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

The ITMIG/IASLC 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 (AJCC/UICC) stage classification. This paper summarizes proposals for classification of the T component of stage classification for use in the 8th edition of the TNM classification for malignant tumors. This represents the output of the International Thymic Malignancies Interest Group and the International Association for the Study of Lung Cancer (ITMIG/IASLC) 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 4 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, 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 TNM classification system for the 8th edition of AJCC/UICC stage classification.

Introduction

Thymic epithelial neoplasms are a rare but well established group of organ-specific neoplasms with varying malignant potential, that comprise thymomas, thymic carcinomas 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 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 proposals to AJCC/UICC for the 8th edition of the stage classification system. Retrospective and prospective databases were created to allow global collection of cases [4].

Initial discussion formed the view that (a) a system based on TNM staging was preferable and (b) 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 paper describes the development of proposals for the descriptors of the T component for the 8th TNM classification system.

METHODS

ITMIG partnered with other organizations devoted to thymic disease to create a collaborative worldwide database involving 105 institutions and 10,808 patients (Figure e1), as has been described previously [4]. Of these, 2663 (25%) were excluded (due to missing endpoints in 1921 [18%], date errors in 62, first treatment prior to 1990 in 258 [2%], missing stage or diagnosis data in 422 [4%]), leaving 8,145 for analysis. Most of the cases were first treated between 2000 and 2010 (Figure e2). 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 (Figure 1). Data were available on pathologic stage in 8084, on clinical stage in 5232, on survival in 8145 (this was one of the inclusion criteria) and on recurrence in 4732. Specific data on involved structures was reported in 7197, with one dimension of size in 6441 and with >1 dimensions in 286. Resection status was noted in 7726 (R0 in 6621, R1 or R2 in 1105). Further details of patients available for analysis by invaded structures are shown in Table e1.

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 figure e3). 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 in all patients regardless of resection status. No further stratification by treatment was possible.

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 vs. Thymic carcinoma and WHO A+AB+B1 vs. B2+B3), type of staging system (Masaoka vs. Masoaka-Koga), geographic region (Asia vs. Europe vs. North + South America; also Japan vs. 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 pitfalls, and 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. OS was estimated by the method of Kaplan and Meier [12] and curves 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) which comprised two thirds of the sample or a validation set (for testing of that cut-point, if a significant cut-point was identified) of the remaining third. The allocation was stratified by pathologic Masaoka or Masaoka-Koga stage, continent on which the patient was treated, and tumor size >10cm 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 log rank 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 histologic type.

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 (a) the number of structures that could be involved, (b) involvement could include only one structure or several structures, and (c) involvement of some structures implied involvement of another but this may be under-reported (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 describe above, plus it was supported by survival and recurrence outcomes which demonstrated no difference for a particular level whether or not a lower level structure was reported as involved. Structures were grouped into a level based primarily 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 as well as 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 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 (Figure 2 and e4). In only a few analyses was there a suggestion of a small difference (CIR by c-stage and in JART 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 mediastinal pleura only involvement was similar to other T1 tumors (Table 2). However, there is a slight difference in CIR in patients from Japan submitted by the JART. Therefore, the TD-SPFC decided, in order 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. The pericardium is the only structure included in the T2 level.

The pericardium is the most commonly involved mediastinal structure (after the mediastinal pleura). Identification of pericardial involvement microscopically is straightforward (in contrast to the mediastinal pleura). While 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 than patients with T1 involvement (either with or without mediastinal pleural involvement) (Figure 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) is 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 only was associated with few recurrences (Figure e5). Various ways of combining involved structures were considered, as well as whether involvement of a single structure should be classified differently from when multiple structures are involved. 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 (Figure 2, 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] vs. 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 structures, as well as practical (simplicity) and surgical aspects, the proposed T3 category was felt to be consistent with outcomes 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 vs. T3; but there were insufficient cases to support statistical inference (Figure 2, 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 was available on 31 patients with aortic, 21 with arch vessel, 20 with pulmonary artery, and 1 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 outcomes data (recognizing that outcomes for all T4 patients is 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 >1 dimensional 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 statistic analysis was performed to identify relevant cutpoints for tumor size. Ten cm was identified as the only valid cutpoint among the any R cohort (Figure e6A); in the R0 cohort 9.5 cm was the best cutpoint 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 (Figure e6C,D). Further analysis stratifying by Masaoka/Masaoka-Koga stage showed that size was only predictive among stage 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 appear 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 (Figure e6B); an additional analysis relative to R0 vs. R1 vs. 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 (Table e2 and Figure e7, e8). 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 histologic type. There were too few neuroendocrine tumors to analyze separately regarding T categories.

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 existing classifications [4]. This paper 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 existing systems are the grouping together as “level one” 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 appear 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 stage IIA and stage 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 stage I and stage II thymomas [19]. One might question whether the use of adjuvant RT 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 RT does not alter recurrence rates in Masaoka Stage I or Stage II patients after an R0 resection [20, 21].

Involvement of the mediastinal pleura has been variably been assigned to stage II or III (or not clearly defined) in prior stage classification systems.[1] Indeed, the mediastinal pleura is poorly defined in anatomic 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 in order 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 level 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 is sufficiently robust 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 over 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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Figures

Figure 1: Overview of the Dataset 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;

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, carcinoid and other).
A Cumulative incidence of recurrence, R0 resected patients; B Overall survival, R0 resected patients; 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. of Recurrence, cumulative incidence of recurrence; N, total number of evaluable patients; OS overall survival; R0, complete resection; Yr, year;

Online Only eFigures

Figure e1: Overview of Data Sources

Overview of data available for analysis by country and contributing organization
ESTS, European Society of Thoracic Surgeons; IASLC, International Association for the Study of Lung Cancer; ITMIG, International Thymic Malignancy Interest Group; JART, Japanese Association for Research in the Thymus; UK, United Kingdom;

Figure e2: Distribution by Year of 1st Treatment

Number of patients available for analysis in database by year of 1st Treatment.

Figure e3: Data Available for Recurrence and Survival Analysis

Number of patients available for recurrence and survival analysis in database by Masaoka or Masaoka-Koga stage and R status. Not shown in the graph are 61 patients with p and c-stage information missing.
CIR, Cumulative Incidence of Recurrence; OS, Overall Survival; R0, complete resection; R1,2,x, Incomplete resection and unknown resection status

Figure e4: Impact of Encapsulation on Recurrence Rate

Impact of involvement of encapsulated tumors vs. tumors extending into the surrounding thymus or mediastinal fat. M/M-K Stage I refers to encapsulated tumors, M/M-K Stage II to tumors with penetration through the capsule into perithymic tissues.
Cum. Inc. of recurrence, cumulative incidence of recurrence; M, Masaoka stage classification; M-K, Masaoka-Koga stage classification; N, total number of evaluable patients; OS overall survival; R0, complete resection;

Figure e5: Isolated involvement of Specific Structures

Impact of exclusive involvement of specific structures. Data includes patients with any type of thymic malignancy (e.g. thymoma, thymic carcinoma, carcinoid, other)
A) Cumulative incidence of recurrence in R0 patients; B) Overall survival in R0 resected patients.

Brach V, brachiocephalic vein (= innominate vein); Med Pleura, mediastinal pleura; Peric, pericardium; Phr N, phrenic nerve;

Figure e6: Impact of Size on Outcomes

Definition of an optimal size cutpoint and assessment of impact thereof in R0 patients, all diagnoses (learning data set).
A) Log rank statistic by size criterion. 3828 patients in learning dataset for OS, any R endpoint (after excluding any patients with neoadjuvant chemo or RT). The graph shows the logrank statistics (y-axis) based on comparing two groups of patients, where the two groups are defined according to whether the tumor is greater than or less than a given size cut-point (x-axis). One logrank statistic is calculated for each value of size, and these (x,y)=(size, logrank statistic) pairs form the graph. The maximum logrank statistic (~35) occurs at size=10 cm, and this indicates that using a cut-point of < 10 cm vs. >=10 cm will "best" separate the two survival curves (when using this particular dataset). The value of the logrank statistic is larger than the 95th percentile, indicating statistical significance at the 0.05 level. Bar graph depicts number of patients by size. B) Impact of the 10cm size criterion on the ability to achieve an R0 resection by clinical stage. C) Overall survival in R0 resected patients. D) Overall survival in R1,2 resected patients.

Figure e7: Outcomes of Thymoma Patients by T Categories.

A) Cumulative incidence of recurrence in R0 patients; B) Overall survival in R0 resected patients; C) Overall survival in all patients (any R status).
Point estimates at 5 and 10 years are provided in the tables. Curves for Level 4 structures not shown due to consistently low sample sizes. The number of events/patients for the recurrence cohort, the OS R0 cohort, and the OS any R cohort are 5/14, 2/16, and 3/28, respectively.
CI, 95% confidence interval; Cum. Inc. of Recurrence, cumulative incidence of recurrence; N, total number of evaluable patients; OS overall survival; R0, complete resection; Yr, year;

Figure e8: Outcomes of Thymic Carcinoma Patients by T Categories.

A) Cumulative incidence of recurrence in R0 patients; B) Overall survival in R0 resected patients; C) Overall survival in all patients (any R status).
Point estimates at 5 and 10 years are provided in the tables. Curves for Level 4 structures not shown due to consistently low sample sizes. The number of events/patients for the recurrence cohort, the OS R0 cohort, and the OS any R cohort are 2/4, 3/7, and 9/25, respectively.
CI, 95% confidence interval; Cum. Inc. of Recurrence, cumulative incidence of recurrence; N, total number of evaluable patients; OS overall survival; R0, complete resection; Yr, year;

Tables

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. For further testing T1 is subdivided into T1a (no mediastinal pleural involvement) and T1b (direct invasion of the mediastinal pleura) *(Level 1 structures – thymus, anterior mediastinal fat, mediastinal pleura)*
T2	A tumor with direct invasion of the pericardium (either partial or full thickness) *(Level 2 structures – pericardium)*
T3	A tumor with direct invasion into any of the following: lung, brachiocephalic vein, superior vena cava (SVC), phrenic nerve, chest wall or extrapericardial pulmonary artery or veins *(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 *(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.

Table 2: Total Proportion of Recurrences or Deaths

	Recurrences		Deaths	
T Category	**%**	**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**

This table depicts 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

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

	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

[a] number of events/total number of patients in entire dataset 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

Table e1: Numbers of Patients Available for Analysis of the T Component

T	Level and Details	Number of patients
T1	Level 1: Localized to thymus (± encapsulated) and perithymic tissues	5487
	Encapsulated (M/MK Stage I)	2777
	Involvement of anterior mediastinal fat (M/MK Stage II)	2358
	Involvement of mediastinal pleura	352
T2	Level 2: Pericardium	239
T3	Level 3: Lung, Brachiocephalic Vein, SVC, Chest Wall, Phrenic Nerve	778
	Single Level 3 structure	296
	Single Level 3 structure + Level 2	125
	Multiple Level 3 structures ± Level 2	357
T4	Level 4: Aorta, Pulmonary Artery, Myocardium, Brachiocephalic Artery	57
	Single Level 4 structure	8
	Single Level 4 structure + Level 2	5
	Single Level 4 structure + Level 3 structure(s) ± Level 2	30
	Multiple Level 4 structures ± Level 2 or 3 structure(s)	14
	Masoaka/Masaoka-Koga Stage III, involved structures not specified	542

Number of patients available for Overall Survival analysis, any R status (R0, R1, R2, Rx)

M/MK, Masaoka or Masaoka-Koga stage classification; SVC, Superior Vena Cava;

Table e2: Total Proportion of Recurrences or Deaths by Tumor Type

	Recurrences		**Deaths**	
T Category	**%**	**n**	**%**	**n**
Thymoma				
T1	5	158/3494	7	328/4890
T2	15	15/103	15	22/147
T3	25	89/350	15	68/447
T4	36	5/14	13	2/16
Thymic Carcinoma				
T1	19	26/139	15	30/197
T2	33	6/18	19	7/36
T3	47	45/95	30	38/126
T4	50	2/4	43	3/7

This table depicts the total number of recurrences or deaths observed at any time out of the total number of evaluable R0 resected patients in each category.

APPENDICES

Appendix 1: IASLC Staging and Prognostic Factors Committee

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Appendix 4: Advisory Board of the IASLC Esophageal Cancer Domain

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