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The Prognostic Role of the Number of Involved Structures in Thymic Epithelial Tumors: Results from the ESTS Database

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ABSTRACT

Background. The role of the number of involved structures (NIS) in thymic epithelial tumors (TETs) has been investigated for inclusion in future staging systems, but large cohort results still are missing. This study aimed to analyze the prognostic role of NIS for patients included in the European Society of Thoracic Surgeons (ESTS) thymic database who underwent surgical resection.

Methods. Clinical and pathologic data of patients from the ESTS thymic database who underwent surgery for TET from January 2000 to July 2019 with infiltration of surrounding structures were reviewed and analyzed. Patients' clinical data, tumor characteristics, and NIS were collected and correlated with CSS using Kaplan–Meier curves. The log-rank test was used to assess differences between subgroups. A multivariable model was built using logistic regression analysis.

Results. The final analysis was performed on 303 patients. Histology showed thymoma for 216 patients (71.3%) and NET/thymic carcinoma [TC]) for 87 patients (28.7%). The most frequently infiltrated structures were the pleura (198 cases, 65.3%) and the pericardium in (185 cases, 61.1%), whereas lung was involved in 96 cases (31.7%), great vessels in 74 cases (24.4%), and the phrenic nerve in 31 cases

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(10.2%). Multiple structures (range, 2–7) were involved in 183 cases (60.4%). Recurrence resulted in the death of 46 patients. The CSS mortality rate was 89% at 5 years and 82% at 10 years. In the univariable analysis, the favorable prognostic factors were neoadjuvant therapy, Masaoka stage 3, absence of metastases, absence of myasthenia gravis, complete resection, thymoma histology, and no more than two NIS. Patients with more than two NIS presented with a significantly worse CSS than patients with no more than two NIS (CSS 5- and 10-year rates: 9.5% and 83.5% vs 93.2% and 91.2%, respectively; $p = 0.04$). The negative independent prognostic factors confirmed by the multivariable analysis were incomplete resection (hazard ratio [HR] 2.543; 95% confidence interval [CI] 1.010–6.407; $p = 0.048$) and more than two NIS (HR 1.395; 95% CI 1.021–1.905; $p = 0.036$). **Conclusions.** The study showed that more than two involved structures are a negative independent prognostic factor in infiltrative thymic epithelial tumors that could be used for prognostic stratification.

Keywords Thymoma · Thymic carcinoma · Staging · Infiltration

Thymic epithelial tumors (TETs) are rare, with a reported incidence of about 1.3–3.2 per million.[1] They are classified according to the World Health Organization (WHO) as thymomas and thymic carcinomas.[2]

The incidence of TETs is slightly higher in thymomas than in thymic carcinomas.[3] However, although the actual crude incidence is about 2.8 per 1,000,000 for thymomas and less than 0.1 per 1,000,000 for thymic carcinomas,[3] this could be underestimated because large epidemiologic studies currently are becoming old, pathologic classifications are changing, and diagnoses in recent years are increasing as collateral findings in chest computed tomography (CT) performed for lung cancer screening or other reasons.[4]

The survival outcome for TETs is excellent, with 10-year overall survival (OS) ranging from 70 to 90% for early stages and 25–70% for advanced stages.[5–7] The recurrence rate is about 8–10%, with a long recurrence time, usually 5–10 years[8,9] after complete resection.

Given the the rarity of TETs, various staging systems have been proposed in the past,[10] but the increasing number of diagnoses and identification of TETs require the adoption of an appropriate staging system. For 40 years, the Masaoka and then the revised Masaoka-Koga staging system were mainly adopted for TETs management and prognosis definition, although they were developed with analysis of data from fewer than 100 patients.[11,12] These staging systems were based on the TET characteristics, taking into account different grades of infiltration of surrounding structures, with nodal or hematogenous spreading showing a lower tendency.

Consequently, the main limitations of these staging system (if present) are a slight survival difference between stages I and II TETs, and a large heterogeneity of patient characteristics in stages III and IV TETs.[13]

On the other hand, recent years have seen the emergence of a need for a new and reliable staging system that can better define different stages and define prognosis and appropriate treatments using the tumor node metastases parameters used for other solid tumors. However, the actual adopted tumor-node-metastasis (TNM) staging system was based on the concept of infiltration levels, categorizing the T factor on the type of infiltrated structures.[14] Although this proposal presented peculiar and interesting characteristics, different validation studies pointed out some limitations, especially in comparison of subgroups.[15,16]

The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee–Thymic Domain, in accordance with their timetable, revised the potentially unsolved issues of the proposal, also considering recent evidences in the literature and individuating other factors that possibly may be evaluated in a future staging system.[17]

Specifically, the number of infiltrated structures was considered as a factor that better defines the clinical stage, with its potential role evaluated in the upcoming ninth edition of TNM staging.[17] However, only a few recent studies have investigated the role of infiltrated structures in TETs, describing two interesting findings in TET patients:[18–20] (1) the majority of patients with infiltrative TETs presented with infiltration of multiple structures and not only one structure, and (2) the number of infiltrated structures was significantly related to survival outcome in surgical patients.

This study aimed to analyze the prognostic role of the number of infiltrated structures in patients with TETs who underwent surgical resection using a large multicentric European database to increase evidence on this topic for the development of the future classification system.

MATERIALS AND METHODS

Participation in the ESTS thymic database was approved by the institutional review board of each participating center.

The study was proposed and accepted by the Steering Committee of the ESTS thymic working group.

The data collected in the ESTS thymic database from 1 January 2000 to 31 July 2019 were reviewed and extracted from the entire database. Patients who underwent thymectomy for TETs and had infiltration of surrounding structures were extracted from the database. Patients with distant metastases were excluded, whereas patients with nodal involvement or pleuro-pericardial nodules were included. Then, patients from centers that inserted more than 20

infiltrative TETs were selected with the aim to include centers with expertise in the field.

After completion of this first selection, every included institution was asked to adhere to the study and to complete the missing data in the database and update the follow-up information. The final database included the adherent institutions in the proposed study.

Infiltrative TETs were defined considering the infiltrataion of pathologic structures (e.g., mediastinal pleura, pericardium, phrenic nerve, lung, great vessels) or pleuropericardial dissemination.

The number of infiltrated structures (NIS) was obtained by counting the different infiltrated organs and also considering the layers between the tumor and the involved structure. In this manner, the total number of infiltration layers was counted. In case of lung infiltration, the mediastinal pleura invasion had to be present and also was counted, resulting in two involved structures. Only the phrenic nerve, mediastinal pleura, and pericardium were counted as one involved structure.

In Masaoka-Koga stage IV disease, pleural and/or pericardial dissemination counted as separated infiltrated structures, with this number added to the infiltrated structures by the primitive tumor. Anonymous vein infiltration with a pleural nodule counted as two infiltrated structures.

Resection status was categorized by the presence of complete resection (R0), microscopic residue of disease/infiltration of the pathologic margins (R1), and macroscopic residue of disease in the operation field (R2).

Statistical analysis

Descriptive statistics were used to summarize pertinent study information. Cancer-specific survival (CSS) was associated with clinical and pathologic characteristics comprising sex, age, histology, presence of myasthenia gravis, neoadjuvant therapy administration, pT, pStage, type of structure infiltrated, completeness of resection, number of involved structures, and adjuvant therapy.

Cancer-specific survival was calculated from the date of surgery until death for TET progression. If a patient was still alive, survival was censored at the time of the last visit. The hazard ratio (HR) and confidence interval (CI) were estimated for each outcome variable of interest using the Cox univariate model and the logistic regression model. A multivariate Cox proportional hazard model also was developed using stepwise regression (forward selection) with predictive variables that were significant in the univariate analyses. The entrance limit was determined by a p value of 0.10, and the removal limit was determined by a p value of 0.15. For all analyses, SPSS (version 21.0; SPSS, Inc., Chicago, IL, USA), a licensed statistical program, was used.
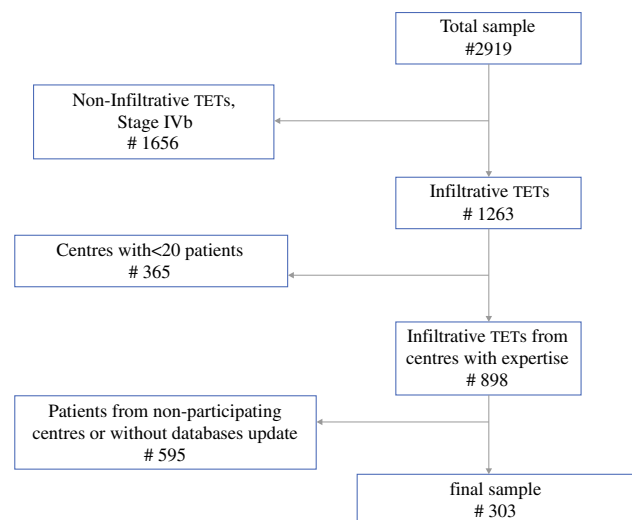

FIG. 1 Study flow chart. TETs, thymic epithelial tumors

RESULTS

The final analysis was performed with 303 patients (Fig. 1). The clinical and pathologic characteristics are reported in Table 1. Histology showed thymoma in 216 patients (71.3 %) and neuroendocrine tumor (NET)/thymic carcinoma (TC) in 87 patients (28.7 %).

The most frequently infiltrated structures were the pleura (198 cases, 65.3%) and the pericardium (185 cases, 61.1%), whereas the lung was involved in 96 cases (31.7%), great vessels in 74 cases (24.4%), and the phrenic nerve in 31 cases (10.2%). A single involved structure was present in 120 cases (39.6%), whereas multiple structures (range, 2–7) were involved in 183 cases (60.4%).

The median follow-up period was 57.9 months (range, 1–449 months), and during this period, 99 patients experienced a recurrence and 90 patients died. However, only 46 patients died of TET recurrence. The CSS recurrence rate was 89% at 5 years and 82% at 10 years.

In the univariable analysis, the favorable prognostic factors for CSS were neoadjuvant therapy administration ($p = 0.023$), absence of myasthenia gravis ($p = 0.006$), Masaoka-Koga stage 3 ($p = 0.029$), absence of metastases ($p < 0.001$), absence of nodal involvement ($p = 0.048$), absence of great vessels involvement ($p = 0.026$), complete resection ($p = 0.001$), and thymoma histology ($p < 0.001$) (Table 2).

The number of involved structures (NIS) was significantly correlated with prognosis when considered as continuous (HR 1.48; 95 % CI 1.094–1.864; $p = 0.009$) and also when categorized as binomial, with the patients who had more than two NIS showing a significantly worse CSS prognosis than the patients with no more than two NIS (5- and 10-year CSS: 89.5% and 83.5% vs 93.2% and 91.2%, respectively;

TABLE 1 Clinical and pathologic characteristics

Variable	n (%)
Sex	
Male	150 (49.5)
Female	153 (50.5)
Age (years)	
< 56	158 (52.1)
> 56	145 (47.9)
Myasthenia gravis	
Yes	117 (58.7)
No	178 (38.7)
Missing	8 (2.6)
Neoadjuvant	
No	190 (62.7)
Yes	78 (25.7)
Missing	35 (11.6)
Pathologic Masaoka-Koga	
3	247 (81.5)
4	56 (18.5)
Pathologic T	
T1	44 (14.5)
T2	97 (32)
T3	149 (49.2)
T4	13 (4.3)
Pathologic N	
No	268 (88.4)
Yes	35 (11.6)
Pathologic M	
No	265 (87.5)
Yes	38 (12.5)
Pathologic TNM stage	
I	33 (10.9)
II	90 (29.7)
III	124 (40.9)
IV	56 (18.5)
Histology	
Thymoma	216 (71.3)
Thymic carcinoma	81 (26.7)
Net	6 (2)
WHO Classification	
AB-B1	64 (21.1)
B2-B3	148 (48.9)
C-NET	87 (28.7)
Missing	4 (1.3)
Pathologic resection status	
R0	234 (77.2)
R1	50 (16.5)
R2	19 (6.3)
Pleura involvement	
No	105 (34.7)
Yes	198 (65.3)
Pericardium involvement	
No	118 (38.9)
Yes	185 (61.1)

Table 1　(continued)

Variable	n (%)
Phrenic nerve involvement	
No	272 (89.8)
Yes	31 (10.2)
Lung involvement	
No	207 (68.3)
Yes	96 (31.7)
Great venous vessels involvement (cava vein, innominate vein)	
No	239 (78.9)
Yes	64 (21.1)
Aorta involvement	
No	293 (96.7)
Yes	10 (3.3)
Other structures involvement	
No	273 (90.1)
Yes	30 (9.9)
Pleural nodules	
No	281 (92.7)
Yes	22 (7.3)
Pericardial nodules	
No	298 (98.3)
Yes	5 (1.7)
Pleura + other structure involvement	
Pleura + pericardium	119 (39.3)
Pleura + other structures	79 (26.1)
No	105 (34.6)
Pericardium + other structure involvement	
Pericardium alone	98 (32.3)
Pericardium +other structures	89 (29.5)
No	116 (38.2)
No. of structures involved	
1	120 (39.6)
2	88 (29)
3	51 (16.8)
4	32 (10.6)
5	9 (3)
6	1 (0.3)
7	2 (0.7)
No. of structures involved (cutoff)	
≤ 2	208 (68.6)
> 2	95 (31.4)
Adjuvant therapy	
Yes	178 (58.7)
No	125 (41.3)
Kind of adjuvant therapy (178 patients)	
Chemotherapy	14 (7.9)
Radiotherapy	72 (40.4)
Radio-chemotherapy	39 (21.9)
Missing	53 (29.8)

TNM tumor-node-metastasis

TABLE 2 Univariable analysis

Variable	Cancer specific survival	
	p value	HR (95 % CI)
Sex Male versus female	0.854	1.068 (0.531–2.145)
Age (years) < 56 versus > 56	0.59	1.216 (597–2.476)
Myasthenia gravis No versus yes	0.006	3.525 (1.432–8.676)
Neoadjuvant therapy No versus yes	0.023	2.492 (1.136–5.466)
Pathologic Masaoka-Koga 4 versus 3	0.029	2.475 (1.098–5.580)
Pathologic T	0.311	
T1 (ref)		
T2	0.189	0.470 (0.152–1.451)
T3	0.958	1.027 (0.380–2.775)
T4	0.669	0.625 (0.073–5.381)
Pathologic N Yes versus no	0.048	2.505 (1.010–6.213)
Pathologic M Yes versus no	< 0.001	5.378 (2.374–12.179)
Pathologic stage IV versus I–II–III	0.018	2.583 (1.176–5.676)
Histology Carcinoma –NET versus thymoma	<0.001	4.784 (2.191–10.445)
Clinical resection status R+ versus R0	0.001	3.397 (1.617–7.139)
Pleura involvement Yes versus no	0.122	1.941 (0.838–4.497)
Pericardium involvement Yes versus no	0.725	1.110(0.524–2.353)
Phrenic involvement Yes versus no	0.953	1.037(0.314–3.418)
Lung involvement Yes versus no	0.057	1.980 (0.979–4.003)
Great venous vessels involvement (cava vein, innominate vein) Yes versus no	0.026	2.361 (1.109–5.207)
Aorta involvement Yes versus no	0.507	21.224 (0.003–177.281)
Other structures involvement Yes versus no	0.229	1.932(0.661–5.644)
Pleural nodules Yes versus no	0.779	1.228(0.292–5.167)
Pericardial nodules Yes versus no	0.200	3.722 (0.499–27.736)
Pleura + other structures involvement Pleura + pericardium involvement versus pleura + other	0.517	0.748 (0.310–1.803)
Pericardium + other structures involvement Pericardium + other versus pericardium alone	0.020	2.856 (1.176–6.935)
No. of involved structures > 2 versus ≤ 2	0.048	2.030 (1.007–4.094)
Adjuvant therapy Yes versus no	0.380	1.367 (0.681–2.745)

HR hazard ratio, *CI* confidence interval, *NET* neuroendocrine tumor
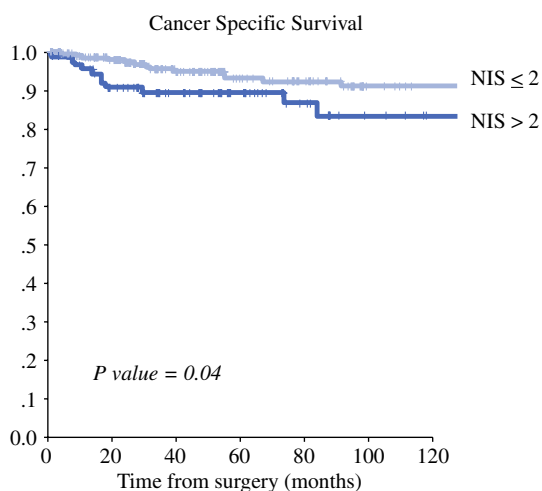
FIG. 2 Cancer-specific survival according to the number of infiltrated structures. NIS, number of infiltrated structures

TABLE 3 Multivariable analysis

Cancer-specific survival

Variable	p value	HR (95 % CI)
Myasthenia gravis No versus yes	0.109	4.27 (0.72–25.17)
Histology Carcinoma/NET versus thymoma	0.053	3.32 (0.98–11.20)
Pathologic resection status R+ versus R0	0.048	2.54 (1.01–6.40)
No. of involved structures > 2 versus ≤ 2	0.036	1.39 (1.02–1.90)

HR hazard ratio, *CI* confidence interval, *NET* neuroendocrine tumor

$p = 0.04$; Fig. 2). No statistically significant correlation between disease-free survival (DFS) and OS was observed ($p = 0.59$), even if the patients with no more than two NIS presented better 5- and 10-year OS rates than the patients with more than two NIS (82.4% and 74.5% vs 73% and 64.3%, respectively; Fig. S1).

Similarly, the patients with thymoma and Masaoka-Koga stage 3 disease showed a significantly better CSS than the patients with NET/thymic carcinoma and Masaoka-Koga stage 4 disease (5-and 10-year CSS: 93.9% and 91.3% for Masaoka-Koga stage 3 disease vs 81.8% and 75.0% for stage 4 disease [$p = 0.02$; Fig. 3a]; 95.7% and 94.7% for thymomas vs 83.0% and 74.9% for NET/thymic carcinomas [$p < 0.001$; Fig. 3b]).

The negative independent prognostic factors confirmed by the multivariable analysis were incomplete resection (HR 2.543; 95% CI 1.010–6.407; $p = 0.048$) and more than two NIS (HR 1.395; 95% CI 1.021–1.905; $p = 0.036$), whereas TC histology raised the statistical significance (HR 3.22; 95% CI 0.985–11.200; $p = 0.053$) (Table 3).

Conversely, other variables included in the multivariable model such as Masaoka-Koga stage, TNM stage, infiltration of great venous vessels, neoadjuvant therapy administration, and nodal and pleuro-pericardial involvement did not result in statistical significance.

Investigation of the possible combinations among the most involved structures (pleura and pericardium) showed that the patients with involvement of the pericardium plus other structures had a significantly worse CSS than the patients with involvement of the pericardium alone (5- and 10-year CSS: 87.8% and 84.9% vs 96.4% and 92.9%, respectively; $p = 0.02$; Fig. 4).
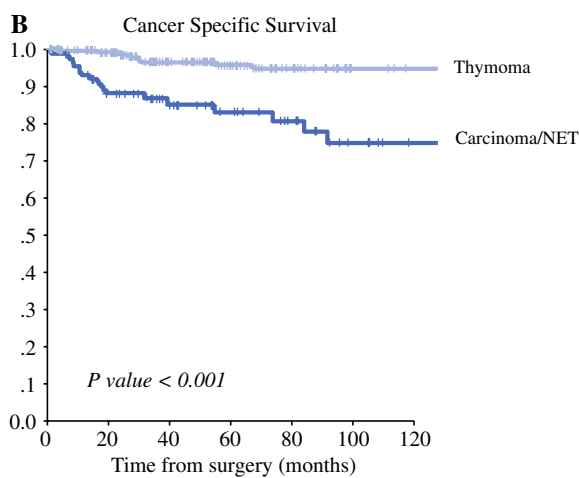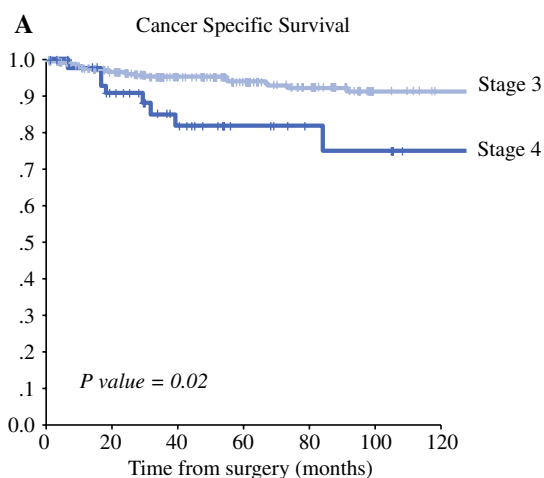
FIG. 3 **A** Cancer-specific survival according to Masaoka-Koga stage. **B** Cancer-specific survival according to histology.

Cancer Specific Survival

P value = 0.02
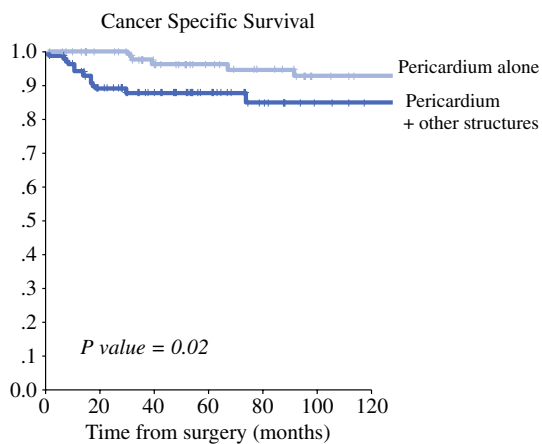
FIG. 4 Cancer-specific survival according to pericardium infiltration alone or in association with other structures.

DISCUSSION

This study analyzed the prognostic role of the number of involved structures in TETs, showing that this factor was significantly correlated with CSS. Furthermore, we found that patients with more than two infiltrated structures experienced a significantly worse CSS than those with fewer than two infiltrated structures. These results are in agreement with our previous paper,[19] which analyzed the role of NIS in thymoma patients only, whereas this study also considered other histologies. This decision considered the comment of the IASLC Staging and Prognostic Factors Committee[17] underscoring the need and concept of a staging system that should be organ-specific. Therefore, it should refer to all thymic histology even if separate survival curves may be interesting to be analyze. Moreover, this is the largest study to analyze the role of NIS in all thymic histology. Most previous studies considered only thymomas, perhaps due to the rarity of thymic carcinomas and the limited number of cases.[18–21] It is important to note that previous results are confirmed with the inclusion of TC/NET also, suggesting that the number of involved structures may be taken into consideration for the upcoming TNM edition and for patients after operative management.

However, the integration of this factor into the staging system remains to be defined. It may contribute to a more precise definition of the T1b–T4 category. Indeed, in the proposal of Nicholson et al.,[22] statistical differences were present between T2 and T3 in terms of DFS, not considering OS, whereas any survival outcome difference was present in the comparison of T3 and T4. Other studies have confirmed this limitation about the T parameter, underscoring that this classification is effective in consideration of DFS, whereas in considering OS, it presents statistical significance only when T1 is compared with other T categories.[15,16,23] Furthermore

all these studies reported a similar outcome between T2 and T3 categories, suggesting that they may be incorporated into the same category, maintaining a different stage compared with T1 and T4.

In our opinion, the T4 category needs to be on its own because independent from the level of infiltration concept, with the inclusion of particular structures, this division may be extremely useful, especially for therapeutic management. Indeed, Nicholson et al.[22] noted that T4 involvement was extremely rare, with a significantly higher rate of incomplete resections. The T4 category was reported for about 100 of patients in a dataset of more than 8000 cases, suggesting also that most cases were from R+ patients who underwent surgical resection. For this reason, this category may prove to be extremely useful for clinical stratification of non-surgical therapies.

On the other hand, the addition of the mediastinal pleura and the pericardium to the T3 category may be interesting and help the prognosis stratification, dividing patients on the basis of the number of involved structures. Indeed, in this study and in our previous analysis on this topic,[19] we found that patients with infiltration of the pericardium and other structures had a significantly worse CSS than those with pericardium infiltration only. This result is in line with the study of Moser et al.,[24] who reported a worse prognosis for patients with stage IV disease and concomitant pericardium invasion.

These evidences seem to confirm that the pericardium may represent a central point for T category determination, but the way to use the possible combination remains to be defined. This new category may present some important advantages. First, it would include the majorty of patients with infiltrative TETs, giving a robust number of patients that may be included. A high number will be essential for stage comparison, limiting the bias of considering groups of patients with extreme number variability. Second, it would include patients with a well-defined therapeutic indication. Indeed, despite the presence of infiltrative thymomas, surgery (in the contest of a multidisciplinary approach) is the treatment indicated by the majority of the guidelines.[4,9,25] It may improve the management of these patients. Finally, the presence of a conspicuous number of patients should be linked to a non-negligible number of survival events, relapses, or death, which may permit an appropriate ad hoc survival analysis.

Indeed, when survival analysis in TETs is considered, different possible confounding factors may be taken into account. Due to their indolent nature, TETs, especially thymomas, present very good long-term survival, with excellent OS 10 years after resection. Moreover, these tumors are frequently associated with myasthenia gravis and other auto-immune diseases.[26] How these diseases could influence survival remains unclear, but they may lead to an increased

number of non-cancer-related deaths. For these reasons, the use of OS as the end point may be not reliable, and it may explain the absence of statistical significance in some studies while a significance was present when DFS was evaluated.[15,16,23]

On the other hand, DFS also may present some limitations, especially because the time until recurrence may be extremely long and because TET recurrences also are treated using mainly surgery, with excellent results in terms of survival.[8,27] For this reason, a short DFS does not imply a short OS, possibly explaining the discrepancies reported in the aforementioned studies. This possible limit was pointed out already 30 years ago by Regnard et al.,[7] who underscored that OS and DFS may not reflect the aggressiveness of TETs due the high number of non-cancer-related deaths among these patients.

Conversely, starting from all these considerations and evaluating our cohort characteristics, we chose CSS as the end point for this analysis. Indeed, as reported in the Results section, 90 patients died during the study period, but only 46 patients died of tumor recurrence, whereas more than twice as many experienced a relapse. In consideration of these numbers, we supposed that CSS might be the most appropriate outcome to consider, as we did in the previous analysis on the topic.[19]

In this study, we observed a statistical significance for NIS as a continuous variable, but recognized the necessity of categorizing the variable for survival analysis and staging purposes. We chose a cutoff of two structures because we noticed that most of patients had invasion of multiple structures, and also because, in line with the "level of invasion concept," in some cases the infiltration of one structure to reach the final organ was unavoidable (e.g., mediastinal pleura to infiltrate lung).

Our results are in line with those of other studies that analyzed the role of NIS and reported a low number of recurrences also in infiltrative TETs,[18,20,21] making subanalysis difficult to perform. Funaki et al.[18] analyzed the role of NIS by categorizing patients into four groups based on progressive NIS, but the difference was significant only in comparisons of groups with no NIS and groups with organ invasion in terms of relapse-free survival and OS. Conversely, the comparison between groups with organ invasion (e.g., NIS 1 vs 2 or 2 vs 3) resulted significance of relapse-free survival only in comparison of NIS 1 with NIS 3. However, the number of events is not reported, and it is hard to interpret these results without this information.

Asamura et al.[21] proposed an alternative staging system in thymoma histology, mixing tumor dimension with organ infiltration in 131 patients who underwent surgical resection. The authors reported recurrence in only 19 patients, and considering OS, they found a statistical difference between patients with single- and multiple-organ infiltration.

However, there also were Masaoka-Koga stages I and II patients, but their number was small and the cause of death was not reported, limiting the interpretation of these results.

Kang et al.[20] analyzed the role of the number of involved structures in 59 stage III TETs, showing that patients with a single involved organ showed a significantly better DFS than patients with multiple infiltrations. This study presented some non-negligible limitations. Only 19 patients experienced a recurrence, and it was not reported how many of them died. Moreover, it was not clear how the authors counted the number of involved structures, reporting 17 cases of "lung-only" infiltration, but if the parenchyma was infiltrated, the tumor must also have infiltrated the mediastinal pleura, so the number of structures was at least two.

In our study we tried to improve the analysis about the number of involved structures, including all the thymic histologies and clarifying how these structures had been counted, also considering the "level of invasion" proposed in the current staging system. Moreover, we excluded patients who underwent only thymomectomy, and we used CSS as the end point. By using the largest cohort of infiltrative TETs from a multicenter European database, we could perform a survival analysis on a large number of quite homogeneous patients, confirming the prognostic role of NIS for these tumors and suggesting consideration of this parameter in the future. Basically, when integrated into a more comprehensive staging system, these results could potentially be a help for physicians in planning an adjuvant treatment after TET resection.

Furthermore, in the recent T component proposal by the IASLC,[28] no significant differences in OS were observed when the new T2 and T3 categories were compared, suggesting that the inclusion of single-organ specification is not enough for a prognosis stratification. On the other hand, in this large study, a significant difference in CSS was present considering the NIS in infiltrative TET.

This study had some limitations, mainly those related to the large multi-institutional dataset and the retrospective nature of the analysis. Specifically, although surgical indication could be quite homogeneous among the participating centers, the administration of the integrated treatments such as neoadjuvant or adjuvant therapy may have varied among institutions, such as part of the follow-up schedules. In particular, we noticed the presence of excellent information about the pre- and intraoperative management of these patients, with quite complete information about neoadjuvant treatments. On the other hand, although it was reported whether patients had any type of adjuvant therapy, the data were incomplete about the type of adjuvant therapy and the reasons for not administering it.

On the other hand, use of the ESTS thymic database, which represents one of the largest thymic databases in the

world dedicated to such rare disease, warrants good data reliability[29,30] and therefore supports our conclusions.

CONCLUSION

This study found that number of involved structures is an independent prognostic factor and seems to be a good prognosticator in thymic epithelial tumors. This parameter may be useful for prognosis stratification and potentially for tailored postoperative treatments and follow-up evaluation, even if further large studies are needed to validate the data in this report.

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