ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: Proposal for a Stage Classification for the Forthcoming (Ninth) Edition of the TNM Classification of Malignant Tumors

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ABSTRACT

Introduction: A TNM-based system for all types of thymic epithelial tumors was introduced in the eighth edition of the TNM classification of thoracic malignancies. The Thymic Domain of the Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer, composed of multispecialty international experts, was charged to develop proposals for the ninth edition. This article outlines the proposed definitions for the T, the N, and the M components and their combination into stage groups.

Methods: A large central database of 11,347 patients with thymic epithelial tumors was assembled thanks to the contribution of the major thymic organizations worldwide and analyses were carried out for the T, the N, and the M components and the stage groups. Overall survival was the outcome measure for patients with completely and incompletely resected tumors, and recurrence for those with complete resection. When the number of patients was sufficient, analyses were performed separately for thymomas, thymic carcinomas, and neuroendocrine thymic tumors.

Results: Tumor size is included in the T1 category as T1a ($\leq$5cm) and T1b ($>$5 cm); the mediastinal pleura is dropped as a T descriptor; invasion of the lung or phrenic nerve is reclassified as T2 (instead of T3). No changes are proposed for the N and the M components from the eighth edition. The stage groups remain the same.

Conclusions: The proposed changes for the ninth edition of the TNM classification set the stage for further progress in the future for these rare tumors.

Keywords: Thymoma; Thymic carcinoma; Staging; Stage classification; TNM

Introduction

Thymic epithelial tumors (TETs) are rare diseases, despite being the most frequent tumors in the anterior mediastinal compartment at all ages. Until recently, the stage classification of these tumors was on the basis of the Masaoka and Masaoka-Koga surgical-pathologic stage classification that was initially derived from data on the basis of a limited patient population.[1]

In 2009, the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) partnered to develop a TNM-based stage classification on the basis of a large worldwide retrospective database including more than 8000 patients. A Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) was created within the IASLC with the aim to provide proposals for stage classification of thymic tumors to be incorporated in the eighth edition of the TNM of thoracic malignancies.[2] The proposals eventually received approvals from the Union for the International Cancer Control (UICC) and the American Joint Commission on Cancer (AJCC) and became effective in 2017 for UICC and in 2018 for AJCC.

Soon after the release of the eighth TNM, the TD-SPFC started working to provide proposals for the ninth edition TNM, expected in 2024.

The present article outlines the stage classification proposals recommended by IASLC TD-SPFC for the ninth TNM. These proposals are published in advance to be circulated to the thoracic community before the final consideration by UICC and AJCC in the official ninth edition TNM classification of thoracic malignancies. Articles detailing the proposals for the T, the N, and the M components for the ninth TNM, an article presenting an overview of the data that were used for the analysis, and an article revising the ITMIG-IASLC nodal map are published alongside the present article,[3–6] representing a comprehensive overview of the activity of the TD-SPFC in the past 5 years for the release of the ninth TNM.

Materials and Methods

A worldwide thymic database managed by Cancer Research And Biostatistics (CRAB) was created, with data provided by the major thymic organizations and large individual centers. Data were submitted from

January 2019 through December 2021. All databases were batch databases that were harmonized, cleared, and merged by CRAB into a central thymic database for analysis. A detailed report of the data overview is the object of a separate publication.[5] Overall, data from 11,347 patients were submitted from 13 data sources and checked for availability to the analysis.

The eighth TNM was used as a reference and the proposals for modifications to the T, the N, and the M categories and stage groups were made on the basis of the eighth TNM general structure. As for the eighth TNM, the group agreed to keep a single TNM-based classification applicable across thymomas, thymic carcinomas, and neuroendocrine thymic tumors (NETT).

The analysis was performed separately for thymoma and thymic carcinoma. NETTs were also analyzed separately; although, for most analyses, data regarding these tumors were sparse.

Death and recurrence were assessed as end points, although the two are not necessarily associated, as reported elsewhere.[7] Overall survival (OS) in complete resection (R0) and any R status (R-any) cases and recurrence in R0 cases were used as outcome measures. Measures of recurrence used were freedom from recurrence (FFR), which censors at death, and cumulative incidence of recurrence (CIR), which adjusts for the competing event of death.[8] In general, for early stage the greatest weight was put on the recurrence-R0 analysis, whereas for late-stage tumors the greatest weight was put on OS-R-Any analyses when making decisions regarding potential stage groups.

Discrimination among the T, the N, and the M components and stage groups was evaluated on the basis of the ability to separate populations with distinct prognoses on the basis of the analysis of outcomes.

The group looked for consistent ordering and discrimination between proposed categories and groups in each tumor type and clinical (c) and pathologic (p) stages. One of the problems the group faced in the analysis was the limited sample size for some cohorts and the small number of events (death, recurrence). In these cases, statistical discrimination was not deemed to be an appropriate criterion and results were evaluated qualitatively in consideration of the totality of the evidence. In addition, practical and clinical aspects were weighed in the deliberations. The group deemed it critical to maintain a single classification system across all TET types and, at the same time, seek strong data as a basis for making changes. Furthermore, aspects of how categories correlate with treatment policies were considered.

Statistical analyses were performed by CRAB using the Statistical Analysis System version 9.4 (Statistical Analysis System Institute, Cary, NC). The OS curves were calculated using the Kaplan-Meier method,[9] and survival curves were compared using the log-rank test.[10] For both OS and recurrence, the outcome was measured from the date of first intervention (as this was the baseline date captured in the database) and patients were censored at the date of last follow-up. Cox regression models[11] were used to obtain hazard ratios (HRs), OS, and FFR. When calculating HR for all diagnoses (thymoma, thymic carcinoma, and NETT), stratification was used to adjust for diagnosis. Multivariate modeling was performed separately for thymomas and thymic carcinomas and adjusted for sex (male versus female), age ($>$65 y versus $\leq$65 y), region (Asia-Australia versus Europe-North America), Eastern Cooperative Oncology Group performance status (0/1 versus $>$1), and for OS models and type of resection. Concordance between a given pair of clinical and pathologic stages was measured as the percentage of patients in whom the clinical stage correlated with the actual pathologic stage.

Results

Data Overview

A total of 11,347 cases were collected from 13 data sources, and 9147 patients met the inclusion criteria of valid histologic type and survival data (Supplementary Table 1). A detailed overview of the data used for the analysis is reported in a separate article.[5]

Most patients received surgical treatment (8830 cases, 96.5%). Nonsurgical treatment was administered in 251 cases (2.7%). Information about OS and recurrence (R0 cohort) was available in 9147 and 3845 patients, respectively.

The distribution of c and p stages was tabulated on the basis of all cases with valid histologic type and survival data on the basis of eighth TNM (Supplementary Table 2). Information on c stage was missing or not determined in 6831 patients (75%), whereas information on both the p stage and c stage was available in 1506 (16%) cases.

TNM Components

A summary of the proposals of the T, N, and M components and the justification for the final decision are herein reported to support the stage group proposals. A detailed report of the analysis of the T, N, and M components is the object of dedicated articles.[3,4]

As for the T component, for the ninth edition, the group agreed to maintain the general structure of the eighth edition of TNM, with division into four categories on the basis of the level of involvement.[12] The group also agreed to keep the same rules for the involvement of the adjacent structures, which have been discussed in detail in a dedicated article.[3]

The group recognized that the significance of tumor size in advanced stages and incomplete resections would be of limited value, and therefore, decided to investigate the prognostic significance of tumor size only in stage I tumors separately in thymomas and thymic carcinomas using FFR (R0).

Tumor size (greatest single dimension pathologically) at a 5-cm threshold was found to be prognostic in early-stage (stage I) tumors. Survival analysis revealed statistically significant discrimination between tumors less than or equal to 5 cm versus greater than 5cm in stage I thymomas (HR 1.87, $p = 0.003$) but not in stage I thymic carcinomas (HR 1.93, $p = 0.11$), possibly because of the relatively small number of early-stage thymic carcinomas.

The role of the mediastinal pleura was reassessed considering the available data, consensus, and expert opinions among the T subcommittee and the entire group. The group recognized that mediastinal pleura invasion is a pathologic finding—of little if any use for the clinical staging. Even pathologically, it is not easily recognized and reported by many pathologists. Finally, the inclusion of both mediastinal pleura and tumor size in the staging would have been overcomplicated.

Another issue that was addressed by the group for the T category was the type of invaded adjacent structures in T3 tumors. The analysis of the available data indicated that T3-phrenic nerve or T3-lung invasion had better survival than other T3 tumors, approaching the survival of T2 tumors. For T2 involvement, from a clinical standpoint, pericardium involvement is generally felt to be straightforward to resect, and management of involvement of the phrenic nerve or adjacent lung parenchyma is regarded as comparable in terms of complexity (as opposed to involvement of the great veins).

In summary, for the T component, the analysis of our data led to the following proposals: (1) to include tumor size (at 5-cm threshold) as T1a ($\leq$ 5cm) and T1b (>5 cm) while dropping mediastinal pleura as a T descriptor; and (2) to reclassify lung and phrenic nerve involvement as T2 (Table 1).

For the N component, the number of N-positive (N+) tumors collected was larger than was collected for the eighth edition. TNM, thanks to the contribution of databases containing more advanced cases (Réseau tumeurs THYMiques et Cancer [RYTHMIC], Korean Association for Research on the Thymus [KART], The Chinese Alliance for Research in Thymomas [ChART]). The analysis of the N component for the stage proposals included the accuracy of the c stage, the nodal prevalence rate, and the prognostic significance of the nodal involvement, along with a refinement of the ITMIG-IASLC thymic nodal map. In our data, the lymph node involvement rate increased with the aggressiveness of thymic tumors (1.5%, 17.6%, and 27.7% in thymomas, thymic carcinomas, and NETT, respectively). On the basis of the current ITMIG-IASLC node map,[13] which divides nodal involvement into N1 (anterior/perithymic) and N2 (deep) regions, the rates of N1 and N2 numerically differed in the different tumors: 1.1% and 0.4% in thymomas, 8.3% and 9.3% in thymic carcinomas, and 22.3% and 5.3% in NETT. Unfortunately, detailed information on the different nodal stations in the N1 and N2 categories was lacking, preventing the group from making data-driven revisions to the node map. Therefore, the group agreed to keep the current lymph node map for staging, including N1 and N2 categories.

The prognostic significance of the N component for the stage groups was evaluated separately for thymoma and thymic carcinoma and in the clinical (cN) and pathologic (pN) settings. A statistically significant discrimination was observed in patients with thymic carcinoma between pN1 and pN0 (HR = 1.5, 95% confidence Interval [CI]: 1.1–2.1, $p = 0.017$) and between pN2 and pN1 (HR = 1.8, 95% CI: 1.2–2.7, $p = 0.006$). In patients with thymoma, there was a statistically significant survival difference between pN1 and pN0 (HR = 2.9, 95% CI: 1.8–4.7, $p < 0.001$) but not between pN2 and pN1 (HR = 1.1, 95% CI: 0.5–2.5, $p = 0.85$). Unfortunately, no data-driven assumptions could be made on cN categories owing to sparse data.

For the M component of the classification, the number of patients with M-positive disease (M1a/M1b) was larger than in the eighth TNM (329 and 142 for thymoma and thymic carcinoma, respectively, in the ninth edition database).

Table 1. Proposed T Component of Thymic Tumors for the Ninth Edition of the TNM Classification of Malignant Tumors

T	Description
T1	Tumor limited to the thymus with or without encapsulation, or directly invades into the mediastinum alone or directly invades the mediastinal pleura but does not involve any other mediastinal structure.
T1a	5 cm or less in its greatest dimension[a]
T1b	larger than 5 cm in its greatest dimension[a]
T2	Tumor directly invades the pericardium (either partial or full-thickness), the lung, or the phrenic nerve
T3	Tumor directly invades any of the following: (1) brachiocephalic vein, (2) superior vena cava, (3) chest wall, or (4) extrapericardial pulmonary arteries or veins
T4	Tumor directly invades any of the following: (1) aorta (ascending, arch, or descending); (2) arch vessels; (3) intrapericardial pulmonary artery or veins; (4) myocardium; (5) trachea; or (6) esophagus.

[a]Irrespective of mediastinal pleura invasion. Mediastinal pleura invasion is to be recorded as an "additional histologic descriptor."

Table 2. Proposed N and M Components of Thymic Tumors for the Ninth Edition of the TNM Classification of Malignant Tumors

N and M Categories	Description
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes (e.g., paratracheal, subcarinal, aortopulmonary window, hilar, jugular, and supraclavicular nodes)
M0	No metastatic pleural, pericardial, or distant sites
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

Information on cM status was limited (25% and 26% for thymomas and thymic carcinoma, respectively), whereas more information was available for the pM (89% and 79% for thymomas and thymic carcinomas, respectively).

Survival analysis was performed using OS as an outcome measure in patients regardless of resection or R status (R-any). Sparse data were available on patients with cM tumors to draw significant conclusions. More granular information was available for pM categories to perform survival analysis. A good curve separation was found in thymic carcinoma between pM1a and pM0 (HR = 1.8, 95% CI: 1.3–2.4, $p = 0.001$) and between pM1b and pM1a (HR = 1.8, 95% CI: 1.1–2.8, $p = 0.014$), and in patients with thymoma between pM1a and pM0 (HR = 3.7, 95% CI: 3.0–4.6, $p < 0.001$). Unfortunately, the granularity of the available data did not allow drawing any conclusions about the prognostic significance of the number of pleural implants and the type of serosal involvement (pleural/pericardial), the number of distant sites (oligometastatic concept), and the possible different significance of intrathoracic (lung) versus extrathoracic sites.

In summary, for the N and the M components, the analysis of our data confirmed the validity of the eighth edition TNM classification,[14] and the group proposed no changes to the current descriptors for the N and the M categories for the ninth edition TNM classification (Table 2).

Stage Groups

On the basis of the proposed recommendations for the T, the N, and the M components, stage groups were tested using the same aggregation that was proposed for the eighth edition classification. Stages I to IIIB are determined primarily by the T component in the N0 and M0 categories. Stage IVA involves N1 or M1a tumors and stage IVB includes N2 or M1b tumors. The group agreed, therefore, not to modify the eighth TNM stage groups, which revealed good prognostic discrimination for FFR in the early stages and for OS in the late stage (R-any cohort) (Table 3). When using the same T, N, and M aggregation, the proposed changes to the T component (T1a-T1b on the basis of size; T3-phrenic nerve or T3-lung downstage to T2) have no impact on which T, N, and M categories are assigned to the stage groups.

Using the proposed ninth edition TNM classification CIR curves illustrate good visual separation and ordering among earlier-stage groups for both thymoma (Fig. 1*A*) and thymic carcinoma (Fig. 1*B*). The CIR curves for higher stages are harder to assess because of the small numbers of patients and events in these cohorts. The CIR for NETT tumors is shown in Supplementary Figure 1 but is inherently difficult to interpret because of the small sample sizes throughout.

Table 4 summarizes the total proportion of recurrences (R0) and deaths (R0 and R-any) in the various stage groups. The proportion of recurrences and deaths by tumor type (thymoma, thymic carcinoma, and NETT) in the current database using the proposed ninth edition classification in comparison to the eighth edition classification is presented in Supplementary Table 3. An increased proportion of deaths and recurrences is consistently observed with increasing stage groups overall and in all thymic tumors using both classifications.

Survival curves were then produced using our current data separately for thymoma and thymic carcinoma. The OS curves (R0 and R-any cohorts) by stage groups defined by the proposed ninth edition classification are illustrated in Supplementary Figures 2 and 3. For comparison, survival curves on the basis of the eighth edition TNM classification are also presented. The visual comparison of the stage groups between the eighth TNM and ninth TNM proposal with the new T categories illustrates a much better curve separation between stage II and stage III for thymoma and thymic carcinoma, supporting the new recommendations.

Table 3. Proposed Stage Groups of Thymic Tumors for the Ninth Edition of the TNM Classification of Malignant Tumors

Stage	T	N	M
I	T1a-b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	T any	N1	M0
	T any	N0,N1	M1a
IVB	T any	N2	M0, M1a
	T any	N any	M1b

Note: Any invasion must be histologically confirmed for the pathologic stage.

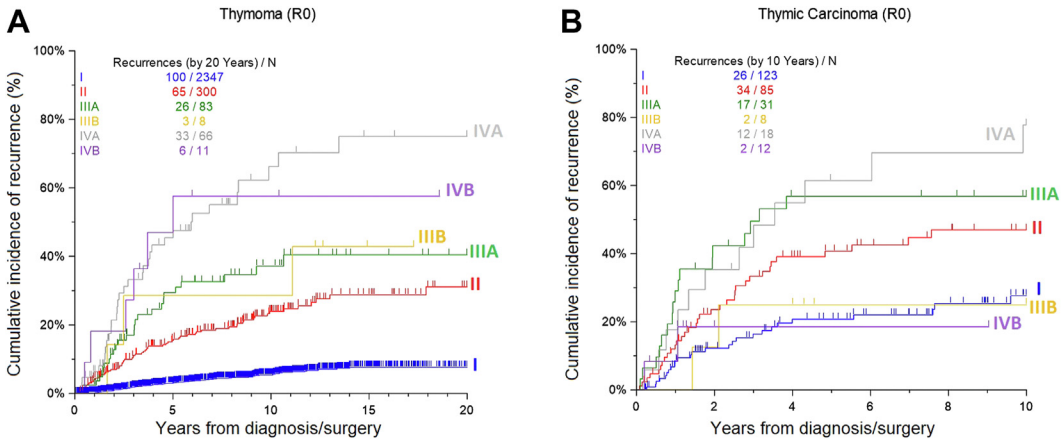

Figure 1. (*A*) CIR in patients with thymoma by stage as defined by the proposed ninth edition TNM classification. (*B*) CIR in patients with thymic carcinoma by stage as defined by the proposed ninth edition TNM classification. CIR, cumulative incidence of recurrence.

The results for NETT are difficult to interpret because of small cohort sizes; OS (R-any) is illustrated in Supplementary Figure 4.

Finally, cox proportional hazard regression analysis was undertaken to compare consecutive stage groups in the entire pathologic stage cohort to check for statistically significant prognostic differences among the groups, adjusted by tumor type (Table 5). This suggests general ordering and statistically significant differences in FFR in early-stage (R0) patients and in late-stage (R-any) patients. Not statistically significant discrepancies in the HR are limited to comparisons involving a limited number of events.

Additional analyses were performed using FFR in R0 and OS in R-any p stage patients, separately in thymomas and thymic carcinomas. The sparse data in patients with NETT prevented carrying out such an analysis in NETT. Multivariate analysis was adjusted for age ($\leq$ >65 y), sex, geographic region (Asia-Australia versus EU-North America), performance status, and OS R status. The consecutive stage groups using the eighth edition and the proposed ninth edition TNM classifications were compared (Supplementary Tables 4 and 5). A significant difference was observed in FFR (R0) and OS between stages II and I ($p < 0.001$) using both classifications (eighth and proposed ninth TNM) in thymomas and thymic carcinomas.

The progressive worsening of outcomes observed with the increasing stage was evident in both thymoma and thymic carcinoma. The group agreed that these findings were both statistically (early stage) and clinically sufficiently robust to support the proposed stage classification for all thymic tumors, despite some limitations in statistical power in some settings (e.g., higher

Table 4. Summary of the Proportion of Recurrences and Deaths (All Diagnoses) by Proposed Ninth Edition TNM Classification

	Recurrences		Deaths	
Pathologic Stage	%	n/N	%	n/N
I	6	138/2491	7	300/4405
I (T1a)	4	55/1372	6	134/2112
I (T1b)	7	78/1045	9	153/1696
II	26	103/390	22	145/646
III	38	50/133	24	49/207
IIIA	38	44/117	24	43/177
IIIB	38	6/16	20	6/30
IVA	54	49/91	22	48/216
N1 M0	42	8/19	26	13/50
N0,1 M1a	67	39/58	34	31/92
IVB	36	9/25	27	21/77
N2 M0,1a, X	0	0/11	27	7/26
N0-2,X M1b	69	9/13	30	13/43
Total	11	349/3130	10	563/5551

Note: n/N equals the total number of recurrences or deaths observed at any time out of the total number of evaluable R0 resected patients in each category.

Table 5. Differences Between Pathologic Stage Groups (All Tumor Types) by Proposed Ninth Edition TNM Classification

	FFR, R0		OS, R0		OS, R-any	
	(349/3130)[a]		(563/5551)[a]		(961/6504)[a]	
Stages	HR	*p*-value	HR	*p*-value	HR	*p*-value
HR vs. adjacent stage						
II vs. I	**4.26**	**<0.0001**	**2.67**	**<0.0001**	**2.77**	**<0.0001**
IIIA vs. II	**1.51**	**0.02**	0.98	0.93	0.84	0.22
IIIB vs. IIIA	0.62	0.28	0.67	0.36	1.46	0.08
IVA vs. IIIB	**2.96**	**0.01**	1.88	0.14	1.22	0.30
IVB vs. IVA	0.53	0.07	1.28	0.34	**1.46**	**0.002**

Note: Hazard ratios and statistical differences (χ^2) by Cox proportional hazards regression models, adjusted for tumor type using stratification. Boldfaced values indicate statistically significant *p*-values.

[a]Number of events/total number of patients in the entire data set for the particular analysis.

FFR, freedom from recurrence; HR, hazard ratio; OS, overall survival; R0, complete resection. R-any, any R status.

stage thymomas and early stage thymic carcinoma). As observed for the 2014 eighth analysis, NETT cases were too few to make any data-driven conclusions. The group, however, agreed that the proposed stage recommendations should be applicable also to NETT, pending further validation through the collection of prospective cases expected for the next revision.

Discussion

The introduction of a TNM-based stage classification for TET in the UICC-AJCC eighth edition of the TNM classification of thoracic malignancies was a major step forward in the management of these tumors, representing a paradigm shift as compared with the previous surgical-pathologic Masaoka-Koga classification. The eighth TNM applies to all TETs and represents a major advance in the development of a common standard of care for these malignancies.

At the outset, the group agreed that any TNM revision should be on the basis of some fundamental assumptions, namely: (1) the TNM only informs the anatomical extent of the disease; (2) any revision should be on the basis of both statistical analysis and clinical significance and should also take into account contributions from published reports; (3) proposed new categories (T, N, M, stage groups) should not make the TNM overcomplicated and should be easily applicable to all countries; (4) should be consistently applied in both clinical and pathologic settings; and (5) should stimulate the acquisition of new data to gain more (ideally) prospective information for future testing and revisions.

On the basis of these, the TD-SPFC started its activity launching a survey to the thoracic community to test the penetration of the eighth TNM soon after its release.[15] Eighty percent of the respondents were in favor of the TNM-based classification, and 50% reported using the ITMIG-IASLC thymic nodal map, whereas lymph node dissection was performed in 50% (N1 nodes) and 21% (N2 nodes) of thymomas and in 66% (N1 nodes) and 41% (N2 nodes) of thymic carcinomas. Overall, the authors concluded that the thoracic community worldwide has started to gain confidence in the eighth TNM of TET.

Since its introduction, several articles have been published testing the efficacy of the eighth TNM[16–18] and several issues have emerged indicating possible areas of refinement for the next revision. Acknowledging these unresolved issues, the TD-SPFC conducted an extensive literature review to focus on the activity of the group for the next (ninth) revision.[19] The group agreed to use the eighth edition classification system as a reference, maintaining its general structure for the components and the stage groups.

As for the T component, the group agreed that a reconsideration of the role of tumor size would be of importance, because of the increasing evidence from published articles of a possible prognostic role in thymic tumors.[20–23]

Tumor size in thymic tumors was not incorporated in the eighth edition classification on the basis of the lack of statistical significance in the entire cohort at what seemed to be an optimal threshold of 10 cm, except in advanced (stage III and IV) tumors and incomplete (R1-R2) resections.[12] In the past, information about the tumor dimension and the lack of a standard measurement criterion in both clinical (imaging) and pathologic settings represented a limitation for the incorporation of tumor size in the stage classification.[24] The analysis of our data supports the proposal to include tumor size at a 5-cm threshold as T subcategories ($\leq$5cm-T1a and $>$5cm-T1b) in stage I TET. Tumor size represents a more valuable, reproducible, easily applicable measure as a T descriptor than mediastinal pleura, and for the sake of simplicity, practicality, and applicability, tumor size alone was chosen as a descriptor in the T1 category. Mediastinal pleura was dropped from the T classification and was included as an "additional histologic descriptor." Involvement of adjacent organs was

included in the T3 to T4 categories in the eighth edition classification, with the exception of the pericardium, which was included in the T2 category. Contributions from the published reports questioned the T2 to T4 classification.[25] Our analysis indicates that some T3 categories, including T3-lung and T3-phrenic nerve have outcomes more similar to T2 than to T3. We were not able to differentiate between different degrees of lung involvement or phrenic nerve involvement, which may have different prognostic impacts. However, corroborated by our analyses, a consensus emerged from the group that there was clinical use in reclassifying lung invasion and phrenic nerve involvement as T2 (instead of T3).

Overall, no changes for the N and the M components are proposed, and our analysis validated the eighth edition categories. A reassessment of the nodal map in view of the most recent published evidence and the contribution of our data was undertaken by the TD-SPFC; the results are discussed in detail in a separate article.[6] Our data confirm reports from the recently published articles[26–30] that N+ involvement in thymic tumors is associated with a poorer prognosis, justifying inclusion at advanced stages. We were able to confirm the current ITMIG-IASLC nodal map, and our analysis found a statistical discrimination between N0, N1, and N2 categories in thymic carcinoma and between N0 and N1 in thymoma. For the M component, our results confirm the differentiation between M1a and M1b and a similar prognosis for intrathoracic versus extrathoracic metastases in M1b tumors. We were not able to determine the prognostic impact of the number of pleural implants and the number of distant sites (oligometastatic disease) as suggested by some recent contributions.[31] For both N+ and M-positive categories our data exposes the limits of the pretreatment imaging to accurately predict the stage and the limited specificity of reported nodal involvement at surgery. For this reason, more detailed sampling and reporting of the nodes at surgical resection, as indicated by ITMIG[32] is, therefore, recommended for future analysis and revisions.

The stage allocation comes from the aggregation of different T, N, and M categories, with the intent to provide stage groups with distinct outcomes. The stage groups as proposed in the eighth edition classification were tested using our data and they were found appropriate in the clinical and pathologic settings and to some extent in all thymic tumors. We, therefore, decided to adopt similar alignment stage groups for the ninth edition classification. The T1 category (including the T1a and T1b subcategories on the basis of tumor size) remains stage I; the T2 category remains stage II (now incorporating the previous T3-lung and T3-phrenic descriptors); the T3 category remains stage IIIA (without the T3-lung and T3-phrenic descriptors); there are no changes for T4 (stage IIIB) and stage IV. The visual comparison of the survival curves with the new proposals provides a better curve separation between stage II and stage IIIA than in the eighth TNM.

AJCC validation criteria of discrimination, calibration, generalizability, clinical relevance, and parsimony were applied to the proposed ninth TNM. Discrimination, the ability of the proposed stage classification to distinguish between patients with different prognoses, was established through pairwise statistical comparisons in survival and recurrence between adjacent groups. Calibration, defined as the agreement between predicted and observed outcomes is primarily applicable to a prognostic prediction model, which was not the focus of the SPFC stage classification initiative. We welcome external application of the proposed stage classification to assess calibration (although it is essential to account for the fact that prognosis is determined by multiple factors in addition to tumor stage). Generalizability, the ability of the staging system to work well in different populations and settings, is a major focus of the SPFC staging initiative. In thymic tumors, this is exhibited through consistent results for clinical and pathologic stages and for thymoma and thymic carcinoma. Although sample size did not permit multiple individual subset analyses, we found consistent results when adjusting for age, sex, geographic region, PS, and R status. Regarding clinical relevance, Mp was dropped, in part, because it is clinically difficult to assess in favor of size which is more easily captured clinically and pathologically; furthermore, the surgical complexity was considered in the decision to reclassify phrenic nerve and lung invasion as T2. Finally, parsimony indicates a staging system is simple and easy to use. Maintaining a consistent classification system across three rare tumor types (thymoma, thymic carcinoma, and NETT, and the change to a size criterion for T1 enhances parsimony. The preparatory survey to assess how well the eighth edition was accepted and the effort to minimize changes unless well supported further enhance this. No external data with sufficient granularity were available for further external validation analyses (e.g., from the U.S. National Cancer Database).

The proposed classification of the TD-SPFC for the ninth edition of TNM has some limitations. First, information about the clinical stage and the pathologic stage was missing in three-quarters and one-quarter of the patients, respectively. This emphasizes the need to make continuous efforts to establish and maintain high-quality prospective clinical databases for the next TNM edition. Second, despite an increased number of advanced and prospective cases, most of the collected data still come from surgical series, representing early stages, and from

retrospective data sets that inherently include challenges with respect to detail. In addition, the frequency of missing variables of interest prevented us from making data-driven conclusions for some issues (e.g., N+ tumors). Many cohorts had small sample sizes and the limited number of events in these cohorts diminished the statistical power of some analyses. Because of the indolent nature of many thymic tumors, in which recurrence probably represents the best outcome measure for most of the patients, the decisions were on the basis of a combination of c and p stage results, OS, FFR, R0, and R-any analyses—this stands in contrast to most malignant tumors that can be evaluated by OS. Finally, the low granularity and sparse data for some subsets of patients (i.e., NETT, distant metastatic sites) did not allow analysis in some subsets and of some questions. Because of the aforementioned considerations, some decisions were made by the group based more on practical and logical factors than on purely statistical grounds. The consensus was reached after a collaborative discussion, with the advantage of having multispecialty representatives in the TD-SPFC.

The proposed TNM stage classification is intended to be a useful system to classify the anatomical extent of the disease of TET. It may be applied in pretreatment and postsurgical settings and applies to all thymic tumors. The basic structure of the eighth edition TNM classification has been maintained. The proposed changes to the T component and the stage groups are meant to be an added value to the stage classification, resulting in a better discrimination of the stage groups.

As for the eighth edition, the proposed stage classification does not represent a prognostic prediction model. The anatomical extent of disease is just one prognostic factor, although a major one, which needs to be integrated with other factors (tumor-related, environmental-related, treatment-related, patient-related, time-related) to construct a valid and effective prognostic model.

In conclusion, the stage classification of TET continues to represent a powerful prognostic factor in these tumors. It provides a fundamental part of cancer care, providing a uniform nomenclature of the anatomical extent of the different thymic tumors, assisting clinicians in the planning of treatment and the evaluation of the treatment results, and facilitating the exchange of information among different institutions. The introduction of a UICC-AJCC TNM-based system for TET in the eighth edition classification represented a major step forward. This report summarizes the activity of the TD-SPFC for the ninth edition TNM classification. The proposed T, N, M components and stage groups are on the basis of an extensive analysis of a large, worldwide database from the major international thymic consortiums and individual institutions, and have been discussed by a panel of experts in thymic tumors from different specialties and different continents. The database and analysis provide confidence that the classification system has a solid foundation. The proposed revision maintains the general structure of the eighth edition classification, with some important proposals for refinement: stage I (T1) includes a size descriptor (5 cm); T2 now includes pericardium, lung, and phrenic nerve involvement; and the N and M components and stage groups remain the same. Stage I, II, IIIA, and IIIB are determined by the T component, IVA and IVB by the N and the M components. Understandably, some limitations because of case numbers exist, but the ninth edition sets the stage for further progress in the future and should be used in clinical practice.

CRediT Authorship Contribution Statement

Enrico Ruffini: Conceptualization, Methodology, Writing- Original draft preparation

final check.

James Huang: Conceptualization, Methodology, Writing- Original draft preparation.

Vanessa Cilento: Data collection and harmonization; formal statistical analysis.

Emily Goren: Data collection and harmonization; formal statistical analysis.

Frank Detterbeck: Supervision, Writing, Reviewing and editing.

Usman Ahmad: Reviewing and editing.

Sarit Appel: Reviewing and editing.

Andrea Bille: Reviewing and editing.

Souheil Boubia: Reviewing and editing.

Cecilia Brambilla: Reviewing and editing.

Ayten Kayi Cangir: Reviewing and editing.

Conrad Falkson: Reviewing and editing.

Wentao Fang: Reviewing and editing.

Pier Luigi Filosso: Reviewing and editing.

Giuseppe Giaccone: Reviewing and editing.

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Francesco Guerrera: Reviewing and editing.

Maurizio Infante: Reviewing and editing.

Dong Kwan Kim: Reviewing and editing.

Marco Lucchi: Reviewing and editing.

Mirella Marino: Reviewing and editing.

Edith M. Marom: Reviewing and editing.

Andrew G. Nicholson: Reviewing and editing.

Meinoshin Okumura: Reviewing and editing.

Ramon Rami-Porta: Supervision, Writing, Reviewing and editing.

Andreas Rimner: Reviewing and editing.

Charles B. Simone II: Reviewing and editing.

Hisao Asamura: Reviewing and editing.

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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.2023.09.002.

Appendix 1

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IASLC Staging and Prognostic Factors Committee Chair: Hisao Asamura.

Lung Cancer Domain

Lung Cancer Domain Chair: Paul Van Schil.

Lung Cancer Domain Vice Chair: Kemp Kernstine.

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Lung Cancer Domain Lepidic & GGO Subcommittee. William Travis (chair), Philippe Joubert (co-chair), Hisao Asamura, Frank Detterbeck, Giuseppe Cardillo, Wendy Cooper, Ritu R. Gill, Jin Mo Goo, Young Tae Kim, Ho Yun Lee, Heber MacMahon, Edith M. Marom, David Naidich, Andrew G. Nicholson, Mizuki Nishino, Helmut Prosch, Ramon Rami-Porta, Valerie Rusch, Shuji Sakai, Yasushi Yatabe, Shun-ichi Watanabe.

Lung Cancer Domain Neuroendocrine Tumors Subcommittee. Ming Tsao (chair), Andrew G. Nicholson, (co-chair), Ricardo Beyruti, Frank Detterbeck, Wilfried Eberhardt, Pier Luigi Filosso, Yolande Lievens, Eric Lim, Geoffrey Liu, José-María Matilla, Natasha Rekhtman, William Travis, Jeff Yang, Yasushi Yatabe.

Lung Cancer Domain Stage. Hisao Asamura (chair), Giuseppe Cardillo, Frank Detterbeck, John Edwards, Kwun Fong, Meredith Giuliani, James Huang, Kemp Kernstine, Edith M. Marom, Andrew G. Nicholson, Ramón Rami-Porta, William Travis, Ming Tsao, Paul Van Schil, Shun-ichi Watanabe.

Lung Cancer Domain Lymph Node Chart Subcommittee. Shun-ichi Watanabe (chair), Jin Mo Goo (co-chair), Hisao Asamura, Hans Hoffman, James Huang, Kemp Kernstine, Yolanda Lievens, Raymond U. Osarogiagbon, Paul Martin Putora, Ramón Rami-Porta, Valerie Rusch, Paul Van Schil, Jeff Yang.

Lung Cancer Domain Validation and Methodology Subcommittee. Frank Detterbeck (chair), Alyson Mahar (co-chair), Hisao Asamura, Meredith Giuliani, Mirella Marino, Raymond U. Osarogiagbon, Valerie Rusch.

Lung Cancer Domain Prognostic Factors Subcommittee. Frank Detterbeck (chair), Raymond U. Osarogiagbon (co-chair), Alex Brunelli, Kwun Fong, James Huang, Young Tae Kim, Mark Krasnik, Hiu Liu, Jan van Meerbeeck, Luis M. Montuenga, Andrew G. Nicholson, Valerie Rusch, Robert Samstein, Navneet Singh, Martin Tammemägi, Ricardo Terra, Ming Tsao, Akif Turna, Terence Williams.

Lung Cancer Domain R Factor Subcommittee. John Edwards (chair), Marcin Ostrowski (co-chair), Souheil Boubia, Jessica Donnington, Hans Hoffman, Maurizio Infante, Mirella Marino, Edith M. Marom, Jun Nakajima, Andrew G. Nicholson, Paul Van Schil, William Travis, Ming Tsao, Yasushi Yatabe.

Lung Cancer Domain Imaging Subcomittee. Jim Mo Goo (chair), Ritu R. Gill (co-chair), Helmut Prosch (co-chair), Samuel Armato, Hui Liu, Heber MacMahon, Edith M. Marom, David Naidich, Charles Powell, Paul Van Schil, William Travis.

Lung Cancer Domain Multiple Pulmonary Nodules Subcommittee. Frank Detterbeck (chair), Alyson Mahar (co-chair), Sarit Appel, Jason Chang, Keneng Chen, Nicolas Girard, Jin Mo Goo, Young Tae Kim, Heber MacMahon, Andrew G. Nicholson, Paul Martin Putora, Natasha Rekhtman, M Patricia Rivera, Lynn Tanoue, Ricardo M. Terra, William Travis, Paula Ugalde.

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Lung Cancer Domain Database. Paula Ugalde (chair), Pietro Bertoglio (co-chair), Sarit Appel, Philippe Joubert, Catherine Labbe, Hongxu Liu, Gustavo Lyons, José-María Matilla, Robert Samstein, Ricardo Terra, Maria Teresa Ruiz Tzukazan, Benny Weksler.

Cancer Research And Biostatistics. Vanessa Cilento, Daniel Dibaba, Megan Eisele, Dorothy Giroux, Emily Goren, Antje Hoering, Katie Nishimura, Adam Rosenthal.

Thymic Epithelial Tumors Domain

Enrico Ruffini (chair), James Huang (co-chair), Usman Ahmad, Sarit Appel, Andrea Bille, Souheil Boubia, Cecilia Brambilla, A K Cangir, Frank Detterbeck, Conrad Falkson, Wentao Fang, Pier Luigi Filosso, Giuseppe Giaccone, Nicolas Girard, Francesco Guerrera, Maurizio Infante, Dong Kwan Kim, Marco Lucchi, Mirella Marino, Edith M. Marom, Andrew Nicholson, Meinoshin Okumura, Andreas Rimner, Anja Roden, Charles B. Simone II. *Thymic Domain T descriptor*: Andrew Nicholson (chair), Cecilia Brambilla, A K Cangir, Maurizio Infante, Mirella Marino, Edith M. Marom, Meinoshin Okumura.

Thymic Domain N descriptor: Wentao Fang (chair), Frank Detterbeck, Pier Luigi Filosso, Marco Lucchi, Edith M. Marom, Charles B. Simone II.

Thymic Domain M descriptor: Nicolas Girard (chair), Usman Ahmad, Sarit Appel, Conrad Falkson, Wentao Fang, Giuseppe Giaccone, Dong Kwan Kim, Edith M. Marom, Andreas Rimner.

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Pleural Mesothelioma Domain

Valerie Rusch (chair), Anna Nowak (co-chair), Pietro Bertoglio, Andrea Billè, Dean Fennell, Françoise Galateau, Ritu R. Gill, Seiki Hasegawa, Hong Kwan Kim, Hedy Kindler, Jan van Meerbeeck, Isabelle Opitz, Harvey Pass, Marc de Perrot, David Rice, Andreas Rimner, Jennifer Sauter, Ming Tsao, David Waller, Andrea Wolf.

Esophageal Cancer Domain

Wentao Fang (chair), Xavier D'Journo (co-chair), Gail Darling, Jeremy Erasmus, Mark Ferguson, Wayne Hofstetter, Hong Kwan Kim, Donald Low, Paula Ugalde.

Appendix 3. Participating Institutions in the third phase of the IASLC Thymic Tumors Staging Project

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