ORIGINAL ARTICLE

The International Thymic Malignancy Interest Group Classification of Thymoma Recurrence: Survival Analysis and Perspectives

Marco Chiappetta, MD,[a,b] Filippo Lococo, MD,[a,b,*] Edoardo Zanfrini, MD,[a,b] Rossana Moroni, MS,[c] Vittorio Aprile, MD,[d] Francesco Guerrera, MD,[e] Dania Nachira, MD,[a,b] Maria Teresa Congedo, MD,[a,b] Marcello Carlo Ambrogi, MD,[d] Stylianos Korasidis, MD,[d] Marco Lucchi, MD,[d] Pier Luigi Filosso, MD,[e] Enrico Ruffini, MD,[e] Isabella Sperduti, MS,[f] Elisa Meacci, MD,[a,b] Stefano Margaritora, MD[a,b]

[a]*Thoracic Surgery, Fondazione Policlinico Universitario Agostino Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy*
[b]*Università Cattolica del Sacro Cuore, Rome, Italy*
[c]*Office of the Scientific Director, Fondazione Policlinico Universitario Agostino Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy*
[d]*Thoracic Surgery, Cardiac Thoracic and Vascular Department, University of Pisa, Pisa, Italy*
[e]*Thoracic Surgery, University of Torino, Torino, Italy*
[f]*Biostatistics, IRCCS Regina Elena National Cancer Institute, Rome, Italy*

Received 16 November 2020; revised 9 June 2021; accepted 4 July 2021
Available online - 10 July 2021

ABSTRACT

Introduction: The International Thymic Malignancy Interest Group (ITMIG) classifies thymoma recurrences on the basis of the topographic location, but its effectiveness in prognosis prediction has not been well investigated yet. Aims of this study are to analyze survival outcome of patients surgically treated for thymoma recurrence according to the ITMIG recurrence classification and to investigate possible alternatives.

Methods: From January 1, 1990, to January 7, 2017, data on 135 surgically treated patients for thymoma recurrence from three high-volume centers were collected and retrospectively analyzed. Patients were classified according to the ITMIG classification as local, regional, and distant. The ITMIG classification and alternative classifications were correlated to overall survival (OS).

Results: According to the ITMIG classification, recurrence was local in 17 (12.5%), regional in 97 (71.8%), and distant in 21 (15.7%) patients, with single localization in 38 (28.2%) and multiple localizations in 97 (71.8%). The 5- and 10-year OS were 79.9% and 49.7% in local, 68.3% and 52.6% in regional, and 66.3% and 35.4% in distant recurrences, respectively, but differences were not statistically significant ($p = 0.625$). A significant difference in survival was present considering single versus multiple localizations: 5- and 10-year OS of 86.2% and 81.2% versus 61.3% and 31.5% ($p = 0.005$, hazard ratio = 7.22, 95% confidence interval: 0.147–0.740), respectively. Combining the localization number with the recurrence site, ITMIG locoregional single recurrence had a statistically significant better survival compared with patients with ITMIG locoregional multiple recurrence or ITMIG distant recurrence ($p = 0.028$). Similarly, a significant difference was present considering intrathoracic single versus intrathoracic multiple versus distant recurrence ($p = 0.024$).

Conclusions: The ITMIG classification for thymoma recurrence did not have significant survival differences comparing local, regional, and distant recurrences. Integrating this classification with the number of the localizations may improve its effectiveness in prognosis prediction.

*Corresponding author.

Disclosure: The authors declare no conflict of interest.

The abstract has been presented at the 10th International Thymic Malignancy Interest Group Annual Meeting, Niagara-on-the-Lake, Canada, 10 to 12 October 2019.

Address for correspondence: Filippo Lococo, MD, Thoracic Surgery, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00100 Rome, Italy. E-mail: filippo.lococo@policlinicogemellli.it

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2021.07.004

Keywords: Thymoma; Recurrence; Surgery; ITMIG

Introduction

Thymomas are rare, but they are the most frequent tumors of the anterior mediastinum, originating from thymic epithelial cells.[1] Despite their usual indolent clinical behavior, thymoma recurrences are even more rare, with extremely variable recurrence rates estimated between 15% and 50%.[2,3] Indeed, the recurrence time may vary according to the initial thymoma stage, with patients with stage I thymoma experiencing recurrences also 10 to 20 years after surgical treatment compared with 3 years in those with stages II, III, and IV. Most recurrences occur inside the mediastinum/pleural cavity,[4,5] whereas distant recurrences are very rare.[6–9]

Various prognostic factors have been identified, which predict survival in thymomas, such as the Masaoka classification, histologic type, radicality of resection, and tumor size; however, few studies in literature evaluate and report data regarding the identification of prognostic factors for recurrences.[6,10,11] The International Thymic Malignancy Interest Group (ITMIG) recently created a classification for thymoma recurrences considering the recurrence site classifying the recurrence as local (mediastinum), regional (pleural cavity), and distant (i.e., hematogenous spreading). Nevertheless, the prognostic role of the recurrence site is still debated, with only few studies analyzing this factor in a heterogeneous and limited group of patients.[11,12] Moreover, the ITMIG classification was not designed for survival analysis, and its validation on a treated cohort of patients is still missing in literature. Finally, considering the rarity of the disease and the treatment option, a classification permitting prognosis stratification may be extremely useful to plan adjuvant treatments. Aims of this study are as follows: (1) to evaluate the long-term survival outcome according to the ITMIG classification in a surgically treated cohort of patients with thymoma recurrence and (2) to investigate alternative classification systems, which include other prognostic parameters.

Materials and Methods

This multicentric, observational, retrospective, cohort study was reviewed and approved by the Fondazione Policlinico Universitario Agostino, Gemelli, ethics committee and partner institutional review boards (study identification: 3027). Data on patients treated for thymoma recurrence from January 1, 1990, to January 7, 2017, in three high-volume centers were collected and retrospectively reviewed. The three centers were selected because they had high-volume and long-term experience in thymoma recurrence management.

Primary Thymoma Workout

The surgical approach during primary thymectomy consisted in complete excision of the thymoma, the entire thymus gland, and the surrounding mediastinal fat. An extended resection was performed in case of surrounding organ infiltration (e.g., lung, pericardium, pleura), to obtain a complete macroscopic resection. R0 resection indicated no residual tumor tissue; R1 resection indicated microscopic residual tumor tissue. Patients with R2 and debulking surgeries were excluded from the study.

The pathologic findings of the primary thymoma were classified using the Masaoka-Koga staging classification,[13,14] the eighth edition of the TNM staging system for thymic neoplasm,[15] and the WHO classification system for thymic epithelial tumors.[16]

Follow-up after thymectomy was conducted as follows: In case of early stage thymomas (Masaoka-Koga stages I–II), a clinical evaluation and a thoracic computed tomography (CT) scan was performed after surgery every 3 to 6 months for two years followed by an annual evaluation for 5 years and biennial follow-up for subsequent 5 years.

In contrast, in stage III/IVa thymomas, clinical evaluation and thoracic CT scan were carried out every 3 to 6 months for 2 years and annually after for 10 years at least.

Patients with thymoma with myasthenia gravis (MG) underwent an additional neurologic surveillance, and a CT scan was anticipated in case of clinical worsening of symptoms.

Recurrence Workout

All patients were preoperatively analyzed to evaluate the possibility of a complete resection of all the recurrence sites avoiding the risk of incomplete resections or debulking surgery. Preoperative CT scan was performed for every patient, whereas magnetic resonance was necessary only in some cases. 18-Fluorodeoxyglucose positron emission tomography was used (for patients treated in the past 10 y) to confirm the presence of suspected recurrence. Pathologic preoperative confirmation was obtained in all doubtful cases through fine-needle aspiration biopsy.

Dedicated pathologist in each involved center reviewed all specimens and re-evaluated histology according to the WHO classification system for thymic epithelial tumors.16 A histologic comparison with the primary thymoma histology was also conducted to reveal WHO upgrading.

Histologic upgrading was defined as a change in histology from the primary thymoma to the recurrence (e.g., from AB thymoma to B3). A centralized revision at the promoting center was performed in cases with doubts. Thymic carcinomas and neuroendocrine thymic tumors were excluded from the analysis, because of their biological and prognostic difference from thymomas. Moreover, a survival analysis has been performed considering the ITMIG classification; in addition, some other characteristics related to the number of localizations and histology were combined.

Recurrence was divided into the following three categories according to the definition proposed by the ITMIG[17–19]:

1. Local recurrence was defined as disease appearing in the anterior mediastinum or tissues immediately contiguous with the resected thymoma (i.e., pleural recurrence in the area of a previously resected stage IVa tumor).
2. Regional recurrence was defined as intrathoracic recurrence (i.e., pleural and pericardial nodules).
3. Distant recurrence included extrathoracic recurrence and intraparenchymal pulmonary nodules.

A multidisciplinary tumor board discussed each single case to decide the treatment indication. Surgery was always the first choice if a radical resection was possible.

Although it is very difficult to retrospectively reconstruct the decision-making process considering few unavoidable differences between the single tumor boards, the overall treatment policy was essentially similar and basically on the basis of the following two main factors: the baseline performance status of the patient (Eastern Cooperative Oncology Group score) and the feasibility of a radical resection. Therefore, a recurrence-directed surgery was proposed as first treatment only in patients with radiologically resectable disease and a good Eastern Cooperative Oncology Group score.

Moreover, in the presence of MG, a dedicated neurologist managed the symptoms and evaluated, in association with the surgeon, the proper timing for surgical treatment. In addition, recurrence surgery was conducted with the aim to achieve a macroscopic complete resection in patients with MG, even in case of distant recurrences or diffuse pleural involvement (pleurectomy and decortication). In selected cases, hyperthermic intrathoracic chemotherapy was associated to complete pleurectomy.

The surgical access depended on recurrence localization. Thoracotomy was mainly performed in case of intrathoracic recurrence and redo-sternotomy in case of mediastinal recurrence. After a careful examination of the entire pleural cavity and mediastinum, a resection was performed, with the aim to obtain 1 cm of macroscopically free margin. In case of parenchymal or other organ resections, detailed palpation was conducted to identify other metastases. If a resection of the diaphragm, pericardium, great vessels, or chest wall was performed, which required reconstruction, a prosthesis was used. In case of incomplete resection, residual tumor was signaled leaving titanium clips as a sign for complementary treatments.

The oncologist or radiotherapist decided the postsurgical approach on the basis of recurrence characteristics, clinical conditions, and previous treatment (induction or adjuvant treatments for the initial thymoma). Chemotherapy regimens changed along the study period, but mostly were cisplatin-based combination regimens and fractionated radiotherapy.

Post-treatment follow-up consisted in clinical evaluation, and thoracic CT scan was carried out every 3 to 6 months for 3 to 5 years and annually after for 10 years at least, even if some difference was present among the different centers.

Statistical Analysis

Given the retrospective and observational nature of the study and the purely descriptive aim of the primary objective, the proposed sample size (N = 135) was considered appropriate.

Descriptive statistics were used to describe the patients' clinical and demographic characteristics (Table 1). Continuous variables were presented as mean (±SD) or median and interquartile range. Categorical variables were presented as absolute frequencies and percentages. The variables considered in our analysis were age, sex, comorbidity, MG, inductive or adjuvant treatment, and recurrence site. OS was defined as time between the first treatment of recurrence and the last follow-up or death from all causes. Disease-free survival (DFS) was defined as the time between the first treatment of recurrence and a re-recurrence diagnosis. The Kaplan-Meier method was used to calculate survival rates and to draw survival curves. Log-rank test was applied to compare survival times. The prognostic ability of each proposed classification was evaluated using Cox's regression also for multiple comparisons. The statistical significance was set at p value less than 0.05. Statistical analyses were performed using Stata software (StataCorp.2015. State statistical software: Release 14. College Station, TX: StataCorp LP) and Statistical Package for the Social Sciences version 25.

Table 1. Clinical and Pathologic Characteristics

Patients	N = 135
Sex	
Male	77 (57)
Female	58 (43)
Age (y, mean)	43 (±16.5)
Myasthenia gravis	90 (66.6)
Surgical approach (thymectomy)	
Sternotomy	107 (79.3)
Sternotomy + thoracotomy	11 (8.1)
Thoracotomy	10 (7.4)
VATS	7 (5.2)
Masaoka-Koga stage (thymectomy)	
I	7 (5.2)
II	41 (30.4)
III	68 (50.4)
IVa	19 (14)
WHO classification (thymectomy)	
A-AB	12 (8.8)
B1	27 (20)
B2	47(34.8)
B2-B3	14 (10.5)
B3	35 (25.9)
Pattern of recurrence (ITMIG)	
Local	17 (12.6)
Regional	97 (71.9)
Distant	21 (15.5)
No. localizations	
Single	38 (28.1)
Multiple	97 (71.9)
Intrathoracic	123 (91.1)
Extrathoracic	12 (8.9)
Site of recurrence	
Pleura	71 (52.6)
Parenchyma	9 (6.6)
Both	16 (11.9)
Other	39 (28.9)
Treatment of recurrence	
Complete resection	109 (80.7)
Incomplete resection	26 (19.3)
Mortality (surgical patients)	
Perioperative	0
90 d	0
Complications	21 (15.5)
Adjuvant chemotherapy/radiotherapy (recurrence)	78 (57.7)
WHO upgrading (recurrence)	22 (16.3)

Note: Values are given in n (%) unless indicated otherwise.
ITMIG, International Thymic Malignancy Interest Group; VATS, video-assisted thoracoscopic surgery.

Results

A total of 160 patients were treated among the involved centers and were included in the study. Five patients with macroscopic residual disease after thymectomy and 20 patients who underwent nonsurgical therapy were excluded. In detail, 20 patients did not underwent surgical treatment owing to the presence of recurrence judged not radically resectable, and five were excluded because surgery was indicated for debulking.

Final analysis was conducted on N = 135 patients.

Clinical and pathologic characteristics of the population regarding the primitive thymectomy and the recurrence are reported in Table 1.

MG was present in 66.6% of the patients, and a complete resection was achieved in 80.7% of the patients.

Most patients were of male sex (77, 57%), and the mean age was 43 (±16.5) years. Induction therapy was performed on 13 patients (9.6%). The most frequently applied surgical approach was sternotomy (107, 79.3%). Adjuvant therapy was performed on 67 patients (49.6%). The most present was Masaoka-Koga stage III (68, 50.4%), and the most frequent group according to WHO classification was B2 (47, 34.8%).

Concerning the recurrence characteristics, the most frequent pattern of recurrence (ITMIG classification) was regional (97, 71.9%), multiple recurrence was present in 71.9% of the cases, and the pleura was the most common involved site (52.6%). Distant recurrences consisted in two peritoneal nodules, three diaphragmatic (abdominal face), seven liver metastases, and nine lung recurrences. In detail, the nine patients with lung recurrence presented only separate lung nodules, whereas the association of lung plus pleura was considered as regional because a direct infiltration of the lung was present starting from pleural recurrence.

Adjuvant radiotherapy/chemotherapy was performed on 78 patients (57.7%); 45 patients underwent adjuvant chemotherapy, 25 adjuvant radiotherapy, eight CTRT, whereas only one patient received neoadjuvant chemotherapy.

WHO upgrading was present in 22 patients (16.3%).

In our cohort, 48 deaths were observed (35.5%): 33 patients died owing to tumor progression, six autoimmune disease (myocarditis, red cell aplasia, and acute lymphatic leukemia in one case and medullar aplasia in three cases), and nine other causes not related to thymic disorders. Median OS was 21.6 years (95% confidence interval [CI]: 14.6–28.6). The 5-year survival rate was 91%, and 10-year survival rate was 67%.

In Table 2, detailed results on survival analysis are presented for the different prognostic factors. When adopting the ITMIG classification, we observed a 5- and a 10-year OS rate of 79.9% and 49.7% in local, 68.3% and 52.6% in regional, and 66.3% and 35.4% in distant recurrences, respectively, but the differences were not statistically significant ($p = 0.625$, Fig. 1*A*).

Only comparing singular versus multiple localization, a statistically difference in survival was present, with a 5- and 10-year OS of 97% and 91% versus 89% and 57% ($p = 0.001$) (Fig. 1*B*). The risk of death was 4.06 times

Table 2. Survival Analysis: OS (Kaplan-Meier, Log-Rank Test)

Sample Characteristics	5-y OS, %	10-y OS, %	*p* Value	Mean OS [95% CI]	Log-rank *p*
Total samples	91	67		19.8 [17.4-22.4]	
ITMIG classification					
Local	94.00	81.00	0.626	20.5 [14.3-26.9]	0.927
Regional	91.00	67.00		18.7 [16-21.5]	
Distant	90.00	56.00		19.6 [13.8-24.5]	
No. of recurrence					
Single localization	97	91	0.001	26.7 [22.7-30.7]	0.001
Multiple localizations	89	57		16.3 [13.7-18.8]	
Recurrence site					
Intrathoracic	91	69	0.904	20.2 [17.6-22.9]	0.376
Extrathoracic	92	54		13.4 [10.4-16.3]	
WHO histology					
Low-grade histology (A, AB, B1)	89	72	0.522	18.4 [14.2-22.6]	0.78
High-grade histology (B2-B3)	92	65		20.3 [17.3-23.3]	
ITMIG modified 2 categories					
ITMIG local + regional	92	70	0.873	19.8 [17-22.6]	0.779
ITMIG distant	90	56.00		19.1 [13.8-24.5]	
ITMIG modified with localization number					
ITMIG local single + regional, single	92	81	0.028	26.3 [21.7-30.9]	0.013
ITMIG local multiple + regional, multiple	63	39		16.2 [13.6-18.9]	
ITMIG distant	66	35		19.1 [13.8-24.5]	
Site of recurrence with localization number					
Intrathoracic single	90	80	0.024	26.5 [22.3-30.6]	0.007
Intrathoracic multiple	62	39		16.7 [13.9-19.4]	
Extrathoracic	71	0		13.3 [10.4-16.3]	

CI, confidence interval; ITMIG, International Thymic Malignancy Interest Group; OS, overall survival.

higher in the multiple localization group as compared with the single localization group ($p = 0.002$, hazard ratio [HR] = 4.06, 95% CI: 1.7–9.7).

Nevertheless, when introducing the variable “number of lesions” (single versus multiple), it was possible to build groups presenting statistically significant differences in long-term survival.

Patients with ITMIG local single plus regional single recurrence had a statistically significant better survival compared with those with ITMIG local multiple plus regional multiple recurrence or ITMIG distant recurrence ($p = 0.028$) (Fig. 2*A* and Table 2). The risk of death for the local multiple plus regional multiple group and distant group was 3.8 and 3.04 times higher compared with the local single plus regional single group ($p = 0.006$, HR = 3.8, 95% CI: 1.4–9.9 and $p = 0.04$, HR = 3.04, 95% CI: 1.02–9.1) (Table 3).

Similarly, patients with intrathoracic single recurrence presented a significantly better survival compared with those with intrathoracic multiple or extrathoracic recurrence ($p = 0.007$). The risk of death in the intrathoracic multiple group and extrathoracic group was 3.6 and 4 times higher compared with that of the intrathoracic single group ($p = 0.004$, HR = 3.6, 95% CI: 1.5–8.8 and $p = 0.019$, HR = 4, 95% CI: 1.2–12.7) (Fig. 2*B*).

The same analysis was conducted in patients who underwent radical recurrence resection, and in these cases, we confirmed the results of the entire population (Table 4). In detail, the number of localization was a strong prognostic factor for OS, whereas the ITMIG classification did not have a significant difference in survival when adopted. Conversely, categorizing patients on the basis of the number of localizations and recurrence site as intrathoracic/extrathoracic or locoregional/multiple, the difference in survival resulted significant.

Regarding the DFS, no statistically significant differences were detected considering the ITMIG classification, whereas a significant survival difference was present comparing intrathoracic versus extrathoracic recurrence: 5- and 10-year DFS at 50% and 31% versus 18% and 0%, respectively ($p = 0.04$) (Supplementary Table). Only the classification including the number of recurrence in association with the site of recurrence revealed a statistical trend: 5- and 10-year DFS at 59% and 43% versus 46% and 25% versus 18% and 0% in intrathoracic single versus intrathoracic multiple versus extrathoracic localizations (Supplementary Table).

Discussion

Our study revealed that the ITMIG classification for thymoma recurrence poorly predicts prognosis.

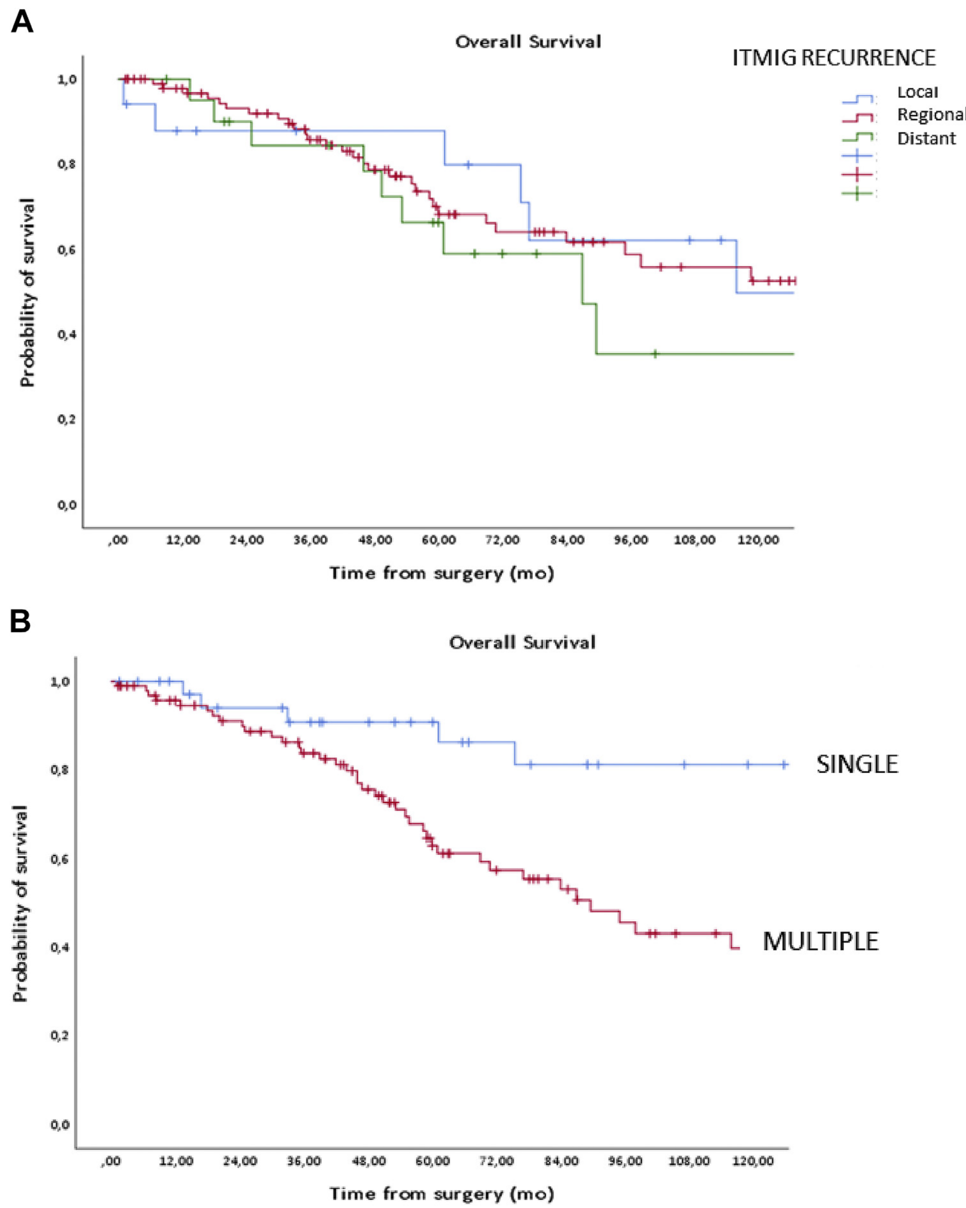

Figure 1. (*A*) Overall survival according to the ITMIG recurrence classification. (*B*) Overall survival according to the number of localizations. ITMIG, International Thymic Malignancy Interest Group.

Considering objective prognostic factors, such as the number of localizations, histology, and recurrence site, we found that only the number of localizations might predict overall survival in a statistically significant manner; therefore, we integrated this factor together with recurrence site as suggested by the ITMIG classification.

In literature, different factors have been evaluated, which might predict survival in thymoma recurrences; the number of localizations resulted to be a prognostic factor in recent experiences of Chiappetta et al.,[11] Margaritora et al.,[20] and Marulli et al.,[21] with more than 200 patients with a quite clear survival stratification according with single versus multiple recurrences.

Nevertheless, the prognostic role of the recurrence site remains a controversial argument; some studies reported significant/remarkable differences in survival,[7,21–23] whereas in other studies, survival was not affected by this factor.[12,20,24] All the mentioned papers performed the analysis on the entire cohort including patients who underwent other treatments different from surgery. This factor may represent a bias considering the possibility that patients with distant recurrence were not susceptible for surgical resection, which resulted to be a favorable factor for survival compared with other treatments in three studies.[20,22,23] Furthermore, the article by Ruffini et al.[7] revealed that surgical treatment ensured a better survival compared with radio-/

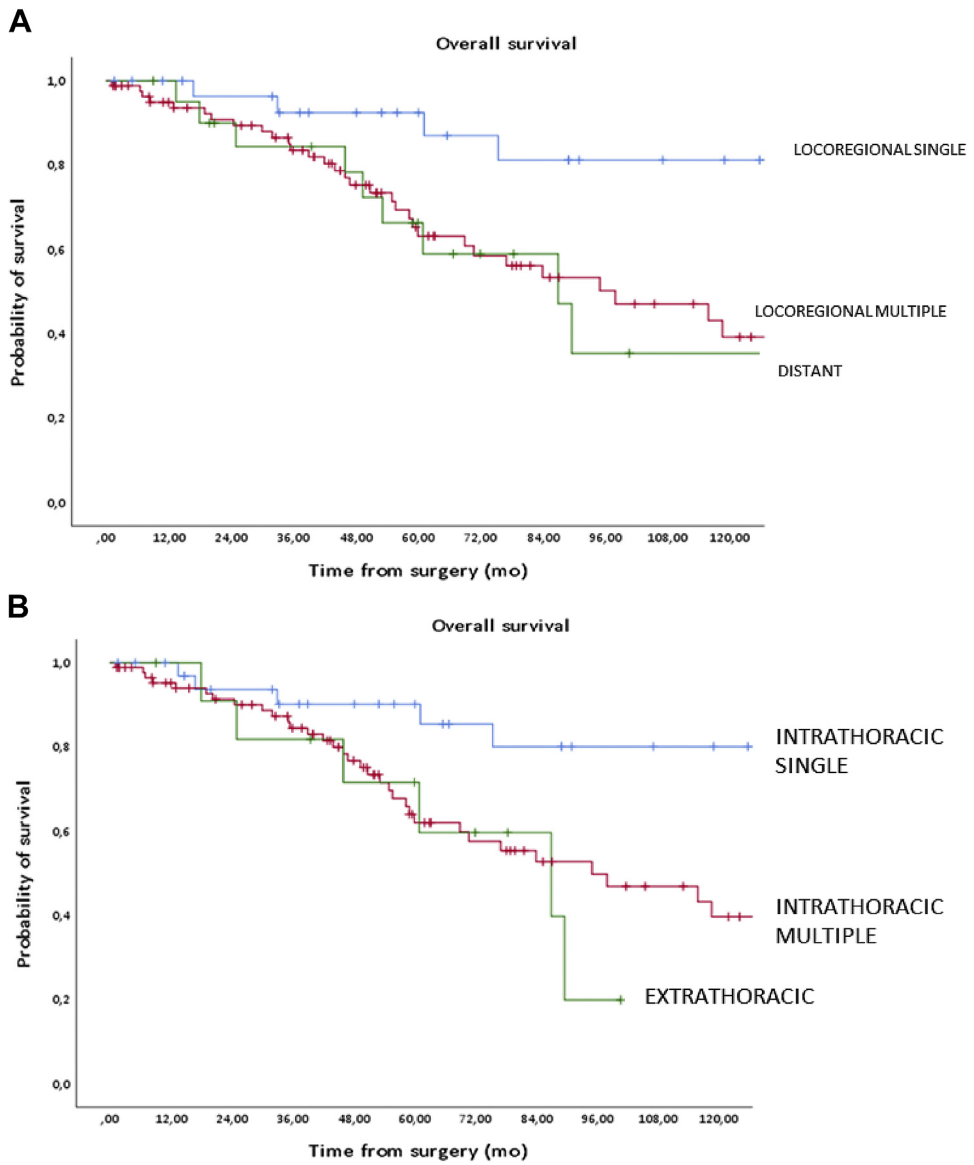

Figure 2. (*A*) Overall survival according to the ITMIG locoregional single versus ITMIG locoregional multiple versus ITMIG distant. (*B*) Overall survival according to the intrathoracic single recurrence versus intrathoracic multiple recurrences versus extrathoracic recurrences. ITMIG, International Thymic Malignancy Interest Group.

chemotherapy even if not statistically significant. Moreover, in any paper, the recurrence site resulted to be an independent prognostic factor for survival suggesting other factors, such as the kind of treatment, may be determining factors.

Many studies and a meta-analysis reported surgical treatment as a strong prognostic factor in patients with thymoma.[3,4,7,20–23] Therefore, a high rate of patients with locoregional disease in the surgery group compared with a higher percentage of patients with distant localizations in the other treatment group may explain the improvement in survival in patients with locoregional recurrence.

For these reasons, we performed a survival analysis only including patients who underwent surgical treatment, with the aim to obtain a homogenous population especially regarding treatment indications. In addition, this allowed us to analyze the pathologic report and to confirm the number of localizations and their characteristics. At the same time, we are conscious that selecting a subpopulation, our analysis may be limited de facto and the correlate results should be carefully interpreted, especially when translating into daily clinical practice. For these reasons, we decided to consider a homogeneous population to evaluate the prognostic role of the ITMIG classification but also of other proposals on

Table 3. Survival According to the Proposed Alternative Classifications

Recurrence Classification	5-y OS, %	10-y OS, %	HR	95% CI	*p* Value
ITMIG modified with localization number					0.013
ITMIG local single + regional single (ref.)	92.4	81.2			—
ITMIG local multiple + regional multiple	63.2	39.2	3.8	1.4-9.9	0.006
ITMIG distant	66.3	35.4	3.04	1.02-9.1	0.04
Recurrence site with localization number					0.007
Intrathoracic single (ref.)	90.2	80.1			—
Intrathoracic multiple	62.0	39.7	3.6	1.5-8.8	0.004
Extrathoracic	71.6	0	4	1.2-12.7	0.019
	5-y DFS, %	10-y DFS, %			
ITMIG modified with localization number ITMIG local single + regional single (ref.)	65	48	1		0.131
ITMIG local multiple + regional multiple	53	23	1.61	0.89-2.90	0.114
ITMIG distant	33	16	2.10	1.0-4.42	0.05
Recurrence site with localization number					0.09
intrathoracic single (ref.)	59	43	1		—
Intrathoracic multiple	46	25	1.29	0.74-2.23	0.369
Extrathoracic	18	0	2.42	1.09-5.35	0.03

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; ITMIG, International Thymic Malignancy Interest Group; OS, overall survival; ref., referent.

the basis of a number of patients which permitted this kind on analysis.

We combined the number of localizations with other recurrence characteristics suggested by the ITMIG, in particular analyzing the impact of survival of single/multiple localization on locoregional recurrence. In this way, we found a clear discrimination in survival considering locoregional single versus locoregional multiple, with a 5- and 10-year survival advantage of 30% and 40%, respectively, in the case of single locoregional recurrence. Moreover, patients with distant recurrences presented a survival rate similar to those with locoregional multiple recurrences; however, both categories presented a risk of death three times higher compared with single locoregional recurrences.

This risk stratification may be useful for future consideration when approaching thymoma recurrences. Indeed, the role of adjuvant therapies after recurrence resection is still of debate, especially owing to relatively low patient numbers and heterogeneity of clinical and pathologic characteristics.[11,20–22] Indeed, only Fiorelli et al.[22] reported a survival benefit after adjuvant therapy in patients with R0, whereas other authors did not.[20–22] It is possible that some benefits of adjuvant therapy may be related to disease characteristics and specific analysis may solve this issue.

Another interesting point regarded the allocation of patients with pulmonary recurrence, which are considered as distant according to the ITMIG classification owing to hematogenous spreading. For this reason, we analyzed the survival outcome including these patients into intrathoracic group recurrences, also considering in three cases, lung metastases were singular. Interestingly, using this category, a clear discrimination, especially regarding long-term survival (10 y), was revealed, with a survival difference of 80% and approximately 40% comparing the intrathoracic single or the intrathoracic multiple group.

It is possible that patients with lung recurrences have a better survival compared with those with other

Table 4. Variable Comparison in the Entire Population and Only Considering R0

Variables	Any R (135 Patients), *p* Value	Only R0 (109 Patients), *p* Value
ITMIG classification (local vs. distant vs. regional)	0.626	0.551
Intrathoracic vs. extrathoracic	0.255	0.267
Single vs. multiple	0.005	0.001
Low-grade histology (A, AB, B1) vs. high-grade histology (B2-B3)	0.603	0.526
Intrathoracic single vs. intrathoracic multiple vs. extrathoracic	0.024	0.006
ITMIG local + regional vs. ITMIG distant	0.334	0.405
ITMIG (local + regional) single vs. ITMIG (local + regional) multiple vs. ITMIG distant	0.031	0.007

ITMIG, International Thymic Malignancy Interest Group; R, resection; R0, complete resection.

recurrences, as reported by Sandri et al.,[24] who revealed a 5- and 10-year OS of 61.4% and 41.3% in lung recurrence versus 40.3% and 0% in patients with other distant localization, respectively. Even in our cohort, the three patients with single lung recurrence had a mean survival of 15 years, but the small subcohort did not permit an ad hoc statistical analysis. Maybe further multicenter analysis on patients with distant recurrences may permit to individuate eventual significant survival difference among the different recurrent locations. Interestingly, we found that the classification of intrathoracic versus extrathoracic permitted a significant/clear stratification for the DFS, and the proposed classification of intrathoracic single versus intrathoracic multiple versus extrathoracic was the only revealing a statistical trend for DFS ($p = 0.08$). Despite further studies are needed, maybe this kind of classification should be the most appropriate for recurrence.

Finally, the same analysis was conducted only in patients who underwent R0 resection, considering complete resection resulted in one of the most important prognostic factors for these patients. Indeed, it is quite clear that complete resection is a strong prognosticator in these patients,[12,20–23] and in particular, the presence of macroscopic residual of disease is a negative prognostic factor. In particular, Margaritora et al.[20] reported a significantly poorer survival in patients who underwent debulking surgery, a result confirmed by Mizuno et al.[3] using data of a large national Japanese database.

Considering patients who underwent complete resection, the ITMIG classification is not effective to predict survival, whereas a singular versus multiple localization and their combination with the recurrence site maintained statistical significance. We believe that this is another confirmation of our proposed rearrangements, eliminating the potential bias of incomplete resection presence, suggesting the combinations of recurrence site and number of localization is a promising association for a better definition of recurrence characteristics and prognosis. In particular, the similar prognosis in patients with multiple intrathoracic/locoregional recurrence and distant recurrence was confirmed, indicating a surgical approach in these categories of patients is considerable when a complete resection is achievable. The ITMIG proposed a recurrence classification with the aim to generate a common language between physicians, even if data on survival regarding this proposal were not clear. In this study, we tried to improve this proposal looking for a common and clear scientific language regarding recurrence characteristics and survival outcome. We pointed out the potential effectiveness of two types of categorization, considering intra-extrathoracic/locoregional disease versus distant disease according to the previous ITMIG classification, creating homogenous classes of patients with recurrence characteristics. These categories may be of great help for physicians to develop a tailored approach in these patients, giving clear information regarding the recurrence characteristics (number and location of neoplastic lesions) and the related prognosis. Moreover, the proposal allows to identify homogenous groups for treatment comparison (chemotherapy/radiotherapy versus surgery), reducing from one side the selection biases and increasing from the other side the robustness of the results in consideration of the homogeneous recurrence characteristics. In the future, other studies should validate these proposals, also confirming the clinical and prognostic roles of each proposal.

This study presents some limitations owing to its retrospective and multicenter nature. Despite only surgical patients with curative intent were included, the preoperative workout could be different among the involved centers even if only high-volume centers with expertise in this disease were involved. Furthermore, we attempted to reduce potential confounding factor excluding patients who received other treatments. In this manner, we in addition excluded patients in poor general condition not fit for surgery and reported only certain localization numbers. Moreover, we repeated the same analysis only on patients who underwent complete resections, with the aim to reduce the possible confounding effect of patients with incomplete resections. Finally, a possible limitation in recurrence valuation regards the difficulties in radiological recurrence number detection, but radiologic and metabolic imaging is drastically improving, especially in the past decade with better CT and magnetic resonance definition that may help the number of localization identification. Moreover, nuclear medicine and positron emission tomography may help in the number of localization detection, so in the near future, the technology might solve this issue.

In conclusion, the ITMIG classification, which is based on recurrence site, did not have a prognostic significance in patients with thymoma recurrence who underwent surgical treatment. Our study suggests integrating recurrence site with the number of localization because it revealed promising results to predict survival in patients with thymoma. Finally, our proposed prognostic factors should be verified on data of another cohort.

CRediT Authorship Contribution Statement

Marco Chiappetta: Conceptualization, Methodology.

Edoardo Zanfrini, Dania Nachira, **Marco Chiappetta, Filippo Lococo, Vittorio Aprile, Francesco Guerrera**: Data curation.

Marco Chiappetta, Filippo Lococo: Writing—original draft preparation.

Marco Lucchi, Enrico Ruffini, Elisa Meacci: Visualization.

Maria Teresa Cogedo, Stylianos Korasidis: Investigation.

Stefano Margaritora, Pier Luigi Filosso*:* Supervision.

Isabella Sperduti, Rossana Moroni: Formal analysis, Validation.

Marcello Carlo Ambrogi, Stefano Margaritora: Writing—reviewing and editing.

Acknowledgments

The authors thank Franziska M. Lohmeyer, PhD, Fondazione Policlinico Universitario Agostino Gemelli, for her support in revising our manuscript.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.07.004.

References

1. Detterbeck FC. Evaluation and treatment of stage I and II thymoma. *J Thorac Oncol*. 2010;5(suppl 4):S318–S322.
2. Luo T, Zhao H, Zhou X. The clinical features, diagnosis and management of recurrent thymoma. *J Cardiothorac Surg*. 2016;11:140.
3. Mizuno T, Okumura M, Asamura H, et al. Surgical management of recurrent thymic epithelial tumors a retrospective analysis based on the Japanese nationwide database. *J Thorac Oncol*. 2015;10:199–205.
4. Hamaji M, Ali SO, Burt BM. A meta-analysis of surgical versus nonsurgical management of recurrent thymoma. *Ann Thorac Surg*. 2014;98:748–755.
5. Huang J, Rizk NP, Travis WD, et al. Comparison of patterns of relapse in thymic carcinoma and thymoma. *J Thorac Cardiovasc Surg*. 2009;138:26–31.
6. Wright CD, Wain JC, Wong DR, et al. Predictors of recurrence in thymic tumors: importance of invasion, World Health Organization histology, and size. *J Thorac Cardiovasc Surg*. 2005;130:1413–1421.
7. Ruffini E, Filosso PL, Oliaro A. The role of surgery in recurrent thymic tumors. *Thorac Surg Clin*. 2009;19:121–131.
8. Venuta F, Rendina EA, Longo F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. *Ann Thorac Surg*. 2003;76:1866–1872.
9. Detterbeck FC, Parsons AM. Thymic tumors. *Ann Thorac Surg*. 2004;77:1860–1869.
10. Blumberg D, Port JL, Weksler B, et al. Thymoma: a multivariate analysis of factors predicting survival. *Ann Thorac Surg*. 1995;60:908–914.
11. Chiappetta M, Zanfrini E, Giraldi L, et al. Prognostic factors after treatment for iterative thymoma recurrences: a multicentric experience. *Lung Cancer*. 2019;138:27–34.
12. Haniuda M, Kondo R, Numanami H, Makiuchi A, Machida E, Amano J. Recurrence of thymoma: clinicopathological features, re-operation, and outcome. *J Surg Oncol*. 2001;78:183–188.
13. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer*. 1981;48:2485–2492.
14. Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. *Pathol Int*. 1994;44:359–367.
15. Brierley J, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*. 8th ed. Hoboken, NJ: John Wiley & Sons, Inc; 2017.
16. Marx A, Ströbel P, Badve SS, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. *J Thorac Oncol*. 2014;9:596–611.
17. Bae MK, Lee CY, Lee JG, et al. Predictors of recurrence after thymoma resection. *Yonsei Med J*. 2013;54:875–882.
18. Huang J, Detterbeck FC, Wang Z Sr, Loehrer PJ. Standard outcome measures for thymic malignancies. *J Thorac Oncol*. 2010;5:2017–2023.
19. Detterbeck FC, Asamura H, Crowley J, et al. The IASLC/ITMIG thymic malignancies staging project: development of a stage classification for thymic malignancies. *J Thorac Oncol*. 2013;8:1467–1473.
20. Margaritora S, Cesario A, Cusumano G, et al. Single-centre 40-year results of redo operation for recurrent thymomas. *Eur J Cardiothorac Surg*. 2011;40:894–900.
21. Marulli G, Margaritora S, Lucchi M, et al. Surgical treatment of recurrent thymoma: is it worthwhile? *† Eur J Cardiothorac Surg*. 2016;49:327–332.
22. Fiorelli A, D'Andrilli A, Vanni C, et al. Iterative surgical treatment for repeated recurrences after complete resection of thymic tumors. *Ann Thorac Surg*. 2017;103:422–431.
23. Bae MK, Byun CS, Lee CY, et al. Clinical outcomes and prognosis of recurrent thymoma management. *J Thorac Oncol*. 2012;7:1304–1314.
24. Sandri A, Cusumano G, Lococo F, et al. Long-term results after treatment for recurrent thymoma: a multicenter analysis. *J Thorac Oncol*. 2014;9:1796–1804.