ORIGINAL ARTICLE

The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma

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ABSTRACT

Introduction: The current T component for malignant pleural mesothelioma (MPM) has been predominantly informed by surgical data sets and consensus. The International Association for the Study of Lung Cancer undertook revision of the seventh edition of the staging system for MPM with the goal of developing recommendations for the eighth edition.

Methods: Data elements including detailed T descriptors were developed by consensus. Tumor thickness at three pleural levels was also recorded. An electronic data capture system was established to facilitate data submission.

Results: A total of 3519 cases were submitted to the database. Of those eligible for T-component analysis, 509 cases had only clinical staging, 836 cases had only surgical staging, and 642 cases had both available. Survival was examined for T categories according to the current seventh edition staging system. There was clear separation between all clinically staged categories except T1a versus T1b (hazard ratio = 0.99, $p = 0.95$) and T3 versus T4 (hazard ratio = 1.22, $p = 0.09$), although the numbers of T4 cases were small. Pathological staging failed to demonstrate a

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**See Appendix for the members of the Staging and Prognostic Factors Committee, Advisory Boards and Participating Institutions.

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survival difference between adjacent categories with the exception of T3 versus T4. Performance improved with collapse of T1a and T1b into a single T1 category; no current descriptors were shifted or eliminated. Tumor thickness and nodular or rindlike morphology were significantly associated with survival.

Conclusions: A recommendation to collapse both clinical and pathological T1a and T1b into a T1 classification will be made for the eighth edition staging system. Simple measurement of pleural thickness has prognostic significance and should be examined further with a view to incorporation into future staging.

Keywords: Mesothelioma; Staging; T component; Prospective

Introduction

It has been difficult to apply the solid tumor T-component paradigm to malignant pleural mesothelioma (MPM) because of its unusual growth pattern, which involves a rind around the pleural cavity rather than development from a concentrically enlarging primary lesion as seen in most other malignancies. Although many other staging systems, including that for NSCLC, have incorporated measures of tumor bulk such as tumor diameter, mesothelioma staging has utilized only anatomical descriptors of disease extent and invasion to date, despite evidence that tumor bulk may have prognostic importance.[1,2]

Historically, a number of mesothelioma staging systems have been proposed and used, most initially developed from small single-institution databases and predominantly retrospective surgical series.[3–6] The most recent and widely adopted TNM staging system was proposed by the International Mesothelioma Interest Group (IMIG) after a meeting in 1994 at which data were presented from large retrospective series and clinical trials. T descriptors were derived by consensus at that meeting and subsequently reviewed by IMIG members before ratification and publication of the staging system.[7] The surgical derivation of this staging system has had the result that some T descriptors have been difficult to apply in clinical staging, particularly the distinction between parietal pleural involvement or both parietal and visceral pleural involvement (which characterizes categories T1a and T1b, respectively). Although this staging system has been widely adopted,[8,9] it has only recently been validated in a database of 3101 predominantly surgical cases collected retrospectively from 15 centers worldwide.[10] The validation generally confirmed the appropriateness of stage groupings and T descriptors, but it did identify discrepancies between clinical and pathological staging and poor discrimination between outcomes for T1 and T2 disease. Furthermore, the utility of individual anatomical descriptors leading to assignment of T categories could not be assessed from this retrospective combined data set, which lacked sufficiently detailed information.

The T component should ideally provide prognostic information; survival should monotonically decrease with increasing T categories, and it should be able to inform evidence-based treatment recommendations. With this goal, the International Association for the Study of Lung Cancer (IASLC) and IMIG developed an international database that was geographically representative and included patients with MPM irrespective of treatment, pathological subtype, and stage to develop a data-driven revision of the current staging system for the eighth edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) staging manuals.

Methods

A mesothelioma subcommittee was formed by the International Staging Committee of the IASLC to review and revise the current staging. The IASLC convened a meeting in London in 2009 at which working parties developed recommendations by consensus on common data elements for a prospective staging database for MPM. The Prospective Staging Project in Malignant Pleural Mesothelioma was initiated at a joint meeting of the IASLC International Staging Committee Mesothelioma Domain and Advisory Board in 2010.

This was an international, multi-institutional cohort study. The study population was patients with newly diagnosed, cytologically or histologically confirmed MPM. Information was collected on the extent of disease, demographic characteristics, comorbidities, treatment, and survival. Disease was staged by investigators according to the seventh edition of the UICC/AJCC staging system.[8,9] Biostatistical support was provided by Cancer Research And Biostatistics in Seattle, Washington.

Data to inform this effort originated from multiple sources. A database of surgically managed cases from 15 centers worldwide had been previously analyzed, resulting in a 2012 publication identifying components of the staging system that would benefit from revision.[10] A more detailed database with broader representation of treatment modalities was needed. A new dictionary was developed and an electronic data capture (EDC) system was created and housed at Cancer Research And Biostatistics. Some of the cases from the initial surgically managed database possessed sufficient detail to be incorporated into the new database, and those cases are included in the present analysis. In addition to cases

entered into the EDC, several institutions contributed retrospective data outside of the EDC, but with data elements that could be mapped to those of the IASLC database. Cases with complete anatomical stage information, complete survival information, and a diagnosis of MPM between January 1995 and June 30, 2013, were eligible. In all, the current database contains 2432 eligible cases from 29 centers on four continents (see the Appendix). All data were collected in compliance with applicable local legislation and only coded, deidentified data were collected for analysis. Each participating institution gained institutional human research ethics committee approval to collect and contribute data, with a waiver of consent from individual patients.

Where available, investigators assigned a pretreatment ("clinical") T category according to the seventh edition of the TNM classification for MPM and recorded the investigations on the basis of which this was determined.[9] Similarly, a postsurgical ("pathological") T category was assigned in cases in which surgery was performed. Additional detailed T-component descriptors were collected as shown in Supplementary Table 1. To develop an approximation of tumor size or bulk, three single linear measurements of pretreatment pleural thickness were also performed by using axial computed tomography (CT) images perpendicular to the chest wall or mediastinum (Fig. 1*A*). Measurements were taken at the level of maximal thickness on either the chest wall or mediastinum in an axial plane in the upper, middle, and lower hemithorax (Fig. 1*B* and Supplementary Table 1 footnote).

Statistical Considerations

To determine overall stage, cases without a complete set of either pathological or clinical T, N, and M stage were excluded. For fully staged cases, not all detail elements were submitted for each case. Cases without a T descriptor to explain T category were not included in the primary analyses of T-component categories or in analyses of individual descriptors. A subset of cases that were T4NX was included.

Prognostic capabilities of the current version of each T category were evaluated using Kaplan-Meier survival curves and Cox proportional hazards regression analysis, with and without adjustment for sex and geographic region. Individual T descriptors were also evaluated by Kaplan-Meier survival analysis to assess whether any specific anatomical factors warranted allocation to a different T category on the basis of survival. This analysis was done for both clinical and pathological staging of descriptors. Formal comparisons between T categories were performed using a Cox proportional hazards regression model. All survival analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). Survival was measured from the date of diagnosis to the date of last contact or death from any cause.

Exploratory analyses of pleural thickness as a prognostic variable were performed by evaluating several summary indices of pleural thickness measured at three levels. Candidate indices were the sum of the three measurements, the maximum of three measurements, and a modified product. We used a running log-rank statistic to evaluate each hypothetical cutpoint for each index in the cM0 (clinically staged) data set.[11] The cutpoints that coincided with the highest log-rank test statistics were chosen as the optimal cutpoints for this data set; survival estimates according to the groups defined by these cutpoints were generated by Kaplan-Meier analysis.

Results

As of the data cutoff on January 20, 2015, 1566 cases had been collected through the EDC system and 1953 cases were collected through data transfer from institutional databases, giving a total of 3519 cases (see the

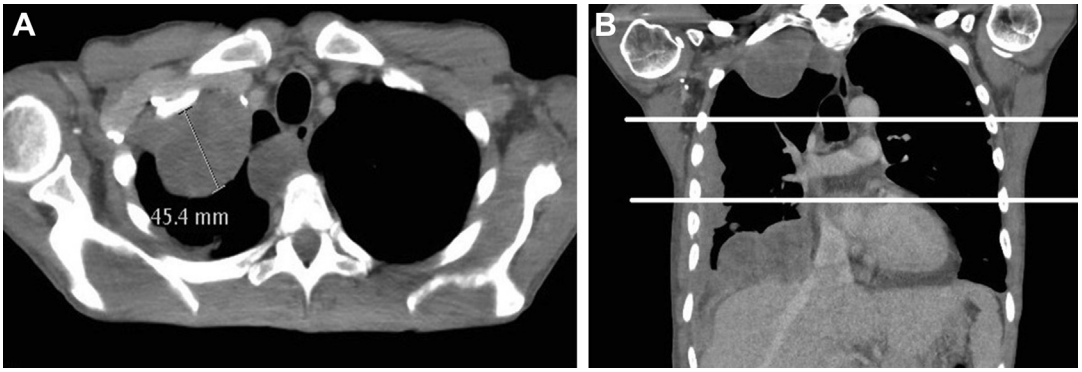

Figure 1. (*A*) Maximal tumor thickness perpendicular to the chest wall or mediastinum was measured for each of three levels on axial imaging. (*B*) Measurements of tumor thickness were made on axial slices, representing the upper, middle, and lower third of the hemithorax. These thirds were defined as follows: the upper level extends from the apex of the lung to the inferior margin of the arch of the aorta; the middle level includes the pleura between the upper and lower levels; and the lower level is pleural, including and inferior to the first image on which the left atrium is seen.

Appendix and Supplementary Fig. 1). Cases diagnosed as early as 1995 were included provided they met data quality standard. Patients with a diagnosis date after June 30, 2013, were excluded, as were those with a missing or erroneous survival time; incorrect or missing histologic type; or missing, incomplete, or internally inconsistent TNM staging. Seventy-nine percent of the cases were accrued after 2003; 21% of eligible cases were accrued between 1995 and 2003.

Demographics of the cases for the T component are shown in Table 1. These comprised 509 cases with only clinical staging information, 836 cases with only pathological staging information, and 642 cases with both clinical and pathological information available. Of those patients with pathological staging information available, 47% had extrapleural pneumonectomy, 15% had pleurectomy/decortication, 6% had extended pleurectomy/decortication, 5% had partial pleurectomy, and 23% had exploration only, with the remainder having an unspecified procedure. As anticipated, cases were predominantly male (78%) and with epithelioid histologic features (73%). Of the patients alive at last contact, 65% were followed up for more than 1 year; the median length of follow-up for all patients alive at last contact was 16.5 months.

Clinical or pathological T1 category was assigned only when involvement of the ipsilateral parietal pleura (T1a) with or without involvement of the ipsilateral visceral (T1b) pleura was recorded. Although the database allowed cases to be recorded as T1 without distinguishing between T1a and T1b or Tx (T category unknown), these cases were not used for the primary T-component analyses. Where a clinical T2 category was assigned, most patients were assigned by using multiple T2 descriptors. Where clinical stage was classified on the basis of a single descriptor only, this was most likely to be invasion of lung parenchyma or involvement of the pleural fissures. Although multiple T2 descriptors were also most common in pathologically staged cases, single-descriptor–based classifications were most likely for confluent involvement of the pleura. Where clinical T3 category was assigned, upstaging on the basis of a single descriptor was more common than for T2 disease, with classification on the basis of either mediastinal fat invasion or chest wall invasion being common and often mutually exclusive. Similarly, pathologically staged T3 cases were typically assigned on the basis of a single descriptor, the most common being pericardial invasion, followed by chest wall invasion. Pathological identification of T3 disease due to mediastinal fat invasion without pericardial involvement was less frequent. Clinical T4 disease was most frequently assigned owing to multiple T4 descriptors. Where single descriptors were used to allocate category, this was most frequently due to diffuse chest wall involvement, diaphragm involvement, or transmural pericardial involvement. With pathological T4 categorization, diffuse chest wall involvement was the most frequent isolated descriptor.

Survival was examined for each T category within the current seventh edition staging system in cases with T-descriptor support and any N category, M0 (n = 1151 clinical and 1478 pathological). In clinically staged cases,

Table 1. Source of Stage Availability (Clinical versus Pathological), Geographic Region, Sex, and Cell Type for Cases Included in the Primary T-Component Analyses

		Available TNM Staging					
		Both		Clinical		Pathological	
Characteristic	All (N)	n	(%)	n	(%)	n	(%)
Region							
Asia	175	57	(8%)	94	(18%)	24	(2%)
Australia	205	3	(<1%)	97	(19%)	105	(12%)
Europe	549	52	(8%)	156	(30%)	341	(40%)
N. Amer.	744	483	(75%)	159	(31%)	102	(12%)
Turkey	324	47	(7%)	3	(<1%)	264	(31%)
Sex							
Female	436	140	(22%)	86	(17%)	210	(25%)
Male	1549	502	(78%)	422	(83%)	625	(75%)
No data	2	0	0	1	(<1%)	1	(<1%)
Histologic type							
Biphasic	305	102	(16%)	57	(11%)	146	(17%)
Epithelioid	1444	474	(74%)	345	(68%)	625	(75%)
Other/NOS	152	49	(8%)	61	(12%)	42	(5%)
Sarcomatoid	86	17	(2%)	46	(9%)	23	(3%)
Total cases	1987	642	(32%)	509	(25%)	836	(42%)

N. Amer., North America; NOS, not otherwise specified.

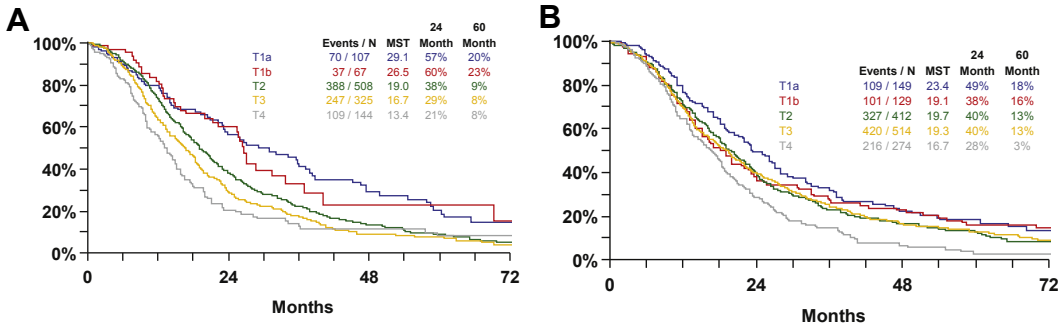

Figure 2. Kaplan-Meier curve for survival by the seventh edition Union for International Cancer Control (UICC) and the American Joint Committee on Cancer T category in cases with T-descriptor support. Clinical staging (*A*) and pathological staging (*B*). Abbreviation: MST, median survival time.

there was clear separation between all T categories with the exception of T1a versus T1b (hazard ratio [HR] = 0.99, $p = 0.95$) and between T3 and T4 (HR = 1.22, $p = 0.089$), although the numbers were small for T4 cases and the HR was similar to that for significant differences between other categories (Fig. 2*A* and Table 2). However, when pathologically staged cases were examined, the current T component failed to demonstrate a survival difference between adjacent categories, with the exception of T3 versus T4 (Fig. 2*B* and Table 2). In particular, there was no evident separation between pathological categories T1b, T2, and T3. On multiple analyses based on survival data using Cox regression with stepwise elimination there was no indication that any current descriptors within T categories should be placed in other categories or eliminated.

In view of the poor performance of discrimination between T1a and T1b on either clinical or pathological staging, these stages were collapsed and examined together in both the clinical and pathological settings and in "best"' stage. Best stage was based on clinical stage where no pathological staging was available, or on pathological staging where only pathological staging or both were available, as per AJCC and UICC guidelines (Fig. 3*A–C*). The performance of the T component as a discriminator between categories for survival was improved with this change (Tables 3 and 4), although for pathological stage there were still no statistical differences between adjacent T categories other than T4 and T3. Node positivity as determined by pathological stage, when added to the model, was a strong predictor of survival ($p = 0.0001$, HR = 1.30). However, adjusting for node positivity did not alter the results of formal comparisons between T categories, with HRs and p values remaining very similar. Node positivity as determined by clinical stage was not independently prognostic for survival, nor did adjusting for node positivity alter the results of the formal comparisons for clinical T-component.

Upstaging of initial clinical T categories was common, with 56% of T1 cases, 54% of T2 cases, and 39% of T3 cases assigned higher pathological T categories, whereas 4% of all cases were assigned a lower pathological than clinical T category. Occult involvement of the chest wall fascia (23%), pericardium (25%), or multiple T3 descriptors (37%) were the predominant reasons for upstaging from clinical T1 or T2 to pathological T3. For those patients with tumors upstaged from clinical T3 to pathological T4 (n = 62), most (76%) were noted to have multiple pathological T4 descriptors, with isolated pericardial (11%), diaphragmatic (3%), or contralateral pleural (5%) involvement being less common.

Absolute measurements of pleural thickness were available for 472 M0 cases, with most being entered through EDC with a range from 0 mm to 153 mm for individual measurements. The median pleural thickness for available cases increased from 9 mm in the upper zone to 10.1 mm in the middle zone and 10.9 mm in the lower zone. Pleural thickness correlated with the seventh edition T categories and overall stage (Supplementary Table 2), with the mean sum of the lower, middle, and upper pleural thickness measurements increasing at higher stages. Exploratory analyses were performed to identify potential cutpoints and methods of interpreting these data. Survival according to

Table 2. Formal Comparisons between Adjacent T-Component Categories for Existing Seventh Edition

Comparison of T-Component Categories	Clinical Stage		Pathological Stage	
	HR	*p* Value	HR	*p* Value
T1b vs. T1a	0.99	0.95	1.16	0.27
T2 vs. T1b	1.50	0.018	1.08	0.50
T3 vs. T2	1.23	0.013	1.01	0.87
T4 vs. T3	1.22	0.089	1.34	0.0005

Note: Cox regression model adjusted for sex and region.
HR, hazard ratio.

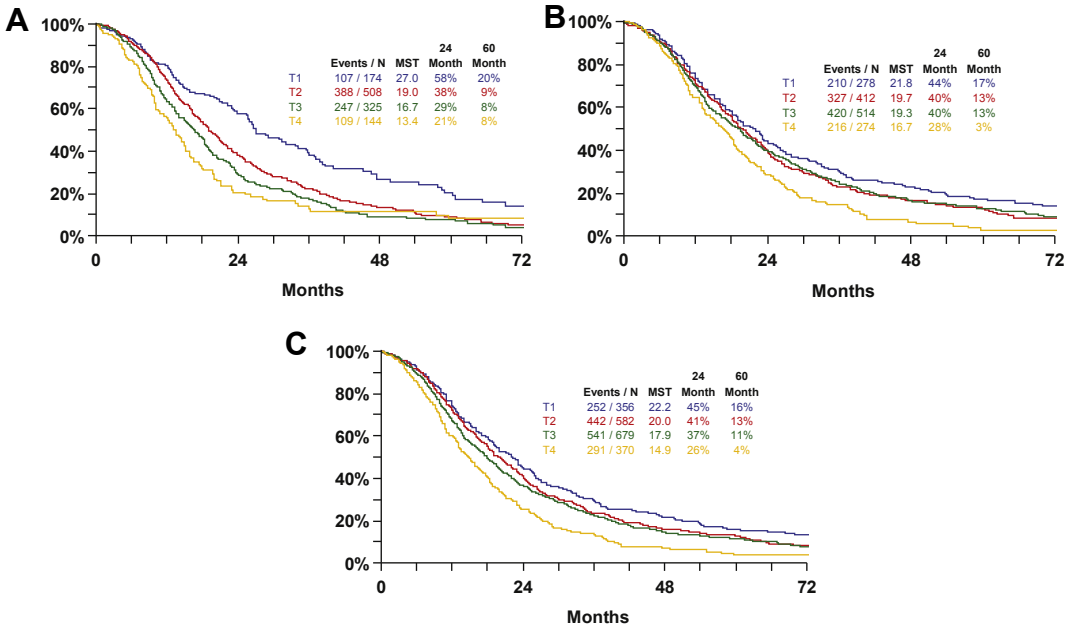

Figure 3. Kaplan-Meier curve for survival by the proposed eighth edition T category in cases with T-descriptor support. Clinical staging (*A*), pathological staging (*B*), and "best" staging (*C*). Abbreviation: MST, median survival time.

the sum of the three pleural measurements was analyzed by using data-driven cutpoints derived by a running log-rank test, and by classification into quartiles. Survival decreased from the lowest to the highest quartile of pleural thickness (Supplementary Fig. 2*A*), with a median survival of 23.4 months for the lowest-quartile tumor thickness (<16.0 mm) compared with a median survival of 13.2 months for the highest-quartile thickness (>50.0 mm) ($p = 0.005$ by log-rank test testing equality across quartiles). When two data-driven cutpoints were derived, these were at 13 mm and 60 mm total pleural thickness (Supplementary Fig. 2*B*, $p < 0.0001$ by log-rank test). Increasing thickness sum according to these cutpoints was significantly associated with cT categories ($p < 0.0001$), node positivity ($p < 0.0001$), and overall stage ($p < 0.0001$) by a chi-square test of association. When survival was analyzed by a single measurement of maximum pleural thickness from all three levels, a single data-driven cutpoint was identified at 5.1 mm, with a median survival of 24.2 months when no pleural thickness was greater than 5.1 mm and 17.7 months with any pleural thickness greater than 5.1 mm ($p = 0.0014$ by log-rank test [Supplementary Fig. 2*C*]). Investigators were also asked to classify the pattern of pleural involvement as *minimal*, *nodular*, and *rindlike*. A minimal pattern of pleural thickening had the best prognosis, with a median survival of 23.4 months, whereas patients with nodular or rindlike patterns of pleural involvement had less favorable outcomes (median survival of 18.2 and 14.5 months, respectively [Supplementary Fig. 2*D*]) ($p = 0.004$ for nodular thickening versus minimal thickening and $p = 0.001$ for rindlike thickening versus minimal thickening.) Survival was not significantly different between patients with nodular thickening and patients with rindlike thickening.

Discussion

This revision of mesothelioma T component is the outcome of the first evidence-based, international collaborative analysis of cases staged both clinically and

Table 3. Overall Outcomes with Categories T1a and T1b Combined

	Clinical Stage				Pathological Stage				Best Stage			
T Categories	n	Median OS (mo)	24-Month OS Rate	60-Month OS Rate	n	Median OS (mo)	24-Month OS Rate	60-Month OS Rate	n	Median OS (mo)	24-Month OS Rate	60-Month OS Rate
T1	174	27.0	58%	20%	278	21.8	44%	17%	356	22.2	45%	16%
T2	508	19.0	38%	9%	412	19.7	40%	13%	582	20.0	41%	13%
T3	325	16.7	29%	8%	514	19.3	40%	13%	679	17.9	37%	11%
T4	144	13.4	21%	8%	274	16.7	28%	3%	370	14.9	26%	4%

Note: Clinical, pathological, and best stage M0 cases only for proposed eighth edition staging nomenclature.
OS, overall survival.

Table 4. Formal Comparisons between Adjacent T-Component Categories after Combining Categories T1a and T1b

Comparison of T-Component Categories	Clinical Stage		Pathological Stage	
	HR	*p* Value	HR	*p* Value
T2 vs. T1	1.49	0.0003	1.17	0.072
T3 vs. T2	1.23	0.013	1.01	0.87
T4 vs. T3	1.22	0.089	1.34	0.0005

Cox regression model adjusted for sex and region.
HR, hazard ratio.

pathologically, heralding an era of data-driven revisions for mesothelioma staging.[12] The updated final recommendation for T descriptors is shown in Table 5. Previous staging recommendations have predominantly drawn from surgical databases, making their applicability to the clinically staged subset unclear. The key change arising from this analysis was to collapse the subclassification of T1a and T1b into a single T1 category. In practice, a distinction between involvement of the parietal pleural (T1a) with or without involvement of the visceral pleura (T1b) was essentially impossible with clinical information alone. More surprising is the lack of distinction between T1a and T1b with pathological staging, suggesting that not only is this distinction difficult to make clinically, but it is also not prognostically relevant, at least in those patients with tumors selected for surgical management (and thus pathologically staged). Extensive review of individual T descriptors could not identify any that may have been misclassified or improve separation of survival curves between T categories, resulting in a recommendation that the key elements of the T component remain unchanged for the eighth edition of the UICC and AJCC staging manuals. Ongoing data collection and analysis of larger numbers of individual T descriptors may allow future analyses to determine their significance.

The better performance of clinical T categories than pathological T categories in prognostication was an unexpected finding. As pathological staging is not available on all patients, this may represent other aspects of the homogeneity of the pathologically staged (i.e., usually surgically managed) group, including a predominance of epithelioid disease, as well as other factors such as comorbidities and performance status. In addition, the surgical procedure performed will influence the chance of subsequent upstaging, with more extensive procedures such as extrapleural pneumonectomy being better placed to identify some T4 descriptors in particular. We hypothesize that there may also be confounding as a result of investigator bias between attributed clinical T categories and tumor bulk, as bulk is more readily appreciated on imaging than sites of anatomical invasion. Furthermore, it is also possible that invasion of individual organs or planes is less important in defining prognosis than tumor volume in mesothelioma, particularly in the

Table 5. Final Recommendations for T Descriptors for the Eighth Edition of the AJCC/UICC Staging Handbook

T Component Staging	T Descriptors
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal ± visceral ± mediastinal ± diaphragmatic pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: • involvement of diaphragmatic muscle • extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but *potentially resectable* tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: • involvement of the endothoracic fascia • extension into the mediastinal fat • solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall • nontransmural involvement of the pericardium
T4	Describes locally advanced *technically unresectable* tumor Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: • diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction • direct transdiaphragmatic extension of tumor to the peritoneum • direct extension of tumor to the contralateral pleura • direct extension of tumor to mediastinal organs • direct extension of tumor into the spine • tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control.

context of effective surgical debulking. Although many cases were upstaged from clinical to pathological staging, it is unclear whether the most sensitive imaging procedures for pericardial, diaphragmatic, or chest wall invasion, such as magnetic resonance imaging, were utilized preoperatively in this group and could increase the sensitivity of clinical staging.

An important contribution of this work is further support for the concept that the bulk of disease is prognostically important in mesothelioma. In this database, three unidimensional measurements of maximal tumor thickness were taken in the upper, middle, and lower affected hemithorax in an attempt to approximate the tumor burden. The decision to use simple, unidimensional measurements was pragmatic and aligned with the concept of maximal tumor dimension used in staging of many other malignancies and with the Response Evaluation Criteria in Solid Tumors modified for mesothelioma.[13] Also, unlike volumetric CT scanning, unidimensional measurement does not require use of software or technology that may not be widely available. The results show support for the concept of incorporating a surrogate measure of tumor size or burden into the staging of mesothelioma and an association between increasing tumor thickness and T category, as well as nodal positivity (which is further described in the accompanying N-component article).[14] However, additional validation and increased numbers of patients with measurements would be needed before proposing to incorporate tumor measurements into the staging system. First, it must be clarified whether tumor thickness is adding independent information to staging by anatomical site of invasion and should be an adjunct staging descriptor, or whether it should replace certain T-component descriptors. Second, it will be important to understand whether tumor thickness adds prognostic information when applied to all stages, or whether it is stage-specific or more relevant only in the absence of nodal involvement. The relatively small number of patients evaluable for tumor thickness in this data set precludes these additional analyses at this point.

Even if tumor thickness were incorporated into a staging system, there is evidence that this metric may be subject to interobserver variability and may benefit from more objective, semiautomated, computer-aided measurements.[15] Although measurements of tumor thickness in MPM are highly correlated between observers, absolute differences may be as great as plus or minus 2 mm even when a fixed outer measurement point is provided.[16] Even with a fixed initial measurement point, there is substantial interobserver variability at measurements less than 7.5 mm, which may have an impact on the reproducibility of staging criteria incorporating unidimensional measurement, thus arguing against the use of the potential dichotomous cutpoint of approximately 5 mm derived from our data.[17] We also acknowledge that prior pleurodesis is a potential confounder when measuring pleural thickness and that although initial pretreatment images were used in this analysis, we did not collect information on whether patients had pleurodesis before CT imaging.

With known limitations and lack of representability for unidimensional measurements, a number of studies have demonstrated an association between mesothelioma tumor volume and survival outcomes.[1,18,19] Although tumor volume can be measured on CT, there are a number of different methodologies in use, requiring variable user input.[18–20] However, there has been no cross-platform validation and no single software fulfils the requirements for widespread adoption in a staging system, namely, being widely available, cheap, and simple to use and requiring minimal user time. Similar considerations surround the use of F-18 fluorodeoxyglucose positron emission tomography for estimation of tumor volume, although a number of different volumetric parameters derived from metabolic imaging have also shown prognostic value.[21–23]

These data have strengthened our understanding of mesothelioma staging through inclusion of both clinical and pathological staging, as well as by including data from patients who were not treated surgically, thus diminishing the selection bias of previous institutional data sets. Although this is the largest database of pleural mesothelioma staging created to date, the numbers remain small in comparison with those used for lung cancer staging revisions. Broad geographical representation was achieved, although we acknowledge that surgical practice, procedure selection, and skills may be variable across regions. However, only a minority of patients had tumor thickness measurements available, allowing us to generate hypotheses but not draw firm conclusions on the value of including a size criterion in staging. It is also possible that staging criteria were applied variably at an institutional level, particularly given the subjective nature and difficulty of assessing many descriptors on CT imaging.

In conclusion, we recommend that the anatomic T descriptors for mesothelioma remain unchanged but the distinction between T1a and T1b be removed from both pathological and clinical staging. Future work should incorporate prospective collection of tumor measurement data to further refine the T component in this disease.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.08.147.

Appendix

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