# The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposals for the T component for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

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**Abstract:** Despite longstanding recognition of thymic epithelial neoplasms, there is no official American Joint Committee on Cancer/Union for International Cancer Control stage classification. This article summarizes proposals for classification of the T component of stage classification for use in the 8th edition of the tumor, node, metastasis classification for malignant tumors. This represents the output of the International Association for the Study of Lung Cancer and the International Thymic Malignancies Interest Group Staging and Prognostics Factor Committee, which assembled and analyzed a worldwide database of 10,808 patients with thymic malignancies from 105 sites. The committee proposes division of the T component into four categories, representing levels of invasion. T1 includes tumors localized to the thymus and anterior mediastinal fat, regardless of capsular invasion, up to and including infiltration through the mediastinal pleura. Invasion of the pericardium is designated as T2. T3 includes tumors with direct involvement of a group of mediastinal structures either singly or in combination: lung, brachiocephalic vein, superior vena cava, chest wall, and phrenic nerve. Invasion of more central structures constitutes T4: aorta and arch vessels, intrapericardial pulmonary artery, myocardium, trachea, and esophagus. Size did not emerge as a useful descriptor for stage classification. This classification of T categories, combined with a classification of N and M categories, provides a basis for a robust tumor, node, metastasis classification system for the 8th edition of American Joint Committee on Cancer/Union for International Cancer Control stage classification.

**Key Words:** Prognosis, Thymoma, Thymic carcinoma, Staging, Stage classification

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Thymic epithelial neoplasms are a rare but well-established group of organ-specific neoplasms with varying malignant potential that comprise thymomas, thymic carcinomas (TC) and thymic neuroendocrine tumors (NETT). However, despite their longstanding recognition, there has never been an official American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) stage classification, perhaps in part due to their relative rarity. At least 15 different stage classification systems have been proposed, beginning as far back as 1978. The various classification systems and their differences have been recently reviewed[1] with the most widely known system being the Masaoka system.[2] This was proposed in 1981 on the basis of an experience with 91 patients, with most other systems being based on roughly similar, relatively small cohorts of patients. The Masaoka system was refined to the Masaoka-Koga system[3] and remains the most widely used system currently.

The International Thymic Malignancies Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC) more or less simultaneously set out to accomplish a staging system for thymic epithelial neoplasms, and subsequently joined forces in 2010, partnering to create a Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC), charged with the development of

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†††See Appendix 1; ‡‡‡see Appendices 2, 3, and 4; and §§§see Appendix 5.

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proposals to AJCC/UICC for the eight edition of the stage classification system. ITMIG provided the engagement of the vast majority of clinicians and researchers active in these diseases, and IASLC provided funding for the project and statistical analysis and its expertise in developing proposals for stage classification. Retrospective and prospective databases were created to allow global collection of cases.[4]

Initial discussion formed the view that (1) a system based on tumor, node, metastasis (TNM) staging was preferable and (2) the staging system should be applicable to all three major subgroups of thymic epithelial neoplasms, not least as there is overlap between tumor subtypes.[5] This would therefore be consistent with staging systems for other organs.

Members of the committee were divided into groups to look at T, N, and M components individually, in similar fashion to the IASLC staging project for the 7th edition of lung cancer staging.[6–9] This article describes the development of proposals for the descriptors of the T component for the 8th edition of TNM classification system.

## METHODS

ITMIG and IASLC partnered with other organizations devoted to thymic disease to create a collaborative worldwide database involving 105 institutions and 10,808 patients (Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A663), as has been described previously.[4] Of these, 2663 of the patients (25%) were excluded (due to missing endpoints in 1921 [18%], date errors in 62, first treatment before 1990 in 258 [2%], and missing stage or diagnosis data in 422 [4%]), leaving 8145 of patients for analysis. Most of the cases were first treated between 2000 and 2010 (Supplementary Figure 2, Supplemental Digital Content 2, http://links.lww.com/JTO/A664). The vast majority of patients were treated with surgery, reflecting both the predominance of this treatment modality and that surgeons and pathologists were more able to provide data (Fig. 1). Data were available on the pathologic stage in 8084 patients, on the clinical stage in 5232 patients, on survival in 8145 patients (this was one of the inclusion criteria), and on recurrence in 4732 patients. Specific data on involved structures were reported in 7197, with one dimension of size in 6441 and with more than one dimension in 286 patients. Resection status was noted in 7726 patients (R0 in 6621, R1 or R2 in 1105). Further details of patients available for analysis by invaded structures are shown in Supplementary Table 1 (Supplemental Digital Content 3, http://links.lww.com/JTO/A665).

For the assessment of the T component, the TD-SPFC assessed the impact of involvement of various mediastinal structures. Data were collected for extent of direct invasion beyond tumor capsule into mediastinal structures (wholly encapsulated, limited to mediastinum, mediastinal pleura, pericardium, lung, superior vena cava, brachiocephalic artery and vein, phrenic nerve, chest wall, pulmonary artery, aorta and myocardium), using recently updated histological definitions based on parameters in the Masaoka-Koga staging system.[10]

The TD-SPFC focused on the endpoints of recurrence and survival. In thymic malignancies, these are not closely linked (recurrence does not necessarily lead to death and deaths are often not due to recurrence). Recurrence is probably the best measure in less advanced tumors.[11] Focusing on only R0 resected patients has the effect of equalizing one of the major treatment modalities. However, this is most applicable to less advanced tumors; the more extensive tumors that are resected likely represent an increasingly selected cohort (see Supplemental Figure 3, Supplemental Digital Content 4, http://links.lww.com/JTO/A666). Survival in all patients regardless of resection status may be the best outcome measure in more advanced tumors, but outcomes then reflect a combination of the effect of the tumor extent itself and efficacy of treatment. As a result of these considerations, the TD-SPFC considered recurrence in R0 resected patients, and overall survival in both R0 and all patients regardless of resection status. No further stratification by treatment was possible.

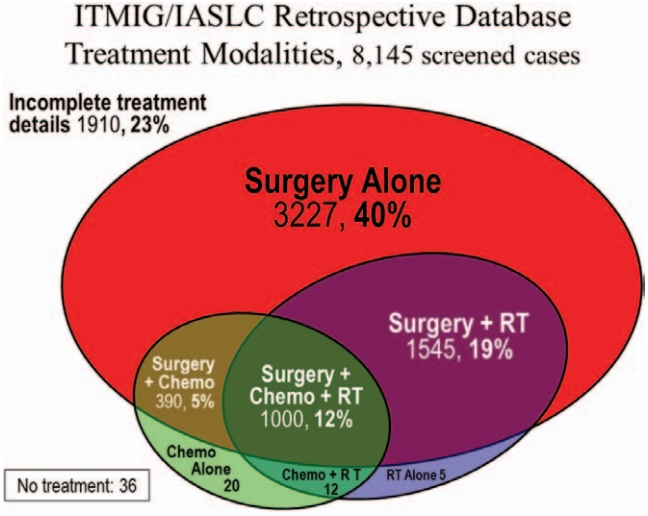



**FIGURE 1.** Overview of the data set by treatment modality. Overview of data available for analysis by treatment modality used. Among cases with known treatment modalities used, surgery was included in 99%. Chemo, chemotherapy; RT, radiotherapy.

Actuarial and cumulative incidence curves relative to these endpoints were generated from multiple different viewpoints, exploring details of relationships, and factors such as histological type and subtype (thymoma versus thymic carcinoma and World Health Organization A + AB + B1 versus B2 + B3), type of staging system (Masaoka versus Masaoka-Koga), geographic region (Asia versus Europe versus North and South America; also Japan versus rest), and other parameters. During this process, approximately 500 different graphs were reviewed by the TD-SPFC. The initial assessment involved visual scrutiny of the curves and consideration of clinical relevance. This allowed the TD-SPFC to achieve an understanding of the data, the limitations, and the pitfalls, and to develop a structure for more detailed statistical analysis.

Statistical analysis of the data was carried out by the Cancer Research and Biostatistics (CRAB) organization using the SAS System for Windows version 9.3. Overall survival (OS) was estimated by the method of Kaplan and Meier,[12] and curves were compared using the logrank test.[13] The cumulative

incidence of recurrence (CIR), which accounts for the presence of the competing risk of death,[14] was used to estimate recurrence. For both OS and CIR, 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.

To assess the impact of size on OS, patients with one-dimensional tumor size ($n$ = 5796) were allocated at random to either a learning set (for the identification of a cut point for size) that comprised two-thirds of the sample or a validation set (for testing that cut point, if a significant cut point was identified) that comprised the remaining one-third. The allocation was stratified by pathologic Masaoka or Masaoka-Koga stage, continent on which the patient was treated, and tumor size greater than 10 cm or not to ensure that these factors were distributed similarly within the two sets. Patients treated with neoadjuvant chemotherapy or radiotherapy were excluded from these analyses. Two methods for choosing tumor size cut points were then applied to the learning set, and outcomes from the resultant cut points were then compared in the validation set. In the first approach, running logrank statistics were used to identify a cut point for tumor size that best separated patients based on outcome.[15] In the second, a recursive partitioning and amalgamation algorithm was used to identify a cut point for size and groupings,[16] based on Masaoka or Masaoka-Koga stage and histological type.

**TABLE 1.** T Categories and Descriptors

| T | Descriptors |
|---|---|
| T1 | A tumor that either is limited to the thymus with or without encapsulation, directly invades into the mediastinum only or directly invades the mediastinal pleura but does not involve any other mediastinal structure<br>For further testing, T1 is subdivided into T1a (no mediastinal pleural involvement) and T1b (direct invasion of the mediastinal pleura)<br>*(Level 1 structures—thymus, anterior mediastinal fat, mediastinal pleura)* |
| T2 | A tumor with direct invasion of the pericardium (either partial or full-thickness)<br>*(Level 2 structures—pericardium)* |
| T3 | A tumor with direct invasion into any of the following: lung, brachiocephalic vein, SVC, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins<br>*(Level 3 structures—lung, brachiocephalic vein, SVC, phrenic nerve, chest wall, hilar pulmonary vessels)* |
| T4 | A tumor with invasion into any of the following: aorta (ascending, arch, or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus<br>*(Level 4 structures—aorta [ascending, arch, or descending], arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus)* |

T categories are defined by "levels" of invasion; they reflect the highest degree of invasion regardless of how many other (lower level) structures are invaded.
SVC, superior vena cava.

## PROPOSED T CATEGORIES

### Overall Approach by "Levels" of Invasion

Initial analyses of potential descriptors of the T component were complex, and many different approaches were assessed. The complexity was due to (1) the number of structures that could be involved, (2) involvement could include only one structure or several structures, and (3) involvement of some structures implied involvement of another, but this may be underreported (e.g., involvement of the lung implies involvement of the mediastinal pleura although this was not always reported).

After informal inspection of outcome data for various cohorts defined according to patterns of invasion, the committee settled on an approach based on "levels" of involvement (Table 1). This meant that a tumor would be counted in a certain "level" of involvement if either one or more than one structure of that level is involved, with or without explicit involvement of structures included in a lower level. This approach was chosen because it allowed management of complexities as described above, and it was supported by survival and recurrence outcomes that demonstrated no difference for a particular level whether or not a lower level structure was reported as involved. Structures were grouped into a level primarily based on how similar or distinct the survival and recurrence outcomes were, but also took into account anatomical considerations and interpreted the results in light of limitations of the database (e.g., limited data on unresected patients).

### T1—Localized to Thymus and Perithymic Fat

T1 includes tumors that are encapsulated and tumors that extend beyond a capsule into the anterior (perithymic) fat. Thus, T1 includes tumors that were classified as stage I or II in the Masoaka or Masaoka-Koga stage classification systems. It also includes tumors classified as either stage IIa or IIb in either of these systems.

Inclusion of these various tumors in T1 was based on the fact that there was no consistent difference in outcomes (recurrence or survival) among the Masaoka or Masaoka-Koga groups or subgroups (Fig. 2 and Supplementary Figure 4, Supplemental Digital Content 5, http://links.lww.com/JTO/A667). In only a few analyses was there a suggestion of a small difference (CIR by c-stage and in Japanese Association for Research in the Thymus cases); however because these small differences were not borne out in other analyses, they did not, in the opinion of the TD-SFPC, justify further separation.

In addition, there was no clinically significant difference across multiple analyses in outcomes of patients with tumors that were otherwise confined to the thymus or perithymic fat (i.e., T1) whether the mediastinal pleura was recorded as being involved or not. There is also a general perception among many pathologists that it is difficult to identify the mediastinal pleura microscopically.[17] Furthermore, the crude rate of recurrence or death with only mediastinal pleura involvement was similar to other T1 tumors (Table 2). However, there is a slight difference in CIR in patients from Japan submitted by the Japanese Association for Research in the Thymus. Therefore, the TD-SPFC decided, to gain more prospective data for further testing, to subcategorize T1 into T1a (no mediastinal pleural involvement) and T1b (involvement of the mediastinal pleura). This involvement should be pathologically confirmed.

## T2—Involvement of Pericardium

T2 denotes tumor with direct invasion of the pericardium (either partial or full-thickness). For pathologic staging, this must be microscopically confirmed; invasion is defined as invasion into the fibrous (parietal) pericardium. The pericardium is the only structure included in the T2 level.

The pericardium is the most often involved mediastinal structure (after the mediastinal pleura). Identification of pericardial involvement microscopically is straightforward (in contrast to the mediastinal pleura). Although radiographic identification of pericardial involvement (i.e., clinical staging) may be imprecise, it is easy to identify a suspicion of involvement when the tumor abuts the pericardium. From a surgical perspective, resection of a potentially involved portion of pericardium is straightforward.

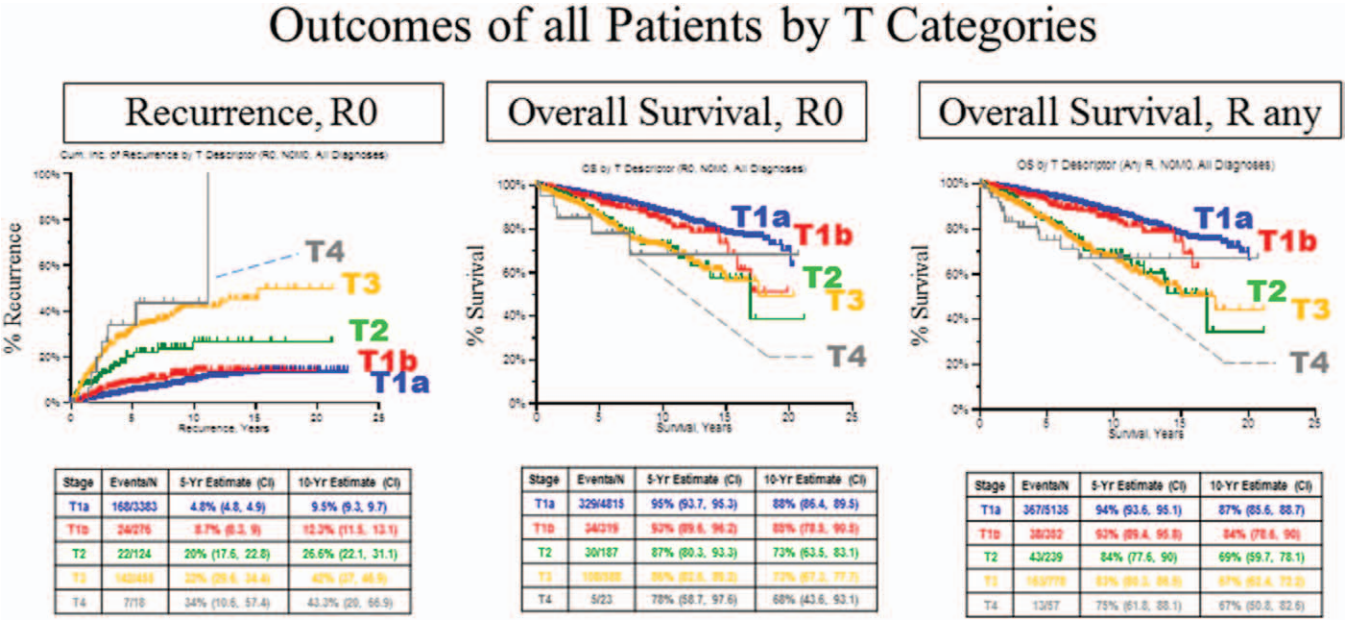
Involvement of the pericardium resulted in a worse rate of recurrence and survival in patients than those with T1 involvement (either with or without mediastinal pleural involvement) (Fig. 2). Furthermore, recurrence was lower than for involvement of level 3 structures.

## T3—Involvement of Lung, Brachiocephalic Vein, Vena Cava, Phrenic Nerve, Chest Wall

Involvement of the lung, brachiocephalic vein, superior vena cava, phrenic nerve, or chest wall is classified as T3. This includes involvement of one or several of these structures, and is classified the same whether lower level tissues (e.g., pericardium) are involved or not. Hilar vascular structures such as extrapericardial pulmonary artery or pulmonary veins are also classified as T3.

An extensive analysis underlies this definition. There are many different ways one could address involved structures, given the number of different structures involved and possible combinations. Involvement of each single structure alone was compared (including pericardium and mediastinal pleura); there were no apparent differences, except that mediastinal pleural involvement was only associated with few recurrences (Supplementary Figure 5, Supplemental Digital Content 6, http://links.lww.com/JTO/A668). Various ways of combining involved structures, and whether involvement of a single structure should be classified differently from when multiple structures are involved were considered. The lack of a consistent difference and the advantage of simplicity led to the proposed grouping by level of invasion, consisting of one or more structures involved within a level (±lower level involvement). Furthermore, from a treatment (i.e., surgical) standpoint, the complexity of involvement of level 3 structures is similar and distinctly better than involvement of level 4 structures, and worse than involvement of pericardium only.

The proposed definition of T3 results in a progressive increase in the rate of recurrence (Fig. 2 and Tables 2 and 3). Recurrence was deemed the more informative outcome for this issue. OS was similar for T2 and T3. Some nuances of observed outcomes deserve mention. Involvement of a single level 3 structure resulted in lower recurrence rates than multiple level 3 structures (10-year CIR 36% [95% CI, 32–41] versus 57% [95% CI, 41–72]). However, the CIR for single level 3 involvement was higher than that for pericardial (T2) involvement (10-year CIR 25% [95% CI, 21–29]). Nevertheless, after considering multiple different outcomes, ways of grouping




| Stage | Events/N | 5-Yr Estimate (CI) | 10-Yr Estimate (CI) |
|---|---|---|---|
| T1a | 168/3383 | 4.8% (4.8, 4.9) | 9.5% (9.3, 9.7) |
| T1b | 24/276 | 8.7% (6.3, 9) | 12.3% (11.5, 13.1) |
| T2 | 22/124 | 20% (17.6, 22.8) | 26.6% (22.1, 31.1) |
| T3 | 14/2453 | 22% (20.6, 24.4) | 40% (37, 46.9) |
| T4 | 7/10 | 34% (10.6, 57.4) | 43.3% (20, 66.9) |

| Stage | Events/N | 5-Yr Estimate (CI) | 10-Yr Estimate (CI) |
|---|---|---|---|
| T1a | 329/4815 | 95% (93.7, 95.3) | 88% (86.4, 89.5) |
| T1b | 34/319 | 92% (89.6, 96.2) | 89% (78.3, 90.8) |
| T2 | 30/187 | 87% (80.3, 93.3) | 73% (63.5, 83.1) |
| T3 | 108/388 | 86% (82.6, 89.3) | 73% (67.3, 77.7) |
| T4 | 5/23 | 78% (58.7, 97.6) | 68% (43.6, 93.1) |

| Stage | Events/N | 5-Yr Estimate (CI) | 10-Yr Estimate (CI) |
|---|---|---|---|
| T1a | 367/5135 | 94% (93.6, 95.1) | 87% (85.6, 88.7) |
| T1b | 38/382 | 92% (89.4, 95.8) | 84% (78.6, 90) |
| T2 | 43/239 | 84% (77.6, 90) | 69% (59.7, 78.1) |
| T3 | 169/779 | 83% (80.3, 86.8) | 67% (62.4, 72.2) |
| T4 | 13/57 | 79% (61.8, 88.1) | 67% (50.8, 82.6) |

**FIGURE 2.** Outcomes of all patients by T categories. Outcomes for all patients with a thymic malignancy of any type (e.g., thymoma, thymic carcinoma, neuroendocrine tumor, and other). *A*, Cumulative incidence of recurrence, R0 resected patients; (*B*) overall survival, R0 resected patients; and (*C*) overall survival, all patients (any R status). Point estimates at 5 and 10 years are provided in the tables. See Table 3 for statistical significance of the differences between the T categories. CI, 95% confidence interval; Cum. Inc., cumulative incidence; *N*, total number of evaluable patients; OS, overall survival; R0, complete resection; Yr, year.

**TABLE 2.** Total Proportion of Recurrences or Deaths

| T Category | Recurrences | | Deaths | |
|---|---|---|---|---|
| | % | n | % | n |
| **T1** | **5** | **192/3659** | **7** | **363/5134** |
| T1a | 5 | 168/3383 | 7 | 329/4815 |
| T1b | 9 | 24/276 | 11 | 34/319 |
| **T2** | **18** | **22/124** | **16** | **30/187** |
| **T3** | **31** | **142/455** | **19** | **108/588** |
| T3 single | 25 | 59/240 | 19 | 65/335 |
| T3 multiple | 39 | 83/215 | 17 | 43/253 |
| **T4** | **39** | **55/1047/18** | **22** | **5/23** |
| **Total** | **10** | **363/4256** | **9** | **506/5932** |

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 3.** Differences between T Categories

| | CIR, R0 (363/4256)[a] | | OS, R0 (506/5932)[a] | | OS, any R (624/6561)[a] | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | ***p*** | **HR** | ***p*** | **HR** | ***p*** |
| HR vs. adjacent T category | | | | | | |
| T2 vs. T1 | 3.10 | <0.0001 | 2.05 | 0.0002 | 2.30 | <0.0001 |
| T3 vs. T2 | 1.67 | 0.025 | 1.03 | NS | 1.00 | NS |
| T4 vs. T3 | 1.30 | NS | 1.00 | NS | 0.94 | NS |

Hazard ratios and statistical differences ($\chi^2$) by cox proportional hazards regression models, adjusted by diagnosis.

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

CIR, cumulative incidence of recurrence; HR, hazard ratio; NS, not significant (*p* values are given if <0.1); OS, overall survival; R0, complete resection.

structures, and practical (simplicity) and surgical aspects, the proposed T3 category was felt to be consistent with outcome data, clinically relevant and practically applicable.

## T4—Involvement of Aorta, Pulmonary Artery, Myocardium, Arch Vessels, Trachea, Esophagus

T4 structures include the myocardium, the intrapericardial pulmonary artery, the aorta (ascending, arch, or descending), the arch vessels (brachiocephalic, carotid, and subclavian arteries), the trachea, and the esophagus. These are grouped as level 4 structures and distinguished from level 3 (T3) structures.

To assess the impact of T4, OS in all patients regardless of R status was considered to be most informative. There was a trend to worse OS for T4 versus T3; but there were insufficient cases to support statistical inference (Fig. 2 and Tables 2 and 3). The number of patients available for analysis with T4 involvement was limited, reflecting the fact that the retrospective database was largely produced by surgeons and pathologists. Even the patients who were operated on but not completely resected likely represent only a subset of all T4 patients. Specifically, data were available on 31 patients with aortic, 21 with arch vessel, 20 with pulmonary artery, and one with myocardial involvement; insufficient numbers of patients were available for analysis with esophageal or tracheal involvement.

Involvement of T4 structures presents major complexity from the standpoint of surgical resection. Such involvement can be suspected from imaging. Furthermore, this classification of structures as T4 is consistent with the classification for lung cancer. Therefore, the proposed T4 category is clinically applicable, practical, and appears to be supported by outcome data (recognizing that outcomes for all T4 patients are almost certainly worse than that of the selected patients in the database).

## Tumor Size

Among the patients with the necessary covariates for the size analyses, a single dimension of tumor size was available in 5796 cases; there were insufficient cases ($n$ = 231) with greater than one dimension measurements to allow a meaningful analysis of area or volume. Using a training and validation set ($n$ = 3828 and 1968 for any R and 3365 and 1715 for R0, respectively), a running log rank statistical analysis was performed to identify relevant cut points for tumor size. Ten cm was identified as the only valid cut point among the any R cohort (Supplementary Figure 6A, Supplemental Digital Content 7, http://links.lww.com/JTO/A669); in the R0 cohort, 9.5 cm was the best cut point but it was not statistically significant. Overall, survival curves demonstrated a difference in the any R cohort. However, this difference was entirely due to a difference in outcomes among incompletely resected patients; there was no difference whatsoever among R0 patients (Supplementary Figure 6C, D, Supplemental Digital Content 7, http://links.lww.com/JTO/A669). Further analysis stratifying by Masaoka/Masaoka-Koga stage showed that size was only predictive among stages III, IV R1,2 patients. A recursive partitioning analysis was performed to assess the importance of size relative to other tumor features. This also showed that other staging characteristics were dominant in separating groups by prognosis, with size playing only a minor role, well behind all other factors.

Although size did not seem to have value for stage classification, the TD-SPFC considered whether it could be useful in predicting the ability to perform a complete resection. However, this was not the case (Supplementary Figure 6B, Supplemental Digital Content 7, http://links.lww.com/JTO/A669); an additional analysis relative to R0 versus R1 versus R2 was also not revealing. Therefore, because size only comes into play postoperatively among R1,2 patients, there is little clinical usefulness for this marker and size was not considered further in the stage classification.

## Thymoma and Thymic Carcinoma

When analyzed separately, the outcomes followed a similar pattern for thymoma and TC as compared with all diagnoses (Supplementary Table 2 [Supplemental Digital Content 3, http://links.lww.com/JTO/A665] and Supplementary Figures 7 [Supplemental Digital Content 8, http://links.lww.com/JTO/A670] and 8 [Supplemental Digital Content 9, http://links.lww.com/JTO/A671]). Specifically, there was no clear difference between T1a and T1b. T2 (pericardium) showed a higher recurrence rate than T1 and a lower recurrence rate than T3; for OS T2 and T3 were fairly similar. There were too few patients with T4 tumors to allow a meaningful assessment of outcomes of

these groups within a specific histological type. There were too few NETTs to analyze separately regarding T categories (NETT cases were not included in the analyses of TC, but only in the analyses of all patients).

## DISCUSSION

The TD-SPFC guiding principles were to develop a stage classification that was simple and straightforward, globally applicable, and as much as possible to be consistent with the existing classifications.[4] This article documents a proposed methodology for the T staging of thymic epithelial neoplasms by assigning levels of direct invasion of mediastinal structures, based on a retrospective analysis of 8145 cases from an international database created by ITMIG and IASLC, with validation of groups when available. Hitherto, only the Masaoka system had been validated in a large cohort (1320 patients).[18] Key changes from the existing systems are the grouping together as "level1" invasion of tumors limited to the mediastinum, independent of capsular invasion, and those with mediastinal pleural involvement only. "Level 2" is limited to pericardium only. Direct involvement of other mediastinal structures are grouped as "level 3" (lung, brachial vein, superior vena cava, chest wall, phrenic nerve) and "level 4" (aorta, myocardium, brachiocephalic artery, pulmonary artery). Size does not seem to be a prognostic factor.

Previous classification systems have advocated stage I disease as being limited to tumors that were either entirely encapsulated or lacked a capsule but had no infiltration into the mediastinal fat.[1] This was to be distinguished from stage II disease where the tumor was limited to the mediastinum, with division into stages IIA and IIB on the basis of the measured extent of extracapsular spread.[1,3] Our data show that there is no significant difference in overall survival between encapsulated tumors and those limited to the mediastinum, with only non-significant differences in CIR found in various sub analyses. These data are similar to those found in a meta-analysis undertaken on 2451 cases from 21 publications, which also found no difference between stages I and II thymomas.[19] One might question whether the use of adjuvant radiotherapy affected the CIR. The TD-SPFC was not able to carry out a separate analysis of this, but other systematic reviews have suggested that adjuvant radiotherapy does not alter recurrence rates in Masaoka stage I or II patients after an R0 resection.[20,21]

Involvement of the mediastinal pleura has been variably assigned to stage II or III (or not clearly defined) in prior stage classification systems.[1] Indeed, the mediastinal pleura is poorly defined in anatomical textbooks and is frequently difficult or impossible to see on microscopic examination. The opinion of the thymic domain committee members was split on whether there should be subdivision of T1 (level 1) into subgroups of T1a and T1b on the basis of extension through the mediastinal pleura, with a marginal consensus to distinguish these subgroups to facilitate accumulation of further evidence to address this in the future.

Most previous classification systems have included involvement of many mediastinal structures within a stage III group.[1] Better distinction of subgroups among these may have the greatest utility in defining outcomes and treatment strategies. The TD-SPFC was only able to partially evaluate this from the available data. We propose a distinction between levels 2, 3, and 4 structures, but recognize that prospective data and future research may provide yet better ways of distinguishing subgroups of these patients.

There are inevitable limitations using a retrospective database in relation to amount of detail, varying interpretations of how a particular data element is defined by different institutions, changing definitions and policies over the course of the data collection, and questions about the comparability of data from different centers despite bearing the same data labels. Also, because thymic epithelial tumors are rare, the amount of data available for analysis of subgroups is limited. Nevertheless, we believe that the data in this analysis are sufficiently robust so that the proposed categories and descriptors for the T component represent a step forward. The timing of the AJCC/UICC process limits the availability of sufficient prospective data to substantially contribute to the 8th edition of the stage classification; however, the ITMIG prospective database, which contains much more detail, should provide a solid basis for analyzing areas of uncertainty in the future.

In conclusion, this study presents evidence from a cohort of more than 8000 patients for the T component of the classification of anatomical extent of thymic epithelial neoplasms based on four levels of direct invasion of mediastinal structures. These can be taken forward for assessment alongside the N and the M components to produce a robust TNM classification system for submission to the 8th edition of TNM staging by the AJCC/UICC.

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