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

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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.

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

Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/14/0909-0S65

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

(*J Thorac Oncol.* 2014;9: S65–S72)

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.

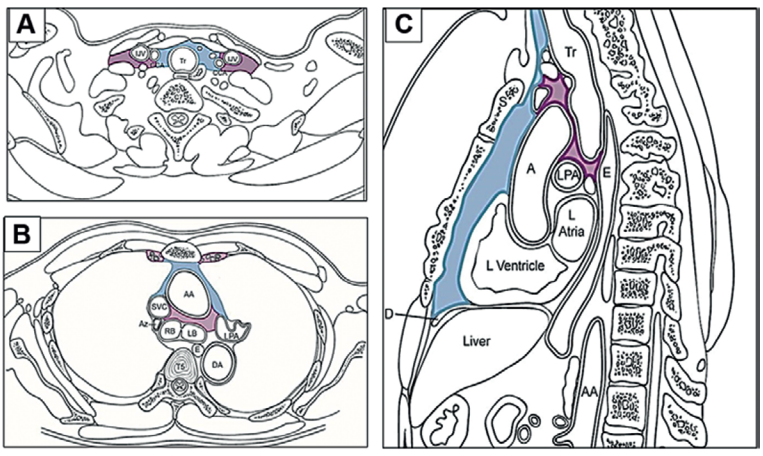

FIGURE 1. ITMIG/IASLC node compartments for thymic malignancies. Graphic depiction of N1 (anterior region, blue) and N2 (deep region, purple) node compartments. *A*, Level of thoracic inlet; (*B*) Level of aortopulmonary window; (*C*) Sagittal view. For further details, see Bhora et al.[12]

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

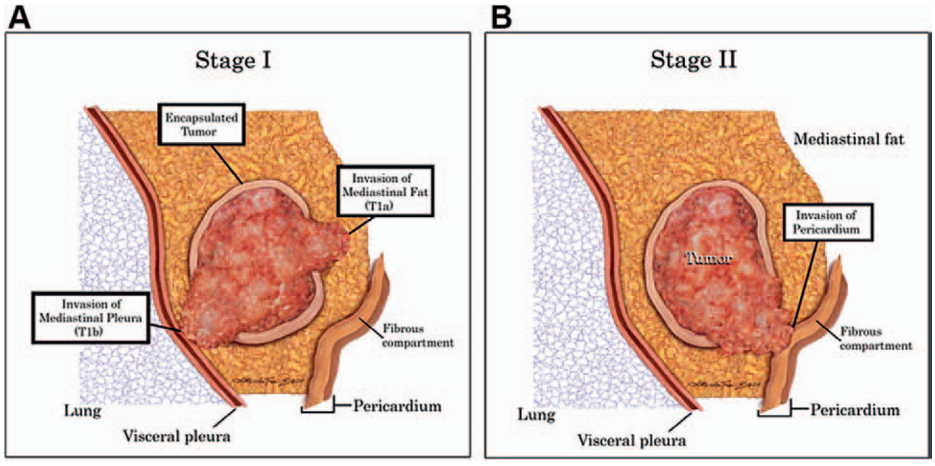

FIGURE 2. Stages I (T1N0M0) and II (T2N0M0). Graphic depiction of Stage group I and II. Copyright © Aletta Ann Frazier, MD. *A*, Stage I: tumor that is either "encapsulated" or extending into the anterior mediastinal fat (T1a) or with direct involvement of the mediastinal pleura (T1b); (*B*) Stage II.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

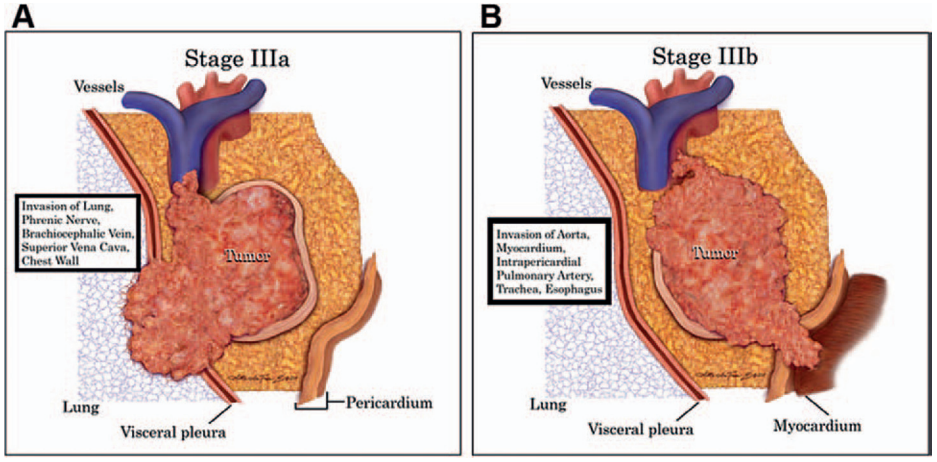

FIGURE 3. Stage IIIa (T3N0M0) and IIIb (T4N0M0). Graphic depiction of Stage group IIIa, b. Copyright © Aletta Ann Frazier, MD. *A*, Tumor invading the lung, brachiocephalic vein, superior vena cava, chest wall, and phrenic nerve; (B) Tumor invading the aorta, intrapericardial pulmonary artery, myocardium,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

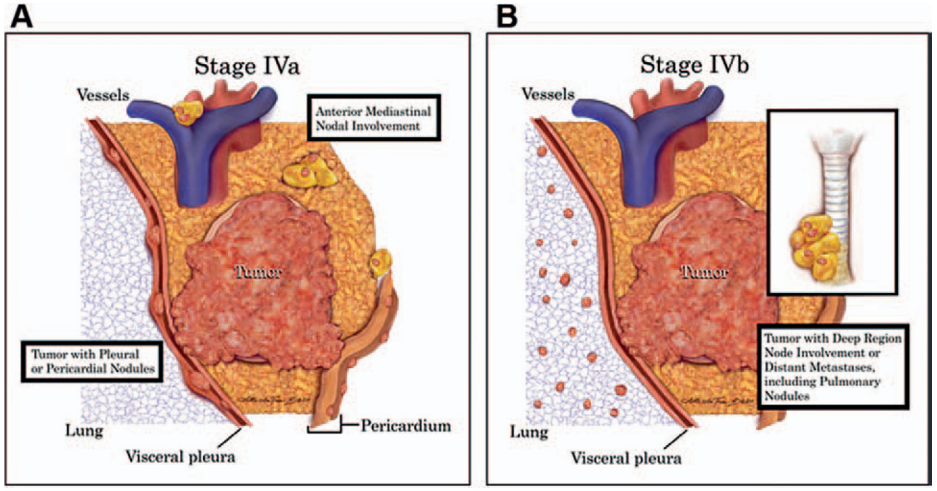

FIGURE 4. Stages IVa and IVb. Graphic depiction of Stage group IVa, b. Copyright © Aletta Ann Frazier, MD. *A*, Tumor with separate pleural or pericardial nodules (M1a) or anterior region node involvement (N1); (*B*) Tumor with deep region node involvement (N2) or distant metastases including intraparenchymal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

ACKNOWLEDGMENTS

A.G.N. was supported by the National Institute of Health Research Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London.

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

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