therapy	14 (9%)
Surgical approach	
Sternotomy	125 (80.6%)
Sternotomy + Thoracotomy	24 (15.5%)
VATS	6 (3.9%)
Radicality	
R0	128 (82.5%)
R1	27 (17.5%)
Masaoka-Koga stage	
I	9 (5.8%)
II	46 (29.7%)
III	78 (50.3%)
IVa	22 (14.2%)
WHO Classification	
A-AB	14(9%)
B1	29(18.7%)
B2	54(34.8%)
B2-B3	40(25.8%)
B3	17(10.9%)
Unknown	1(0.8%)
Adjuvant Therapy	76(49%)

Table 2
Recurrences characteristics in patients with I, II and III recurrences. Data are referred to patients with complete resection after I and II recurrence respectively.

	I Recurrence	II Recurrence	III Recurrence
Number of Patients	155	60	11
Pattern of recurrence (ITMIG)			
Local	21 (13.5%)	18 (31%)	
Regional	111 (72.2%)	29 (48.4%)	8 (72.7%)
Distant	23 (14.3%)	13 (21.6%)	3 (18.2%)
Single	44 (28.4%)	22 (36.6%)	5 (45.5%)
Multiple	111 (71.6%)	38 (63.4%)	6 (55.5%)
Site of recurrence			
Pleura	77 (49.6%)	20 (33.3%)	5 (45.5%)
Parenchyma	10 (6.4%)	10 (13.3%)	3 (27.2%)
Both	21 (13.5%)	5 (8.4%)	1 (9%)
Other	47 (30.5%)	25 (45%)	2 (18.3%)
Treatment of recurrence			
Complete resection	109 (70.4%)	18 (30%)	9 (81.8%)
Incomplete resection	26 (16.7%)	13 (21.6%)	
CT/RT	20 (12.9%)	29 (48.4%)	2 (18.2%)
Mortality (Surgical Patients)			
Peri-operative	0	0	0
90 days	0	1 (3.2%)	0
Adjuvant CT/RT	78 (50.3%)	31 (51%)	4 (36.5%)
Myasthenia Gravis	107 (69 %)	40 (66.6%)	9 (81.8%)
WHO upgrading	24 (15.5%)	6 (10%)	2 (18.2%)
Disease Free Interval(months)	78 (± 102)	54 (± 44.3)	38 (± 27.2)
≤36 months	46 (29.6%)		
Overall Survival (months)	135 (± 81.8)	156 (± 98.7)	184 (± 62.7)
	115 (median)	121 (median)	168 (median)

Sixty (38.7%) patients died during follow-up due to cancer-related causes, 57 (36.7%) are disease free and 38 (24.6%) live with recurrences.

3.1. Overall and disease free survival

Five and ten-year OS after first recurrence treatment were 70.2% and 44.4% respectively. Mean follow-up was 65.7 ± 53.7 months

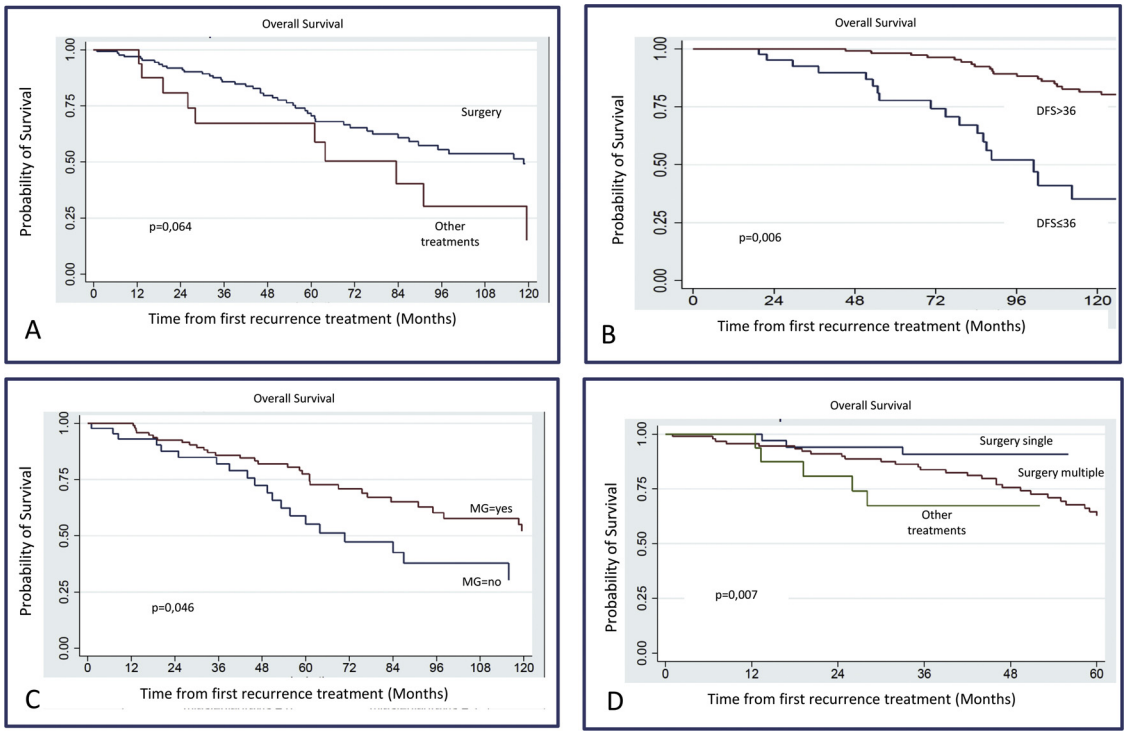

Fig. 1. Overall Survival (OS) after first recurrence treatment according to kind of treatment(a),Disease Free Survival(DFS) after thymectomy(b), presence of Myasthenia Gravis(MG)(c) and according the number of localization and other treatments(d).

Table 3
Multivariable analysis and Risk factors for multiple recurrences.(DFS:Disease Free Survival).

Multivariable analysis

Variables	Hazard Ratio	*p*	[95%Confidence Interval]
Age	1.01	0.433	0.98 - 1.04
Radicality (yes vs no)	0.35	0.080	0.11 - 1.13
Myasthenia Gravis (yes vs no)	0.45	0.046	0.20 - 0.98
Number (Multiple vs Single)	2.13	0.136	0.78 - 5.78
DFS (≤36vs > 36months)	0.97	0.006	0.96 - 0.99

Risk Factors for Iterative Recurrence

Variables	Odds Ratio	*p*	[95%Confidence Interval]
Gender	1.36	0.342	0.72 - 2.57
Age	0.98	0.249	0.96 - 1.01
Masaoka-Koga Staging III-IVvsIII-IV	2.17	0.023	1.11 - 4.25
Histology High vs Low ITMIG	0.81	0.577	0.40 - 1.66
Regional vs Local	1.59	0.331	0.62 - 4.08
Regional vs Distant	0.62	0.430	0.56 - 3.76
Distant vs Local	1.46	0.345	0.82 - 1.73
Number of localizations Multiple vs single	1.27	0.507	0.62 - 2.59
DFS Thymectomy > 36months vs ≤36months	0.21	0.001	0.08 - 0.52

Female gender (p = 0.013), MG (p = 0.016), age (p = 0.016), single localization (p = 0.010) and DFS > 36 months (p < 0.001) resulted as favorable prognostic factors. Furthermore, surgical treatment showed survival benefits compared to other treatments, with a 5 and 10-year OS of 70.5% and 49.1% vs 67.3% and 15,1%, even if not statistically significant (p = 0.064) (supp. Table 1,Fig. 1A). No differences in OS comparing low grade vs high grade thymomas (p = 0.914). Multivariable analysis confirmed as independent favorable prognostic factors the DFS after first recurrence treatment, (HR 0.9; 95% CI 0.96-0.99, p = 0.006) (Fig. 1B) and presence of MG (HR 0.45, 95% CI 0.20-0.98, p = 0.046) (Fig. 1C) (Table 3).

In particular, 5 and 10-year OS in patients with and without MG were 77.4% and 52.8% vs 55.2% vs 30.2% (p = 0.016) while 5 and 10-year OS in patients with DFS > 36 vs DFS ≤ 36 months were 72.7% and 49.2% vs 63.9% and 32.9% (p < 0.001), respectively.

Patients with single metastasis who underwent surgical resection had a significantly better OS, independently of the localization, compared to patients with multiple recurrences who underwent surgery (HR 3.05; 95% CI: 1.36–6.8; p = 0.007) or compared to patients who underwent other treatments (HR 4.50; 95% CI: 1.70–11.9; p = 0.002). Moreover, patients with multiple surgically treated recurrences are associated to better survival than patients excluded from surgery and addressed to other treatments (HR1.91; 95% CI: 0.96–3.79; p = 0.064) (Fig. 1D).

No statistically significant differences in OS comparing patients who underwent complete versus incomplete resection were demonstrated, even if a trend in favor for the first group was noted (p = 0.086).

Analyzing the different prognostic factors for DFS after surgical treatment, incomplete resection (p = 0.001) and Masaoka-Koga stage III/IV at the moment of thymectomy (p = 0.018) are significantly associated with a shorter DFS, also distant localization was, even though not statistically significant (HR 2.21, 95% CI 0.74–2.40, p = 0.066). Multivariable analysis confirmed Masaoka-Koga stage III/IV at the moment of thymectomy as independent risk factor for a shorter DFS after first recurrence resection (HR 4.95, 95% CI 0.72–2.17, p = 0.041), while statistical significance was not reached for resection completeness (HR 1.62, 95% CI 0.97–2.70, p = 0.062).

3.2. Iterative recurrences and treatments

Sixty patients had a second recurrence after radical treatment, which was loco-regional in 47 and distant in 13 patients of which 10 were with lung involvement, 2 with peritoneal implants and one with

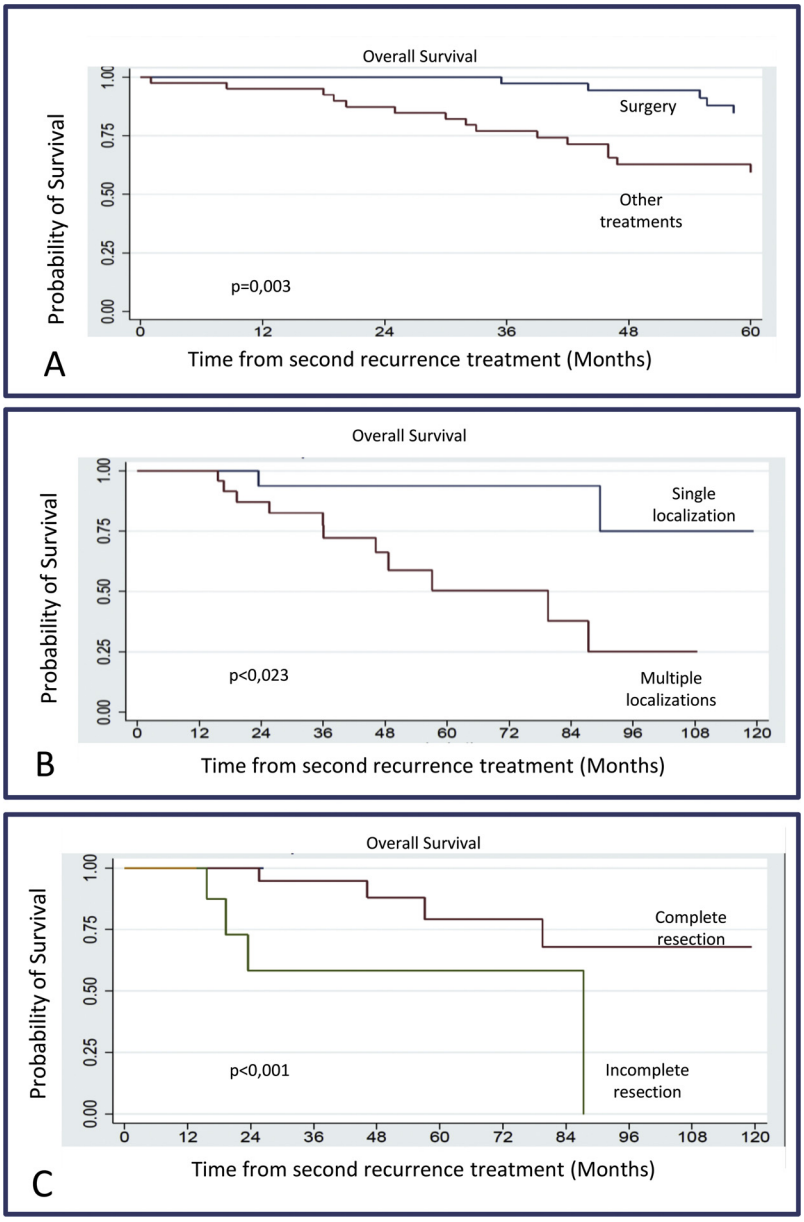

Fig. 2. Overall Survival (OS) after second recurrence treatment according with the treatment(a), with the number of localizations(b)and completeness of resection(c).

rib metastasis. Surgical treatment in patients with distant localizations was considered suitable only in patients with single localization (8 cases).

Surgery was performed in 31 patients, obtaining a complete resection in 18 patients. Regarding the other treatments, 19 received CT, 4 RT only, 2 RT/CT, 3 only supportive care and for one patient no information was available.

At univariable analysis, surgical treatment versus other treatments (84.5% vs 59.4%, $p = 0.003$), single versus multiple localization (93.7% vs 50.4%, $p = 0.023$) and complete versus incomplete resection/other treatments (79.1% vs 58.3%, $p < 0.038$) are associate with a 5-year OS improvement (Fig. 2a–c).

At multivariable analysis only surgical complete resection resulted as an independent prognostic factor (HR1.45, 95% CI: 0.20–10.01, $p = 0.010$).

Finally, three or more recurrences occurred in 11 patients after complete resection, and, in particular, single distant recurrences occurred in 3 patients - all pulmonary and surgically treated. Iterative surgical resections have been proposed in 9 patients (range 1–4). Surgical treatment seems to have a favorable impact compared to other treatment approaches in surgical patients, even if not statistically significant (HR 3.7; 95% CI 0.67-21.2. $p = 0.126$).

Five and 10 year survival was 79.6% and 64.6% in patients treated with surgery for all iterative recurrences. A remarkable difference is observable comparing survival after surgery with survival after chemo or radiotherapy (56.7% and 21.5% respectively, HR 2.96; 95% CI 1.69–5.20; $p < 0.001$) (Fig. 3a). Moreover, in the surgically treated group, the number of iterative treated recurrences (one, two or three or more) did not affect the prognosis ($p = 0.226$) (Fig. 3b).

We identify Masaoka-Koga stage ($p = 0.023$) and a DFS from thymectomy to first recurrence $\leq$36months ($p = 0.001$) as risk factors (Table 3), analyzing the risk factors for iterative recurrences after the first complete recurrence resection.

4. Discussion

In our multicentric cohort, consisting of recurrent thymoma patients, MG was identified as favorable independent prognostic factor.

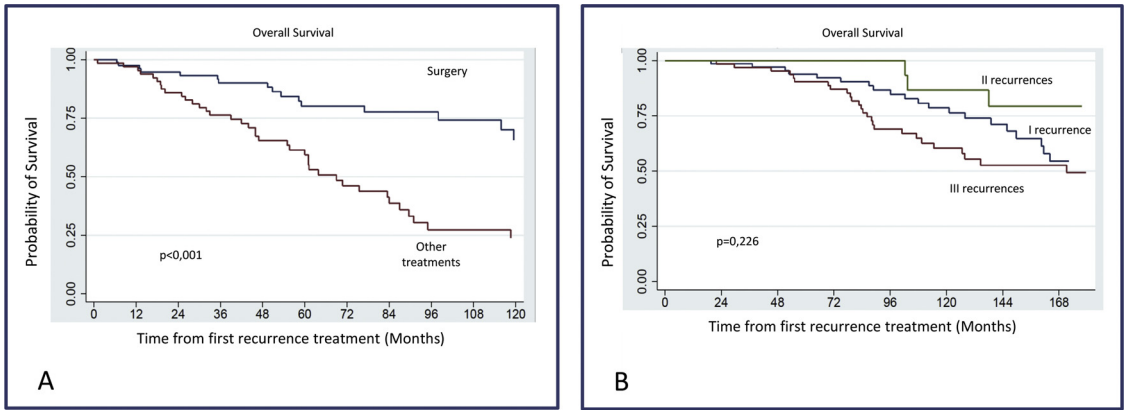

Fig. 3. Overall survival in patients who underwent iterated surgery for every repeated recurrence compared to patients who underwent other treatments (a); Overall survival according to the number of relapses in patients surgically treated (b).

This issue is very debated in literature with controversial results. Filosso and colleagues reported an association between MG and early stage thymomas, resulting in direct association between MG and positive prognosis, even if not confirmed in multivariable survival analysis [22]. Other authors reported a different impact on survival based on thymoma stage, with a poor prognosis in early but better prognostic outcomes in advanced stages [23]. In the present study,we did not identify remarkable differences in terms of localization quantity, histology type or longer DFS in thymoma patients with or without MG. Moreover, our series is influenced by the fact that centers involved in the present study are considered national landmarks for the treatment of myasthenia gravis, explaining the huge percentage of MG in our population. Considering that such patients had a dual strict surveillance (oncological and a neurological, from a theoretical point of view, a relapse of disease could be early diagnosed, this leading to a potential survival advantage. In absence of a clear evidence on that, we can assume that the relationship between MG and thymoma prognosis remains unclear and should be further investigated.

We analyzed outcomes, stratifying prognosis according to recurrence characteristics, to determine the effectiveness of surgical treatment in single metastasis compared to multiple metastases or other treatment approaches, as reported above. Surgery was proposed to a heterogeneous patient group, ranging from single loco-regional metastasis to diffuse pleural involvement, requiring pleurectomy in combination with HITOC or extrathoracic spreading treated with peritoneal or liver resections. In our study and in agreement with other authors [24], surgical resection showed a better survival rate after first recurrence treatment, even if not statistically significant. Discordant results reported in literature might be related to treatment indication; surgery in single or oligo-metastastic disease in patients in good clinical conditions; CT/RT in diffuse and unresectable disease or patients with poor clinical conditions [15,25].

Patients who underwent iterative surgery for repeated recurrences are associated with better survivals when compared to patients who underwent other treatment approaches. Other authors previously suggested the efficacy of iterative surgery [4,25], which was confirmed by Fiorelli et al. [15] and by our results, reporting positive survival outcome. However, there is a discrete selection bias (see below) that should be consider (in this study as in others) and that substantially precludes any conclusion about the absolute superiority of surgical treatment over “other modalities” in thymoma recurrences.

Thymoma recurrence should be considered as a “chronic/long term disease”, because the recurrence rate after complete resection is very high compared to the recurrence rate after thymectomy, which is 55% after the first recurrence and 61% after the second complete recurrence resection in our study, compared to 50–69% in literature [15,25]. Thus, one of the factors that probably had a significant impact in long-term outcomes of recurrent thymoma patients was correlated to the treatment type of the further recurrences. In fact, in our study, the surgical treatment of the second relapse is an independent prognostic factor for survival in all patient subgroups. Moreover, OS was significantly better in patients selected for iterative surgery compared to those excluded from surgery and addressed for other treatments, which is in agreement with results by Fiorelli [15]. Nevertheless, as reported above, a patients selection bias may partly explain these results.

The favorable outcome after surgical treatment compared to CT/RT may also be explained considering reduced therapeutic possibilities for secondary or iterative recurrences. Indeed, RT may be contraindicated, if previous administered, while CT might not be indicated due to patient conditions or previous treatments. Moreover, restricted chemotherapic regimens were available in the previous 5–10 years (compared to now), reducing in a quite consistent way past treatment options. In our study, 17/60 s recurrence patients had induction therapy before thymectomy, 76 had adjuvant therapy after thymectomy, 78 had adjuvant therapy after first recurrence and 24 patients received multiple RT/CT considering the treatment for the thymectomy and the first recurrence (supp.table2). This treatment overlap and second or third line CT need may influence the efficacy of these treatments, explaining the significant improvement in survival when surgery is performed independently by the quantity of localization for iterative recurrences [10,11]. On the other hand, integrated treatments before or after recurrence surgery may influence the prognosis of these patients, but several combinations of treatment produce several subgroups (few cases in each of them) this limiting a lot the statistical analysis. Thus, it is very hard to get a reliable statistical analysis and to draw definitive conclusions in the present study. Further prospective studies may be useful to clarify this intriguing issue.

In our experience, surgical treatment seems to be a valid option to obtain rewarding long-term survivals in recurrent thymoma patients selected for surgery (patients with potentially resectable tumors and clinically fit for surgery). A direct comparison between surgery and CT/RT is methodologically not correct because a patients selection bias is present and it may influence our results.

Another interesting issue concerns the biological behavior of thymoma, which was very variable in our experience. In fact, in our analysis we identified a short DFS between thymectomy and recurrence as an independent prognostic factor for OS and for iterative recurrences. To our knowledge, only Marulli [25] analyzed the role of this parameter in recurrent thymomas, without a significant association to OS. Marulli categorized the DFS as $>$ or $<$ to 60 months, compared to our study with a DFS cut-off $>$ or $\leq$ to 36 months, which can be defined as early relapse time, considering the mean relapse time for thymoma of 60 months [7,8]. As logical consequence, a shorter DFS may be a direct sign of an aggressive disease, but, in our study, a short DFS was

independent of Masaoka-Koga stage, B3 histology, microscopical residual disease of the initial thymectomy and migration in histology. This condition suggests that an early relapse time may be considered as an indication to pre- or post-operative treatment of the recurrence with the aim to treat a potentially aggressive disease.

Advanced Masaoka-Koga stage resulted as a risk factor for iterative relapses, suggesting that the recurrent thymoma needs a more general consideration. Indeed, thymoma stage is not only related to the possibility to develop a first recurrence [10,11,25], but also to the possibility to develop iterative relapses, even after an initial radical thymectomy. Interestingly, in our study adjuvant therapies had no effect on OS or DFS, as reported by other authors [8,13,25], confirming that the role of these treatments in this kind of patients is still unclear.

Finally, a consideration regarding the possible role of debulking surgery in these patients may be reported. We showed an improvement in survival in R0 patients compare to incomplete resections, but we also observed a better (although not statistically significant) outcome in patients with incomplete resection compared to patients underwent RTCT (data not showed). Our data are comparable with previous literature [14,15,24], but a survival comparison of these subgroups should be carefully evaluated due the strong bias in patients selection. Thus, at this moment is extremely hard to support the routinely use of debulking surgery in recurrent thymoma patients because no robust evidences support this strategy of care. Some cases are an exception to this (i.e. palliative debulking surgery in case of ulcerative mass). At the same time, we strongly encourage investigation on its role in the framework of a clinical trial and probably in combination with other complementary therapies such as HITOC.

4.1. Limitations and strengths

This study presents several limitations. First, it is a retrospective multi-institutional study and this should be considered when interpreting the overall results of the present analysis. Furthermore, thymoma rarity and, recurrence as well as the long observation period are factors that strongly hamper a randomized clinical trial planning on this topic, as clearly notable by reviewing the pertinent literature [8,12,14,15,24,25]. Secondly, a patient selection bias may be considered. Indeed, despite it's extremely hard to retrospectively reconstruct the decision-making processes, surgical treatment was proposed especially in potentially resectable disease (more favorable stages) and in patients able to tolerate this approach, limits our results further. This is an intrinsic bias present in the major part of papers, analyzing thymoma recurrence treatment. Therefore, in the absence of a balanced control group, we cannot exclude that patients selected for surgery might have had a positive outcome even without surgery. Nevertheless, current guidelines suggest a surgical approach for thymoma recurrence, whenever possible [11,21]; thus the choice of a different approach may be in contrast with patient's survival possibility and correct therapeutic indications. On the basis of the previous considerations, the aim of this study is to analyze the prognostic factor and the efficacy of the iterative surgery in thymoma recurrences, and we showed a remarkable survival using this strategy, while a direct comparison with other treatments should be considered with caution on the basis of the patient's selection bias.

Finally, we explore the feasibility and long-term results after surgery with curative intent in recurrent thymomas even when the relapse pattern was a diffuse pleural involvement or distant metastases, underlining surgical feasibility for relapse even in case of distant, multiple localizations and iterative surgery, confirming the validity of this therapeutic strategy in a large multi-institutional database.

5. Conclusion

Patients with thymomas recurrence represent various disease manifestations that may be considered as "chronic/long term". Patients affected by MG and with a DFS after thymectomy > 36 months had a better OS prognosis, such as patients who underwent surgical treatment for single localization. A short DFS and advanced Masaoka-Koga stages at time of diagnosis are risk factors for iterative recurrences.

Patients who were candidate for iterative surgery for further recurrences had a rewarding long-term survival while those patients who underwent other treatments presented a poor prognosis, also if a direct comparison between the two groups is not feasible thus precluding the demonstration of an absolute superiority of surgery in this setting.

Nevertheless, considering also the good early results after iterative surgery reported herein, we recommend this approach in patients with iterative recurrences, which are considered "fit" for surgery and in case of technical feasibility.

Ethical statement

The study was approved by the Ethic Committee of our Centre

Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.09.024.

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