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.

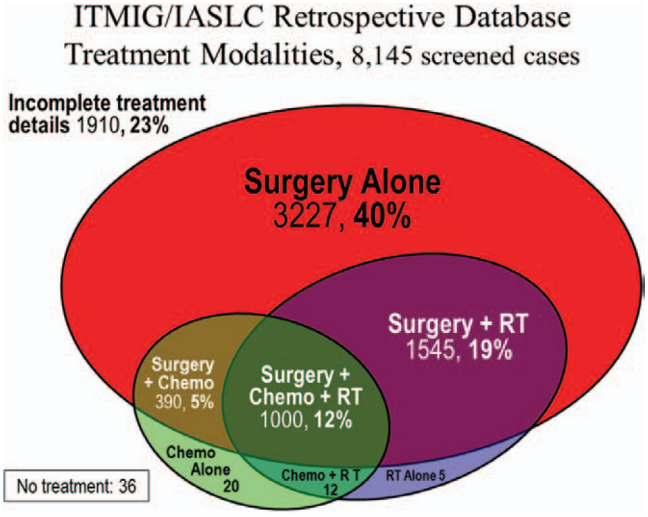

FIGURE 1. Overview of the data set by treatment modality. Overview of data available for analysis by treatment modality used. Among cases with known treatment modalities used, surgery was included in 99%. Chemo, chemotherapy; RT, radiotherapy.

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