complications. The long-term outcomes were also analyzed to evaluate the significance of surgery for malignancies of the lungs in patients with a history of HNSCC.

Patients and methods

The present study is a retrospective analysis of consecutive patients with a history of head and neck squamous cell carcinoma who underwent pulmonary resection for thoracic malignancies between 1994 and 2011 in our hospital. During this period, a total of 45 pulmonary resections were performed on 39 patients (six patients underwent repeat thoracotomy). In the six patients who underwent repeat pulmonary resection, only the data for the first pulmonary resection were analyzed in the present study. Thirty-seven patients were male, two patients were female, and the mean age of all patients was 64.0 years (median 66.0 years; range 23–81 years). The patient characteristics are summarized in Table 1. The criteria used for chronic obstructive pulmonary disease (COPD) in this study were according to the "guidelines for the diagnosis and treatment of COPD 3rd edition" published by the Japanese respiratory society [6].

Table 1 Patient characteristics

Characteristics	No. of patients
Sex	
Male	37 (95 %)
Female	2 (5 %)
Age (years)	
Mean ± SD	64.0 ± 11.4
Range	23–81
Smoking status	
Current	4 (10 %)
Ex	33 (85 %)
Never	2 (5 %)
Brinkman index	
Mean ± SD	1195 ± 906
Range	0–5000
Body mass index	
Mean ± SD	21.8 ± 3.6
Range	15.2–31.8
Medical history	
Malignancy besides HNSCC	11 (28 %)
COPD	7 (18 %)
Hypothyroidism	6 (15 %)
Coronary artery disease	4 (10 %)
Hypertension	9 (23 %)
Diabetes mellitus	3 (8 %)
Chronic liver disease	2 (5 %)
Chronic kidney disease	1 (3 %)

The patients in the present study were all heavy smokers, had relatively low body mass indices (BMI) (a BMI <18.5 kg/m^2 is defined as underweight according to the WHO BMI cut-off points [7]), and showed high incidences of a history of malignancy besides HNSCC and comorbidities such as COPD. Eleven patients had a history of malignancy besides HNSCC: seven patients had esophageal cancer, two patients had gastric cancer, one patient had both gastric and colon cancers and one patient had both esophageal and gastric cancers. In all of these patients, the other malignancies had been previously treated at the time of pulmonary resection. Six patients had hypothyroidism due to radiotherapy for primary HNSCC.

All patients had been treated for primary HNSCC with curative intent, as summarized in Table 2. Seven patients

Table 2 Clinical characteristics of the patients with head and neck squamous cell carcinoma

Characteristics	No. of patients
Location of primary HNSCC	
Oral cavity	11 (28 %)
Oropharynx	4 (10 %)
Nasopharynx	1 (3 %)
Hypopharynx	9 (23 %)
Larynx	14 (36 %)
Stage of primary HNSCC	
I	7 (18 %)
II	4 (10 %)
III	12 (31 %)
IVA	9 (23 %)
IVB	1 (3 %)
Unknown	6 (15 %)
Treatment of primary HNSCC	
S,C,R	7 (18 %)
S,R	7 (18 %)
C,R	14 (36 %)
S	5 (13 %)
R	6 (15 %)
History of local relapse	
Yes	9 (23 %)
No	30 (77 %)
Tracheostoma	
Yes	2 (5 %)
No	37 (95 %)
Time interval between treatment for primary HNSCC and detection of pulmonary nodule(s) (months)	
Mean	29
Median	15
Range	0–163

S surgery, *C* chemotherapy, *R* radiation

underwent a combination of surgery, chemotherapy and irradiation (including concurrent and sequential regimens), seven patients underwent surgery and radiotherapy, 14 patients underwent chemotherapy and radiotherapy (including concurrent and sequential regimens), five patients underwent surgery alone, and six patients underwent radiotherapy alone. The follow-up after treatment for primary HNSCC was generally based on chest X-rays or chest computed tomography (CT) and cervical CT, and physical examinations and a blood chemistry analysis were performed every six to 12 months after treatment. Pulmonary nodule(s) and primary HNSCC were detected simultaneously in six patients and metachronously in 33 patients. The mean and median time intervals between the treatment for primary HNSCC and detection of pulmonary nodule(s) were 29 and 15 months, respectively (range 0–163 months).

Preoperative diagnostic procedures to treat pulmonary nodules were attempted in 20 patients (transbronchial biopsy was performed in 14 patients and CT-guided percutaneous core needle biopsy was performed in six patients), and a pathological diagnosis of malignancy was confirmed preoperatively in 18 patients. When pulmonary metastases from HNSCC were suspected preoperatively, patients underwent resection of the pulmonary metastases if they met the following criteria: (1) the pulmonary nodules were deemed completely resectable, (2) the absence of apparent mediastinal lymph node metastases was determined by a preoperative radiological examination, (3) metastatic disease was limited to the lungs or extrapulmonary distant metastasis was controlled or controllable if present, (4) locoregional control of the primary HNSCC was achieved, and (5) good overall general conditions and adequate respiratory function to tolerate lung resection were present. The type of resection was selected according to the size and location of the tumors and the overall general conditions and respiratory function of the patients. A lesser resection was preferably selected as long as a curative resection was possible. When primary lung cancer was suspected preoperatively, lobectomy and mediastinal lymph node dissection were generally performed. Sublobar resection and/or omission of mediastinal lymph node dissection were performed in patients with an impaired general condition or respiratory function.

The medical, surgical and anesthesia records were thoroughly reviewed to analyze operation-related factors and postoperative complications. In the present study, a difficult airway was defined as one with Cormack Lehane grade III or IV [8], the need for devices besides a direct vision laryngoscope or the need for tracheostomy for airway management. Postoperative complications were graded according to the Clavien–Dindo classification of surgical complications [9]. All specimens obtained from pulmonary resection were reviewed by pathologists. When the pulmonary lesions were pathologically diagnosed as "squamous cell carcinoma, difficult to distinguish primary lung cancer from metastases from HNSCC," it was determined whether the lesions were primary lung cancer or metastases from HNSCC based on the clinical factors, i.e. determined by thoracic and head and neck surgeons who considered the stage of the primary HNSCC, the preoperative radiological findings and the clinical course of the patient.

Postoperative chemotherapy was performed in two patients with primary lung cancer and seven patients with pulmonary metastases from HNSCC. The follow-up was generally based on chest CT, physical examination and laboratory blood tests performed every six to 12 months after lung resection. Follow-up information was obtained from the hospital medical records and letters from general practitioners. The overall survival was defined as the time interval between the date of lung resection and death or the last follow-up for living patients (censored). The time interval between lung resection and the latest follow-up in the present study ranged from one to 213 months (median 38 months).

The following factors were assessed for an association with the development of postoperative complications using a univariate analysis: age (<65 years/≥65 years), smoking status (current/ex, never), BMI (<18.5/≥18.5), medical history (malignancy besides HNSCC, COPD, hypothyroidism, coronary artery disease, hypertension, diabetes mellitus, chronic liver disease, chronic kidney disease), treatment of primary HNSCC (including/not including surgery), the presence of tracheostoma, time interval between treatment for primary HNSCC and pulmonary resection (<24 months/≥24 months), the surgical approach, type of resection and the extent of lymph node dissection (mediastinal/hilar or none). All statistical analyses were conducted using the Stat View 5.0 software program (SAS Institute, Berkley, CA). The data are expressed as the mean values ± SD. Differences in clinical variables between two groups were evaluated using Fisher's exact test. The overall survival was analyzed with the Kaplan–Meier method using the date of pulmonary resection as the starting point. The significance of differences between groups was analyzed by the log-rank test. A p value <0.05 was considered to be statistically significant.

Results

The mean and median time intervals between the treatment for primary HNSCC and pulmonary resection were 34 and 24 months, respectively (range 4–166 months). A complete resection was achieved in 37 patients (95 %). Eight patients (21 %) had difficult airways, and one of these eight patients required a planned tracheostomy for airway

management. All of these patients had undergone treatment for primary HNSCC with radiotherapy, and four of these eight patients had already undergone surgery. The patient who required a planned tracheostomy was a 66-year-old male. He had undergone chemoradiotherapy for hypopharynx cancer 28 months before the pulmonary resection. A physical examination by an anesthesiologist revealed that he had difficulty in opening his mouth, with an opening smaller than two fingerbreadths, and also had decreased neck mobility. After a consultation with otolaryngologists and anesthesiologists, we performed a preoperative tracheostomy and left upper lobectomy with mediastinal lymph node dissection. He suffered from Grade II arrhythmia, however, he recovered well without major airway complications.

The operation-related factors are summarized in Table 3. No surgery-related mortalities occurred. Nine patients (23 %) developed postoperative complications. The postoperative complications are summarized in Table 4. Two patients developed a pyothorax that required surgical intervention under general anesthesia. One patient had glossoptosis in the early postoperative period on the day of surgery that resulted in hypoxic ischemic encephalopathy due to difficult airway management caused by decreased neck mobility. The results of the univariate analysis are shown in Table 5. A low BMI (<18.5), a history of malignancy besides HNSCC and COPD were each significantly associated with the development of postoperative complications. Both the patients who suffered from a pyothorax had COPD.

Table 3 Operation-related factors

Intraoperative factors	No. of patients
Difficult airway	8 (21 %)
Size of tumor	
Mean ± SD	26 ± 10
Range	8–50
No. of tumors	
Solitary	32 (82 %)
Multiple	7 (18 %)
Approach	
VATS	11 (28 %)
Open	28 (72 %)
Type of resection	
Lobectomy	27 (69 %)
Segmentectomy	8 (21 %)
Wide wedge resection	4 (10 %)
Lymph node dissection	
None	4 (10 %)
Hilar	17 (44 %)
Hilar and mediastinal	18 (46 %)
Length of operation (min)	
Median	220
Range	72–450
Blood loss (g)	
Median	195
Range	15–1360

VATS video-assisted thoracoscopic surgery

Table 4 Postoperative complications classified according to the Clavien–Dindo classification

Complications	No. of patients	
	Grade I, II	Grade III, IV
Prolonged air leak	3	0
Pyothorax	0	2
Airway obstruction	0	1
Arrhythmia	2	0
Wound infection	0	1
RNP	1	0
Total	9*	

RNP recurrent nerve palsy

* One patient had two complications

Based on the pathological examinations and the combination of clinical factors, 15 patients (38 %) were diagnosed with pulmonary metastases from HNSCC, while 24 patients (62 %) were diagnosed with primary lung cancer. The histological type of the primary lung cancer was adenocarcinoma in nine patients, squamous cell carcinoma in 14 patients and pleomorphic carcinoma in one patient. The pathological stage of the primary lung cancer was IA in 12 patients, IB in nine patients and IIB in three patients. The 5-year survival rate of all patients was 80 %, that of the patients with pulmonary metastases from HNSCC was 70 %, and that of the patients with primary lung cancer was 86 % (Fig. 1). Postoperative chemotherapy did not influence the survival ($p = 0.13$). The treatment of the primary HNSCC (including/not including surgery) also did not influence the survival ($p = 0.33$).

Discussion

In the present study, we analyzed the outcomes of surgery for pulmonary malignancies in patients with a clinical history of HNSCC. Patients with a history of HNSCC occasionally show poor general conditions associated with smoking and the treatment used for the primary HNSCC. HNSCC is associated with a high likelihood of developing secondary primary malignancies due to the effects of tobacco and alcohol, i.e. esophageal and lung cancer [10].

Table 5 Results of the univariate analysis

Variable	Postoperative complications + ($n = 9$)	Postoperative complications − ($n = 30$)	P value
Age (<65 years/≥65 years)	7/2	15/15	N.S.
Smoking status (current/ex, never)	1/8	3/27	N.S.
Body Mass Index (<18.5/≥18.5)	5/4	3/27	0.003
Malignancy besides HNSCC (yes/no)	5/4	6/24	0.038
COPD (yes/no)	5/4	2/28	<0.001
Hypothyroidism (yes/no)	3/6	3/27	N.S.
Coronary artery disease (yes/no)	2/7	2/28	N.S.
Hypertension (yes/no)	4/5	5/25	N.S.
Diabetes mellitus (yes/no)	0/9	3/27	N.S.
Chronic liver disease (yes/no)	0/9	2/28	N.S.
Chronic kidney disease (yes/no)	0/9	1/29	N.S.
Treatment of primary HNSCC (including/not including surgery)	4/5	15/15	N.S.
Tracheostoma (yes/no)	0/9	2/28	N.S.
Time interval between treatment for primary HNSCC and pulmonary resection (<24 months/≥24 months)	5/4	15/15	N.S.
Approach (VATS/open)	3/6	8/22	N.S.
Type of resection (lobectomy/sublobar resection)	7/2	20/10	N.S.
Lymph node dissection (mediastinal/hilar or none)	5/4	13/17	N.S.

It has been reported that patients with a history of HNSCC are frequently malnourished. Radiation-induced fibrosis and surgical defects caused by the treatment of primary HNSCC are both reported to be followed by excessive weight loss and malnutrition [11, 12]. It has also been reported that patients with a history of HNSCC have relatively higher incidences of comorbidities such as hypertension or COPD [13]. In agreement with these reports, the patients in the present study were all heavy smokers, had relatively low body mass indices and showed high incidences of a history of malignancy besides HNSCC and comorbidities such as COPD.

In the present study, the patients with a history of HNSCC were more likely to have difficulties associated with airway management. Because all eight patients with difficult airways had previously undergone radiotherapy, it is speculated that the decreased neck mobility due to radiotherapy is associated with the development of a difficult airway. In addition, anatomical changes of the airway due to surgery for primary HNSCC, such as reconstruction of the tongue, also affect airway management. We experienced one difficult case that had glossoptosis in the early postoperative period on the day of the operation that resulted in hypoxic ischemic encephalopathy. After the experience with this case, we proactively consider preoperative tracheostomy, and one patient who underwent a planned tracheostomy recovered well postoperatively

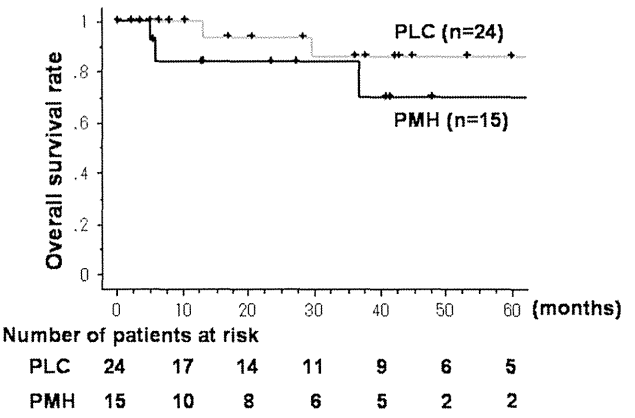

Fig. 1 The survival rate of patients after the resection of pulmonary metastasis from head and neck cancer and primary lung cancer. The 5-year survival rate of the patients with pulmonary metastases from head and neck cancer was 70 %, and that of the patients with primary lung cancer was 86 %. *PLC* primary lung cancer, *PMH* pulmonary metastases from head and neck cancer

without major airway complications. The airway management of patients with a history of HNSCC should be carefully undertaken via a multidisciplinary approach involving otolaryngologists, anesthesiologists and thoracic surgeons, since postoperative complications following pulmonary resection can be related to upper airway dysfunction. We believe that use of preoperative tracheostomy

is an optional strategy to prevent such postoperative complications in high-risk patients.

In the present study, a low BMI (<18.5), a history of malignancy besides HNSCC and the presence of COPD were each significantly associated with the development of postoperative complications. However, because of the small number of patients, definitive conclusions regarding the factors affecting complications cannot be drawn. A low BMI and the presence of COPD were previously reported to be risk factors for prolonged air leakage after pulmonary resection [14, 15]. In 11 patients with a history of malignancy besides HNSCC, eight had a history of esophageal cancer. The treatment for esophageal cancer (surgery, definitive chemo-radiotherapy) might cause a vulnerability of the visceral pleura and intrathoracic adhesions, which might contribute to the development of postoperative complications. We believe that the most important points that should be noted in the perioperative management of pulmonary resection in patients with a history of HNSCC are as follows: (1) preoperative assessment of the nutritional status is mandatory, and nutritional support should be given to patients with malnutrition; (2) careful attention to prevent air leakage should be provided during surgery.

It is often difficult to preoperatively distinguish pulmonary metastases from HNSCC and a second primary lung cancer. In the present study, a preoperative pathological diagnosis of the malignancy was confirmed preoperatively in 18 patients, and four of these patients were diagnosed to have adenocarcinoma, i.e. primary lung cancer. Except for these four patients, it was difficult to distinguish between pulmonary metastases from HNSCC and primary lung cancer preoperatively. Moreover, distinguishing pulmonary metastases from HNSCC and primary lung squamous cell carcinoma based on morphology alone is quite difficult. In addition to the morphological resemblance and degree of differentiation, the stage of the primary HNSCC (a higher stage might imply metastasis), the time interval between the treatment for primary HNSCC and detection of pulmonary nodule(s) (a shorter time interval might imply metastasis) and the number of pulmonary nodules (the presence of multiple nodules might imply metastasis) were taken into account when determining the diagnosis of HNSCC vs. primary lung squamous cell carcinoma.

Distinguishing between pulmonary metastases from HNSCC and metastasis from esophageal cancer is also difficult. In the eight patients who had a previous history of esophageal cancer (squamous cell carcinoma), the histological type of the pulmonary lesions was squamous cell carcinoma in six patients and adenocarcinoma in two patients. Of these six patients with squamous cell carcinoma, four were diagnosed to have pulmonary metastases from HNSCC and two patients were diagnosed with primary lung cancer in the present study after carefully considering the clinical factors, such as the stages of the esophageal cancer and the primary HNSCC, and the disease-free intervals of these diseases. However, the possibility that these pulmonary lesions were metastases from esophageal cancer cannot be completely ruled out.

The present study demonstrated that pulmonary resection for pulmonary malignancies in patients with a history of HNSCC provides favorable long-term outcomes. In the present study, the 5-year survival rate of patients with pulmonary metastases from HNSCC (70 %) was better than the reported 5-year survival rate of patients who underwent pulmonary metastasectomy for HNSCC (21–59 %) [2, 16, 17]. The patient selection and period of the study might have influenced the outcome, because more recent studies have taken advantage of more accurate imaging modalities and new chemotherapy regimens. On the other hand, the use of surgery for primary lung cancer in patients with a history of HNSCC also provided a favorable outcome, with a 5-year survival rate of 86 %. This favorable outcome could be attributed to the relatively early detection of lung nodules, i.e. the nodules were detected during the follow-up for primary HNSCC. Because of the favorable outcomes in both patients with pulmonary metastases from HNSCC and in those with primary lung cancer, aggressive surgical management should be considered for treating pulmonary malignancies in patients with a history of HNSCC as long as the patient status is preserved.

This study had some limitations. First, the analysis was of patients treated over a decade, with changing radiological and therapeutic modalities. In particular, the outcome of surgery for pulmonary metastases was largely affected by the assessment of extrapulmonary metastasis. Second, the follow-up period was relatively short (median 38 months). Third, the difficulty in distinguishing between pulmonary metastases from HNSCC and primary lung cancer might also have affected the outcomes. Finally, because this study included a variety of postoperative complications with a wide range of severity in only nine patients, it is difficult to draw definitive conclusions regarding the risk factors associated with postoperative complications.

Conclusions

The airway management of patients with a history of HNSCC should be carefully undertaken. However, because favorable outcomes can be achieved with both surgical resection of pulmonary metastases from HNSCC and surgical resection of second primary lung cancers, aggressive surgical management should be considered for the

treatment of pulmonary malignancies in patients with a previous history of HNSCC.

Conflict of interest Ryu Kanzaki and co-authors have no conflicts of interest to declare.

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The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

Frank C. Detterbeck, MD, Kelly Stratton, MS,† Dorothy Giroux, MS,† Hisao Asamura, MD,‡ John Crowley, PhD,† Conrad Falkson, MBChB,§, Pier Luigi Filosso, MD,‖, Aletta A. Frazier, MD,‖‖‖ Giuseppe Giaccone, MD,¶, James Huang, MD,#, Jhingook Kim, MD,**, Kazuya Kondo, MD,††, Marco Lucchi, MD,‡‡, Mirella Marino, MD,§§, Edith M. Marom, MD,‖‖, Andrew G. Nicholson, MD,¶¶, Meinoshin Okumura, MD,##, Enrico Ruffini, MD,‖, Paul Van Schil, MD,*** on behalf of the Staging and Prognostic Factors Committee,††† Members of the Advisory Boards,‡‡‡ and Participating Institutions of the Thymic Domain§§§*

Abstract: A universal and consistent stage classification system, which describes the anatomic extent of a cancer, provides a foundation for communication and collaboration. Thymic epithelial malignancies have seen little progress, in part because of the lack of an official system. The International Association for the Study of Lung Cancer and the International Thymic Malignancies Interest Group assembled a large retrospective database, a multispecialty international committee and carried out extensive analysis to develop proposals for the 8th edition of the stage classification manuals. This tumor, node, metastasis (TNM)-based system is applicable to all types of thymic epithelial malignancies. This article summarizes the proposed definitions of the T, N, and M components and describes how these are combined into stage groups. This represents a major step forward for thymic malignancies.

*Thoracic Surgery, Yale University, New Haven, CT; †Biostatistics, Cancer Research and Biostatistics, Seattle, WA; ‡Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan; §Radiation Oncology, Queen's University, Ontario, Canada; ‖Thoracic Surgery, University of Torino, Torino, Italy; ¶Medical Oncology, Georgetown University, Washington, DC; #Thoracic Surgery, Sloan Kettering Cancer Center, New York, NY; **Thoracic Surgery, Samsung Medical Center, Seoul, South Korea; ††Thoracic Surgery, University of Tokushima, Tokushima, Japan; ‡‡Thoracic Surgery, University of Pisa, Pisa, Italy; §§Pathology, Regina Elena National Cancer Institute, Rome, Italy; ‖‖Radiology, MD Anderson Cancer Center, Houston, TX; ¶¶Pathology, Royal Brompton Hospital, London, UK; ##Thoracic Surgery, Osaka University, Osaka, Japan; ***Thoracic Surgery, Antwerp University Hospital, Antwerp, Belgium; and ‖‖‖Thoracic Radiology, University of Maryland, Baltimore, Maryland.
†††See Appendix 1;‡‡‡see Appendices 2, 3, 4;§§§see Appendix 5.
Disclosure: The authors declare no conflict of interest.
Address for correspondence: Frank C. Detterbeck, MD, Department of Surgery, Division of Thoracic Surgery, Yale University School of Medicine, BB205 333 Cedar Street, New Haven, CT 06520. E-mail: frank.detterbeck@yale.edu

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Thymic epithelial malignancies are rare tumors. There have been many obstacles to progress in these diseases. Among these has been the lack of an official, consistent stage classification system put forth by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) —the bodies responsible for defining stage classification throughout the world. At least 15 different stage classification systems have been proposed and used.[1] These have been largely empirically derived, based on data from small numbers of patients. Perhaps the most widely used have been the Masaoka classification (derived from data on 91 patients),[2] and the Koga modification of this (based on 76 patients).[3] Even among centers using one of these classification systems, often the definitions have been interpreted differently because of vague wording, thus hampering the ability to collaborate effectively.[4]

In 2009, both the nascent International Thymic Malignancies Interest Group (ITMIG) and the International Association for the Study of Lung Cancer (IASLC) recognized the need for a consistent stage classification system for thymic malignancies. These organizations formed a partnership to address this, with ITMIG providing the engagement of the vast majority of clinicians and researchers active in these diseases, and IASLC providing funding for the project and statistical analysis and its expertise in developing proposals for stage classification from its experience in doing this in lung cancer.[5] A Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) was established collaboratively by IASLC and ITMIG (Appendix 6). IASLC led discussions and received approval from AJCC and UICC to develop proposals for stage classification of thymic malignancies that

would help define thymic stage classification in the 8th edition of the stage classification manuals. This article describes the stage classification proposals developed by IASLC/ITMIG for the AJCC/UICC to consider. These proposals are published in advance of formal definition of stage classification so that a broader discussion can also be considered as the final classification is defined by AJCC/UICC. Additional articles describe details of the T, N, and M descriptors that are used in the proposed stage classification.[6,7]

METHODS

A worldwide retrospective database was created by ITMIG, which included cases submitted by North and South American, European, and Korean institutions and the Chinese Alliance for Research in Thymoma; this was supplemented by cases from the Japanese Association for Research in the Thymus (JART) and additional cases from the European Society of Thoracic Surgeons. Together, this represents the collaborative effort of 105 institutions worldwide and includes 10,808 patients (Appendix 5). Details of this database have been described earlier.[5]

The TD-SPFC strove to develop a stage classification that was tumor, node, metastasis (TNM) based, and applicable to thymoma as well as thymic carcinoma.[5] While recognizing differences between these tumors, these are offset by the benefit of having a single system in a rare disease. Definition of dividing lines between T, N, or M categories or stage groupings was based partially on the ability to separate prognostically distinct groups. Overall survival (OS) and recurrence were assessed as endpoints, recognizing that in thymic malignancies, these two outcomes are only partially linked (recurrence does not necessarily lead to death and deaths are often not due to recurrence). OS was evaluated both in an R0 resected cohort, which makes a major part of treatment reasonably consistent, as well as in all patients (any R status). Cumulative incidence of recurrence (CIR) was assessed in R0 patients. However, other factors besides these outcomes were considered in defining distinct T, N, and M categories and stage groups, since prognosis is impacted by many factors beyond tumor extent. Priorities included development of a system that was simple, applicable to clinical staging, and able to be used consistently. The stage classification is meant only to describe the anatomic extent of disease; development of a prognostic index being reserved for a subsequent effort.[5]

Statistical analysis of the data was carried out by the Cancer Research and Biostatistics organization. OS was estimated by the method of Kaplan and Meier[8] and curves were compared using the log rank test.[9] The cumulative incidence of recurrence, which accounts for the presence of the competing risk death,[10] 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. Cox regression models[11] were used to obtain hazard ratios for OS and recurrence adjusted for diagnosis (thymoma, thymic carcinoma, and others, which included neuroendocrine thymic tumors [NETT]). Although it was of interest to adjust for geographic region, we were unable to do this given the final stage groupings, because cases with sufficient detail regarding stages IVa and IVb consisted primarily of patients from a single region (Japan).

PROPOSED STAGE CLASSIFICATION

The T component of the proposed stage classification is divided into four categories (Table 1). These correspond to "levels" of involvement, as is discussed in more detail in another article.[6] A tumor is classified in a particular "level" if one or more structures in that level is involved, regardless of whether other structures of a lower level are involved or not. This approach manages the complexity of many different structures that may be involved, either alone or in combination with others. In the proposed T classification, encapsulation of the tumor is not included, because this did not have a clinically significant impact on outcomes among cases in the retrospective database. Pathologically proven involvement of the pericardium is designated as T2, and several different structures are included in the T3 category because they had similar outcomes. Similarly, T4 includes several structures that represent more extensive local invasion of a thymic malignancy.

Lymph node involvement is common in thymic carcinoma but is relatively uncommon in thymoma. Lymph nodes are assigned in two groups according to their proximity to the thymus: anterior (perithymic) and deep cervical or thoracic nodes. These correspond to an N1 and an N2 staging category (Table 2). Involved nodes outside these regions (e.g., axillary, subdiaphragmatic) are outside the N category and considered a distant metastasis. Further details regarding the N and M stage classification are provided elsewhere.[7]

To achieve clarity and consistency regarding node classification, ITMIG assigned a workgroup which together with the IASLC TD-SPFC developed a node map for thymic malignanies, published in detail elsewhere.[12] Representative diagrams are shown in Figure 1. The anterior region, corresponding to N1, is bordered by the hyoid bone and diaphragm craniocaudally, the medial edge of the carotid sheaths and mediastinal pleura laterally, the sternum anteriorly, the pericardium and great vessels posteriorly in the middle, and extending to the level of the phrenic nerves posterolaterally. The deep region extends from the edges of the anterior region to the lateral

TABLE 1. T Descriptors

Category	Definition (Involvement of)[a,b]
T1	
a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
b	Extension into mediastinal pleura
T2	Pericardium
T3	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus

[a]Involvement must be pathologically proven in pathologic staging.
[b]A tumor is classified according to the highest T level of involvement that is present with or without any invasion of structures of lower T levels.

TABLE 2. N and M Descriptors

Category	Definition (Involvement of)[a]
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial, or distant sites
M1	
a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

[a]Involvement must be pathologically proven in pathologic staging.

border of the sternocleidomastoid muscle and the anterior edge of the vertebral column, and includes jugular, supraclavicular, aortopulmonary window, hilar, paratracheal, subcarinal, esophageal, internal mammary, and supradiaphragmatic nodes.

The M component is divided into three categories (Table 2). Absence of tumor outside the primary mass (or nodal metastases) is classified as M0. M1a is used to designate pleural or pericardial nodules (this does not include direct extension of the primary tumor into the pleural or pericardial space). M1b designates pulmonary intraparenchymal nodules or distant metastases (to extrathoracic organs or sites).[7]

The TNM categories are organized into distinct stage groups as shown in Table 3 and Figures 2 to 4. Stages I, II, IIIa, and IIIb are determined primarily by the T component. Stages IVa and IVb are determined by the presence of N1 or M1a disease for IVa and N2 or M1b disease for IVb.

There were many more patients for analysis in the lower stages, consistent with the fact that most patients with thymic malignancies present with locally confined tumors and the fact that data were available predominantly in resected patients. Table 4 lists the numbers of patients and events that were available for analysis in the various stage groups, along with the overall rate of recurrence or death. A progressive increase by stage in the overall rate of recurrence and death is generally observed. This is particularly apparent for recurrence in the lower stages and for OS in any R patients in advanced stages, consistent with the assessment that recurrence (in R0 patients) is a better marker of the impact of disease in the lower stages and OS (in any R patients) in the more advanced stages. For some of the groups (particularly in stages IIIb, IVa, and IVb), the number of patients is limited, hampering a robust analysis. Furthermore, these data are skewed because the database contained very few patients who were not resected; the IIIb, Iva, and especially IVb cohorts likely represent highly selected patients who were considered amenable to resection.

Definition of the T, N, and M categories and stage groups was based heavily on analysis of outcomes. However, there was variability between geographic regions and histologic types. Therefore, Cox proportional hazards regression models were constructed, adjusted by diagnosis (Table 5). Outcome curves are shown in Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A657). In general, a progression of outcomes was seen; each of the analyses offers a different view with advantages and disadvantages. Recurrence is probably the best measure in less advanced tumors.[13] Survival in all patients regardless of resection status may be best in more advanced tumors, although the number of patients is limited. The stage groupings were determined using a combination of these outcomes as well as practical and anatomic considerations.

The proposed stage classification scheme is applicable to both thymoma and thymic carcinoma(TC). Recurrence and OS tables and curves were constructed for these histologic types and demonstrated similar progression of worsening outcomes as in the entire patient cohort (Supplemental Tables 1 and 2 [Supplemental Digital Content 2, http://links.lww.com/JTO/A658] and Supplemental Figures 2 and 3 [Supplemental Digital Content 3, http://links.lww.com/JTO/A659, and Supplemental Digital Content 4, http://links.lww.com/JTO/A660]). However, splitting into smaller stage groups by histologic type results in smaller patient cohorts, precluding the ability to have sufficient power to evaluate statistical significance between individual groups. There were too few NETT to analyze separately regarding stage grouping (NETT cases were not included in the analyses of TC, only in the analyses of all patients). Nevertheless, the proposed stage classification system is recommended to be applied to NETT for consistency. This is an area for validation through prospective data collection.

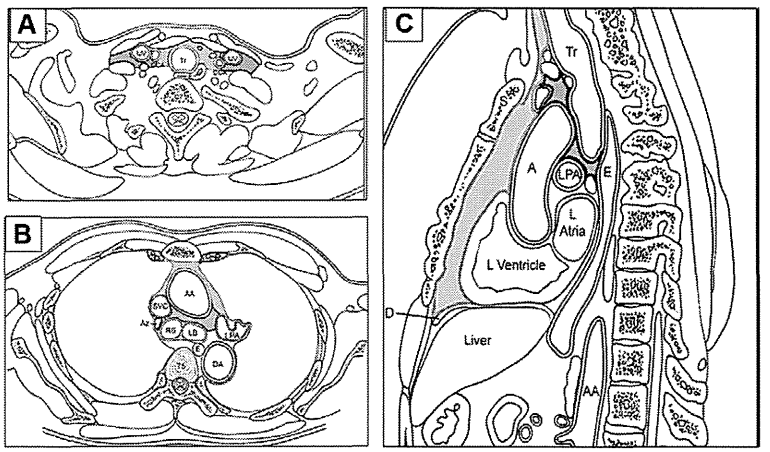

FIGURE 1. ITMIG/IASLC node compartments for thymic malignancies. Graphic depiction of N1 (anterior region, blue) and N2 (deep region, purple) node compartments. *A*, Level of thoracic inlet; (*B*) Level of aortopulmonary window; (*C*) Sagittal view. For further details, see Bhora et al.[12]

TABLE 3. Stage Grouping

Stage	T	N	M
I	**T1**	N0	M0
II	**T2**	N0	M0
IIIa	**T3**	N0	M0
IIIb	**T4**	N0	M0
IVa	T any	**N1**	M0
	T any	N0,1	**M1a**
IVb	T any	**N2**	M0,1a
	T any	N any	**M1b**

DISCUSSION

The TD-SPFC carried out an extensive analysis of a large worldwide database to develop a proposed stage classification system for the 8th edition of the AJCC/UICC stage classification manual. A formally adopted AJCC/UICC stage classification for thymic malignancies would be a major step forward in these diseases by providing a single standard as a foundation for collective assessment of outcomes. Furthermore, the proposed system is a major advance by being based on a careful analysis of a large database with thoughtful input from a multispecialty international panel of experts.

The Masaoka stage classification provided a starting point for stage classification in 1981, based on 91 patients. Many other classifications and modifications have been proposed, but in general these have been built on the framework of the Masaoka system. Indeed, the stage classification proposed by the TD-SPFC also bears some similarities; at the same time, there are also significant differences.

One of the prominent differences is omission of a focus on whether a tumor is encapsulated or extends into the thymus and perithymic fat. This is driven by the fact that analysis of the data did not demonstrate a clinically relevant difference between these situations. Indeed, this corroborates observations made by many other authors.[14] It appears that the previous focus on encapsulation was driven primarily by a speculation that this may distinguish benign thymomas; however, current thinking is that all thymomas are considered malignant.[15] Furthermore, it is worth noting that the capsule is not a normal anatomic structure but is induced somehow by the tumor. At any rate, the data demonstrate that the capsule has little clinical impact.

Involvement of the mediastinal pleura also appears to have little impact in the IASLC/ITMIG database. There is a widespread impression among pathologists that it is often difficult to identify the mediastinal pleura on resected specimens, regardless of invasion (verbal communication, 2nd ITMIG Pathology workshop, Heidelberg, Germany, December 2–3, 2011). However, in analyses of data collected by JART, involvement of the mediastinal pleura does have an impact on freedom from recurrence. After deliberations that are outlined in further detail elsewhere,[6] the TD-SPFC decided to retain the mediastinal pleural involvement as a distinction between T1a and T1b for further testing; without such a designation, collection of sufficient data for further study would be undermined.

The concept of levels of invasion to define T categories is a novel feature of the proposed classification.[6] This represents a logical way to deal with the complexity of involvement of various structures alone or in combination, and potential under-reporting of involvement of lower level structures. However, this needs to be tested in further analyses because the amount of available data with sufficient details was limited. Separation of IIIa and IIIb stage groups appears to be logical, but was not able to be robustly tested in the available data. The distinction of N1 and N2 node groups is supported by data collected by JART, but the amount of data is too limited to assess statistical significance.[7] Finally, inclusion of subpleural nodules in M1a and intraparenchymal pulmonary nodules as M1b was speculative, as the available data on this detail were too limited to compare outcomes between these groups.[7]

Decisions regarding how to organize cohorts into stage groups and definitions of the T, N, and M categories were made after extensive deliberations by the TD-SPFC. This relied heavily on consideration of outcomes; the amount of importance given to particular outcomes (e.g., recurrence, survival) and cohorts (e.g., R0, histologic type, region) was determined by what was judged to be most relevant. Interpretation of the data required accounting for limitations in the data and details available. Practical applicability and clinical implications

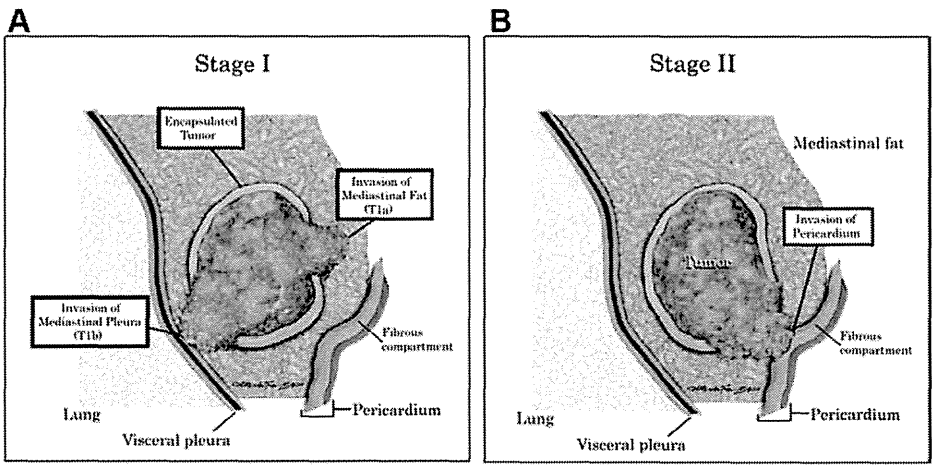

FIGURE 2. Stages I (T1N0M0) and II (T2N0M0). Graphic depiction of Stage group I and II. Copyright © Aletta Ann Frazier, MD. *A*, Stage I: tumor that is either "encapsulated" or extending into the anterior mediastinal fat (T1a) or with direct involvement of the mediastinal pleura (T1b); (*B*) Stage II. Tumor invading the pericardium (either partial or full thickness).

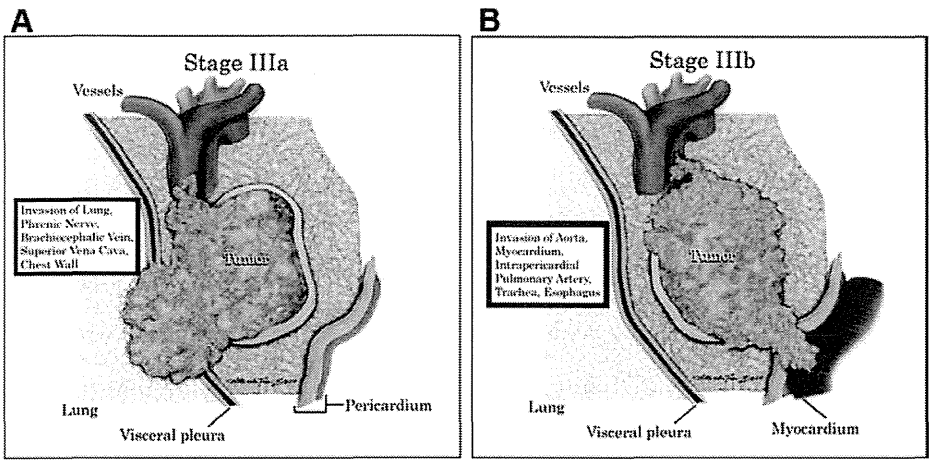

FIGURE 3. Stage IIIa (T3N0M0) and IIIb (T4N0M0). Graphic depiction of Stage group IIIa, b. Copyright © Aletta Ann Frazier, MD. *A*, Tumor invading the lung, brachiocephalic vein, superior vena cava, chest wall, and phrenic nerve; (B) Tumor invading the aorta, intrapericardial pulmonary artery, myocardium, trachea, and esophagus.

were also considered. Finally, the proposed classification was vetted through the general IASLC process of review by all domains of the SPFC.

Clearly, the proposed classification system has weaknesses and limitations. The available data were heavily weighted toward surgical cases—likely representing the greater ability of surgeons and pathologists to have collected data to contribute. More advanced tumors are probably underrepresented, beyond their simple lower incidence compared to earlier stage tumors. Furthermore, the limited availability of details despite the unprecedentedly large database means that some aspects had to be decided upon primarily by consensus after consideration of practical, anatomic and logical factors. It is hoped that the prospective data collection that has been initiated by ITMIG will overcome this in subsequent updates to the stage classification.

The proposed classification is applicable to thymoma, as well as thymic carcinoma, as shown by subgroup analysis of the data. Despite the difference in biologic behavior between thymoma and thymic carcinoma, and therefore differences in prognosis and the proportion of patients in various categories, the lines of separation into distinct groups appear to be justified in each histologic type. Furthermore, there is precedence for applicability of a stage classification to tumors with different degrees of aggressiveness (i.e., the lung cancer stage classification applies to carcinoid tumors, non-small cell lung cancer, and small cell lung cancer). Finally, there is a major advantage in the simplicity of having one-stage classification for thymic tumors in diseases that are already rare and encountered by most clinicians only sporadically.

In clinical use, the T, N, and M categories should ideally be recorded, not just the stage group. Doing this facilitates further research into details that could not be assessed in the retrospective analysis, despite the unprecedented size of the database. It is particularly important to record this even in patients who do not undergo surgery, since little data are available on such patients.

The stage classification system is meant to be a clinically useful classification of the anatomic extent of disease of thymic malignancies. While the anatomic extent has a major impact on prognosis, and while outcomes were used to judge how to organize the cohorts of patients, the stage classification cannot serve as a prognostic prediction model. Prognosis is complex, being influenced by multiple tumor-related, patient-related, treatment-related, and environment-related factors.[16] Furthermore, it is dependent on the clinical scenario, the outcome of interest, and time at which it is assessed; it is also

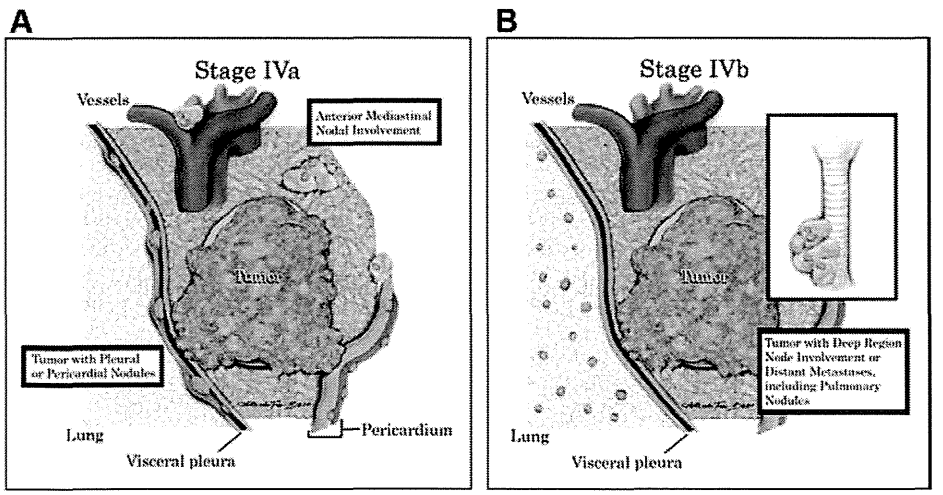

FIGURE 4. Stages IVa and IVb. Graphic depiction of Stage group IVa, b. Copyright © Aletta Ann Frazier, MD. *A*, Tumor with separate pleural or pericardial nodules (M1a) or anterior region node involvement (N1); (*B*) Tumor with deep region node involvement (N2) or distant metastases including intraparenchymal pulmonary nodules (M1b).

TABLE 4. Total Proportion of Recurrences or Deaths

Stage	Recurrences		Deaths	
	%	n	%	n
I	**5**	**192/3659**	**7**	**363/5134**
I (T1a)	5	168/3383	7	329/4815
I (T1b)	9	24/276	11	34/319
II	**18**	**22/124**	**16**	**30/187**
III	**32**	**149/473**	**18**	**113/611**
IIIa	31	142/455	18	108/588
IIIb	39	7/18	22	5/23
IVa	**59**	**119/201**	**30**	**75/251**
N1 M0	54	21/39	28	11/40
N0,1 M1a	60	98/162	30	64/211
IVb	**49**	**17/35**	**33**	**14/43**
N2 M0,1a, x	45	9/20	36	9/25
N0-2,x M1b	53	8/15	28	5/18
Total	**11**	**499/4492**	**10**	**595/6226**

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

continually changing over time. The TD-SPFC specifically postponed development of a prognostic prediction model to be addressed after the stage classification proposals were complete.

CONCLUSION

Stage classification is a fundamental aspect of cancer care, providing a consistent uniform nomenclature that permits communication, collaboration, and application of observed results to the care of new patients. The lack of an official stage classification system has contributed to the lack of progress in thymic malignancies. This report briefly summarizes the extensive work conducted by an international multispecialty panel with extensive analysis of a worldwide database that is unprecedented in thymic malignancies. The proposed T, N, and M categories and stage groupings, applicable to thymoma and thymic carcinoma, provide a basis for the 8th edition of the AJCC/UICC stage classification, due to be defined and published in 2016. This marks the first official stage classification system based on an extensive statistical analysis.

TABLE 5. Differences between Stage Groups (all Diagnoses)

	CIR, R0 (499/4492)[a]		OS, R0 (595/6226)[a]		OS, any R (876/7314)[a]	
Variable	**HR**	***p***	**HR**	***p***	**HR**	***p***
HR vs. adjacent stage						
II vs. I	3.21	<0.0001	2.05	0.0002	2.28	<0.0001
IIIa vs. II	1.72	0.02	1.03	NS	1.00	NS
IIIb vs. IIIa	1.30	NS	1.01	NS	0.94	NS
IVa vs. IIIb	1.67	NS	1.72	NS	2.00	0.02
IVb vs. IVa	0.77	NS	1.29	NS	1.26	NS

Hazard ratios and statistical differences χ^2 by Cox proportional hazards regression models, adjusted for 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.

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Tieu, Oregon Health and Science University, Portland, Oregon, USA; Wentao Fang and Jie Zhang, Shanghai Chest Hospital, Jiaotong University Medical School, Shanghai, China; Zhentao Yu, Tianjin Medical University Cancer Hospital, Tianjin, China; Yongtao Han, Sichuan Cancer Hospital, Chengdu, China; Yin Li, Henan Cancer Hospital, Zhengzhou, China; Keneng Chen, Beijing University Cancer Hospital, Beijing, China; Gang Chen, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China; Meinoshin Okumura, Osaka University, Osaka, Japan; Yoshitaka Fujii, Nagoya City University, Aichi, Japan; Hisao Asamura, National Cancer Center Hospital, Tokyo, Japan; Kanji Nagai, National Cancer Center Hospital East, Chiba, Japan; Jun Nakajima, University of Tokyo, Tokyo, Japan; Norihiko Ikeda, Tokyo Medical University, Tokyo, Japan; Shuji Haraguchi, Nippon Medical School, Tokyo, Japan; Takamasa Onuki, Tokyo Women's Medical University, Tokyo, Japan; Kenji Suzuki, Juntendo University, Tokyo, Japan; Ichiro Yoshino, Chiba University, Chiba, Japan; Masanori Tsuchida, Niigata University, Niigata, Japan; Shoji Takahashi, Shizuoka Cancer Center, Shizuoka, Japan; Kohei Yokoi, Nagoya University, Aichi, Japan; Masayuki Hanyuda, Aichi Medical University, Aichi, Japan; Hiroshi Niwa, Seirei Mikatahara General Hospital, Shizuoka, Japan; Hiroshi Date, Kyoto University, Kyoto, Japan; Yoshimasa Maniwa, Kobe University, Hyogo, Japan; Shinichiro Miyoshi, Okayama University, Okayama, Japan; Kazuya Kondo, Tokushima University, Tokushima, Japan; Akinori Iwasaki, Fukuoka University, Fukuoka, Japan; Tatsuro Okamoto, Kyusyu University, Fukuoka, Japan; Takeshi Nagayasu, Nagasaki University, Nagasaki, Japan; Fumihiro Tanaka, University of Occupational and Environmental Health, Fukuoka, Japan; Minoru Suzuki, Kumamoto University, Kumamoto, Japan; Kazuo Yoshida, Shinsyu University, Nagano, Japan; Yusuke Okuma and Hirotoshi Horio, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo, Japan; Akihide Matsumura, Kinki Chuo Chest Medical Center, Osaka, Japan; Masahiko Higashiyama, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; Hiroshi Suehisa, Shikoku Cancer Center, Ehime, Japan; Takuya Onuki, Tsuchiura Kyodo Hospital, Ibaragi, Japan; Yoshifumi Sano, Ehime University, Ehime, Japan; Keishi Kondo, Hokkaido Cancer Center, Hokkaido, Japan; K. Al Kattan, King Khaled University Hospital, Riyadh, Saudi Arabia; R. Cerfolio, University of Alabama, Birmingham, AL, USA; C. Gebitekin, Uludag University School of Medicine, Bursa, Turkey; D. Gomez de Antonio, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; K.H. Kernstine, Southwestern Medical Center and School of Medicine (SW), University of Texas, Dallas, TX, USA; N. Altorki, The New York Hospital, Cornell Medical Centre, New York, USA; N. Novoa, Salamanca University Hospital, Salamanca, Spain; E. Ruffini and P.L. Filosso, University of Torino, Torino, Italy; S. Saita, University of Catania, Catania, Italy; M. Scarci, Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, UK; L. Voltolini, Università di Siena, Siena, Italy; W. Weder, University Hospital, Zurich, Switzerland; Wojciech Zurek, Medical University of Gdansk, Gdansk, Poland; A. Arame, Hopital Europeen Georges-Pompidou and Hopital Laennec, Paris, France; C. Casadio, Chirurgia Toracica, Novara, Italy; P. Carbognani, Università di Parma, Parma, Italy; G. Donati, Ospedale di Aosta, Aosta, Italy; S. Keshavjee, University of Toronto, Toronto, Canada; W. Klepetko and B. Moser, Medical University of Vienna, Vienna, Austria; C. Lequaglie, Thoracic Surgery, Rionero in Vulture, Italy; Moishe Liberman, Centre Hospitalier de l'Université de Montréal, Montréal, Canada; M. Mancuso, Ospedale Alessandria, Alessandria, Italy; M. Nosotti, Policlinico, Milan, Italy; L. Spaggiari, Istituto Europeo di Oncologia (IEO), Milan, Italy; P.A. Thomas, Hôpital Nord—Université de la Méditerranée, Marseille, France; E. Rendina, University La Sapienza, Ospedale Sant' Andrea, Rome, Italy; F. Venuta and M. Anile, Policlinico Umberto I, Rome, Italy; J. Schützner, Teaching Hospital Motol, Prague, Czech Republic; G. Rocco, Pascale Institute, Napoli, Italy.

APPENDIX 6: MEMBERS OF THE THYMIC DOMAIN OF THE STAGING AND PROGNOSTIC FACTORS COMMITTEE AND ADVISORY BOARD

Hisao Asamura, National Cancer Center, Tokyo, Japan; John Crowley, Cancer Research and Biostatistics, Seattle, WA, USA; Frank Detterbeck, Yale University, New Haven, CT, USA; Conrad Falkson, Queen's University, Ontario, Canada; Pier Luigi Filosso, University of

Torino, Italy; Giuseppe Giaccone, Georgetown University, Washington, DC, USA; Dorothy Giroux, Cancer Research and Biostatistics, Seattle, WA, USA; James Huang, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Jhingook Kim, Samsung Medical Center, Seoul, Korea; Kazuya Kondo, University of Tokushima, Tokushima, Japan; Marco Lucchi, University of Pisa, Pisa, Italy; Mirella Marino, Regina Elena National Cancer Institute, Rome, Italy; Edith M. Marom, MD Anderson Cancer Center, Houston, TX, USA; Andrew G. Nicholson, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, UK; Meinoshin Okumura, Osaka University, Osaka, Japan; Enrico Ruffini, University of Torino, Paul Van Schil, Antwerp University Hospital, Antwerp, Belgium; Kelly Stratton, Cancer Research and Biostatistics, Seattle, WA, USA.

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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

Andrew G. Nicholson, MD, Frank C. Detterbeck, MD,† Mirella Marino, MD,‡ Jhingook Kim, MD,§ Kelly Stratton, MS,‖ Dorothy Giroux, MS,‖ Hisao Asamura, MD,¶ John Crowley, PhD,‖ Conrad Falkson, MBChB,# Pier Luigi Filosso, MD,** Giuseppe Giaccone, MD,†† James Huang, MD,‡‡ Kazuya Kondo, MD,§§ Marco Lucchi, MD,‖‖ Edith M Marom, MD,¶¶ Meinoshin Okumura, MD,## Enrico Ruffini, MD,** and Paul Van Schil, MD,*** on behalf of the Staging and Prognostic Factors Committee†††, Members of the Advisory Boards,‡‡‡ and Participating Institutions of the Thymic Domain§§§*

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

(*J Thorac Oncol.* 2014;9: S73–S80)

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

*Pathology, Royal Brompton Hospital, London, United Kingdom; †Thoracic Surgery, Yale University, New Haven, Connecticut; ‡Pathology, Regina Elena National Cancer Institute, Rome, Italy; §Thoracic Surgery, Samsung Medical Center, Seoul, South Korea; ‖Biostatistics, Cancer Research And Biostatistics, Seattle, Washington; ¶Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan; # Radiation Oncology, Queen's University, Ontario, Canada; **Thoracic Surgery, University of Torino, Torino, Italy; ††Medical Oncology, Georgetown University, Washington, District of Columbia; ‡‡Thoracic Surgery, Sloan Kettering Cancer Center, New York, New York; §§Thoracic Surgery, University of Tokushima, Tokushima, Japan; ‖‖Thoracic Surgery, University of Pisa, Pisa, Italy; ¶¶Radiology, MD Anderson Cancer Center, Houston, Texas; ##Thoracic Surgery, Osaka University, Osaka, Japan; and ***Thoracic Surgery, Antwerp University Hospital, Antwerp, Belgium.

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

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Address for correspondence: Frank C. Detterbeck, MD, Department of Surgery, Division of Thoracic Surgery, Yale University School of Medicine, BB205 333 Cedar Street, New Haven, Connecticut. E-mail: frank.detterbeck@yale.edu

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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

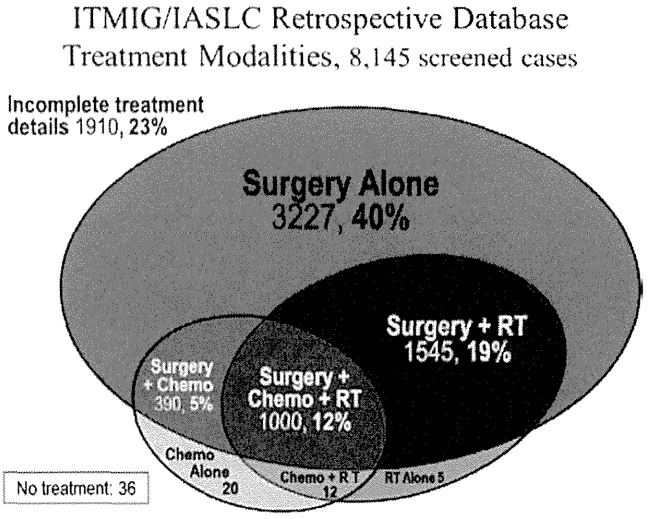

FIGURE 1. Overview of the data set by treatment modality. Overview of data available for analysis by treatment modality used. Among cases with known treatment modalities used, surgery was included in 99%. Chemo, chemotherapy; RT, radiotherapy.

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.

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 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, 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.
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

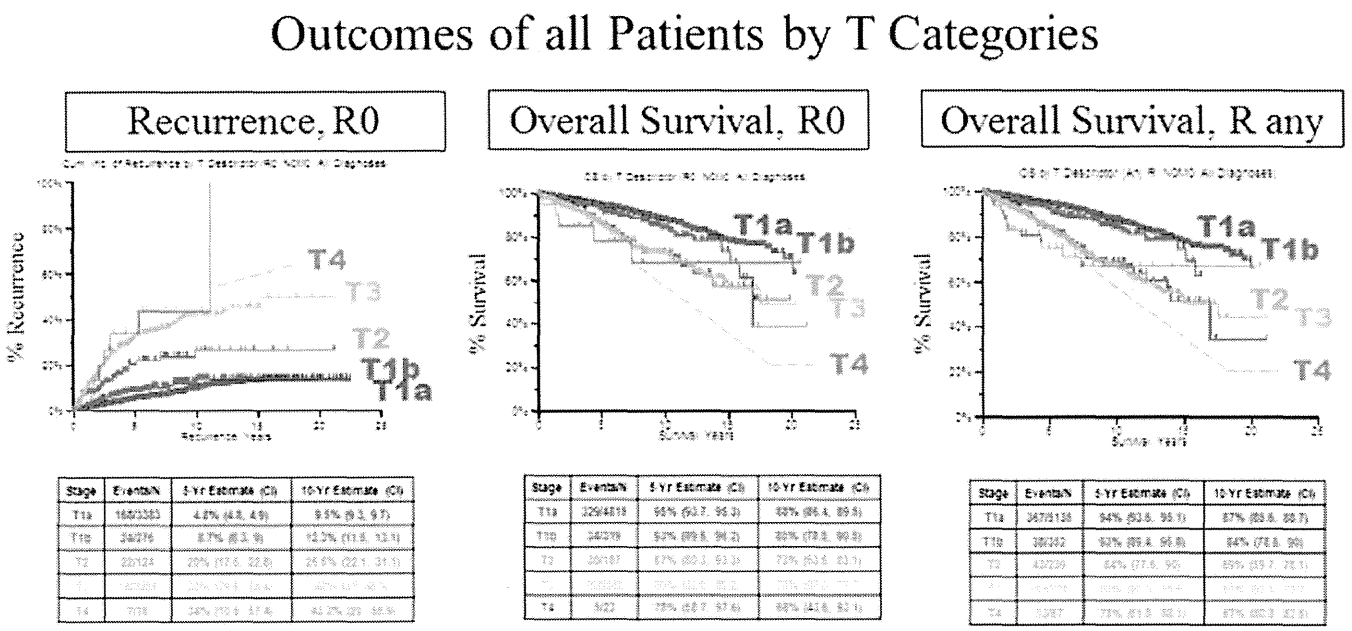

FIGURE 2. Outcomes of all patients by T categories. Outcomes for all patients with a thymic malignancy of any type (e.g., thymoma, thymic carcinoma, neuroendocrine tumor, and other). *A*, Cumulative incidence of recurrence, R0 resected patients; (*B*) overall survival, R0 resected patients; and (*C*) 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

	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**

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 (χ^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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APPENDIX 1. IASLC STAGING AND PROGNOSTIC FACTORS COMMITTEE

Peter Goldstraw, Past Chair, Royal Brompton Hospital and Imperial College, London, United Kingdom; Ramón Rami-Porta, Chair, Hospital Universitari Mutua Terrassa, Terrassa, Spain; Hisao Asamura, Chair Elect, National Cancer Center, Tokyo, Japan; David Ball, Peter MacCallum Cancer Centre, Melbourne, Australia; David Beer, University of Michigan, Ann Arbor, Michigan; Ricardo Beyruti, University of Sao Paulo, Brazil; Vanessa Bolejack, CRAB, Seattle, Washington; Kari Chansky, CRAB, Seattle, Washington; John Crowley, CRAB, Seattle, Washington; Frank Detterbeck, Yale University, New Haven, Connecticut; Wilfried Ernst Erich Eberhardt, Department of Medical Oncology, West German Cancer Centre, University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany; John Edwards, Northern General Hospital, Sheffield, United Kingdom; Françoise Galateau-Sallé, Centre Hospitalier Universitaire, Caen, France; Dorothy Giroux, CRAB, Seattle, Washington; Fergus Gleeson, Churchill Hospital, Oxford, United Kingdom; Patti Groome, Queen's Cancer Research Institute, Kingston, Ontario, Canada; James Huang, Memorial Sloan-Kettering Cancer Center, New York, New York; Catherine Kennedy, University of Sydney, Sydney, Australia; Jhingook Kim, Samsung Medical Center, Seoul, Korea; Young Tae Kim, Seoul National University, Seoul, South Korea; Laura Kingsbury, CRAB, Seattle, Washington; Haruhiko Kondo, Kyorin University Hospital, Tokyo, Japan; Mark Krasnik, Gentofte Hospital, Copenhagen, Denmark; Kaoru Kubota, Nippon Medical School Hospital, Tokyo, Japan; Antoon Lerut, University Hospitals, Leuven, Belgium; Gustavo Lyons,