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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The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T descriptors in the forthcoming Eighth edition of the TNM classification for pleural mesothelioma

Running title: **Revisions of the T descriptors for pleural mesothelioma staging**

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* See Appendix

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ABSTRACT (Word limit = 250)

Introduction

Current T component for malignant pleural mesothelioma (MPM) has been predominantly informed by surgical datasets and consensus. The International Association for the Study of Lung Cancer undertook revision of the 7th Edition staging system for MPM with the goal of developing recommendations for the 8th 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

3,519 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 7th edition staging system. There was clear separation between all clinically staged categories except T1a vs. T1b (HR 0.99, p=0.95) and T3 vs. T4 (HR 1.22, P=0.09), although numbers of T4 cases were small. Pathological staging failed to demonstrate a survival difference between adjacent categories with the exception of T3 vs. T4. Performance improved with collapse of T1a and T1b into a single T1 category; no current descriptors were shifted or eliminated. Tumour thickness and nodular or rind-like 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 8th edition staging system. Simple measurement of pleural thickness has prognostic significance and should be examined further with a view to incorporation into future staging.

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INTRODUCTION

It has been difficult to apply the solid tumor T component paradigm to malignant pleural mesothelioma (MPM) due to its unusual growth pattern which involves a rind around the pleural cavity rather than developing from a concentrically enlarging primary lesion as seen in most other malignancies. Whilst many other staging systems, including that for non-small cell lung cancer, have incorporated measures of tumor bulk such as tumor diameter, mesothelioma staging has utilised 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) following 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 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 characterises 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 3,101 predominantly surgical cases collected retrospectively

from 15 centres worldwide.[10] The validation generally confirmed the appropriateness of stage groupings and T descriptors, but 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 was unable to be assessed from this retrospective combined dataset which lacked sufficiently detailed information.

T component should ideally provide prognostic information; survival should monotonically decrease with increasing T categories, and 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 which was geographically representative and included patients with malignant pleural mesothelioma irrespective of treatment, pathological subtype, and stage, in order to develop a data-driven revision of the current staging system for the 8th 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 (ISC) 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 malignant pleural mesothelioma. The Prospective Staging Project in Malignant Pleural Mesothelioma was initiated at a joint meeting of the IASLC-ISC 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 malignant pleural mesothelioma. Information was collected on the extent of disease, demographic characteristics, comorbidities, treatment, and survival. Disease was staged by investigators according to the 7th edition of the UICC/AJCC.[8, 9] Biostatistical support was provided by Cancer Research And Biostatistics (CRAB) in Seattle, WA, USA.

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 publication in 2012 identifying components of the staging system that would benefit from revision.[10] A more detailed database was needed with broader representation of treatment modalities. A new dictionary was developed and an electronic data capture (EDC) system was created and housed at CRAB. 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 malignant pleural mesothelioma between January 1995 and June 30 2013 were eligible. In all, the current database contains 2,432 eligible cases from 29 centers on 4 continents (Appendix). All data were collected in compliance with applicable local legislation and only coded, de-identified data was 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 pre-treatment ('clinical') T category according to the seventh edition of the tumor, node, metastasis (TNM) classification for MPM, and recorded the investigations on which this was determined. [9] Similarly, a post-surgical ('pathological') T category was assigned where surgery was performed. Additional detailed T component descriptors were collected as shown in Supplementary Table 1. In order to develop an approximation of tumor size or bulk, three single linear measurements were also performed of pre-treatment pleural thickness using axial CT images, perpendicular to the chest wall or mediastinum (Figure 1a). 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 (Figure 1b; Supplementary Table 1 footnote).

Statistical considerations

In order 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 based on 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. 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; 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 dataset; survival estimates according to the groups defined by these cutpoints were generated via Kaplan-Meier analysis.

RESULTS

As of the data cut-off on January 20 2015, 1,566 cases had been collected through the electronic data capture system, and 1,953 cases were collected through data transfer from institutional databases, giving a total of 3,519 cases (Appendix, Supplementary Figure 1). Cases diagnosed as early as 1995 were included provided they met data quality standard. Patients with a diagnosis date after June 30th, 2013 were excluded, as were those with a missing or erroneous survival time, incorrect or missing histologic type, or where TNM staging was missing, incomplete, or internally inconsistent. Seventy-nine percentof cases were accrued since 2003; 21% of eligible cases were accrued between 1995 and 2003.

Demographics of included cases for 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 (P/D), 6% had extended P/D, 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 histology (73%). Of 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 (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 b, or Tx (T-category unknown) these cases were not used for the primary T-component analyses. Where a clinical T2 category was assigned, the majority of patients were assigned 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. Whilst 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 commonly 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 commonly assigned due to multiple T4 descriptors. Where single descriptors were used to allocate category this was most commonly due to diffuse chest wall involvement, diaphragm involvement, or transmural pericardial involvement. With pathological T4 categorisation, diffuse chest wall involvement was the most frequent isolated descriptor.

Survival was examined for each T category within the current 7th edition staging system in cases with T descriptor support and any N category, M0 (n=1,151 clinical; n=1,478 pathological). In clinically staged cases, there was clear separation between all T categories with the exception of T1a vs T1b (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 significant differences between other categories (Figure 2a and Table 2). However, when pathologically staged cases were examined, current T component failed to demonstrate a survival difference between adjacent categories, with the exception of T3 vs. T4 (Figure 2b 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 the pathological settings, and in 'best' stage. Best stage was based on clinical stage where no pathological staging was available, or pathological staging where only pathological staging or both were available, as per AJCC and UICC guidelines (Figure 3 a-c). The performance of 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=.0001, HR=1.30). However, adjusting for node positivity did not alter the results of formal comparisons between T categories, with hazard ratios 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 a higher pathological T categories, whilst 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), a

majority (76%) was 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, the majority entered via electronic data capture, with a range from 0mm to 153mm for individual measurements. The median pleural thickness for available cases increased from 9mm in the upper zone to 10.1 mm in the middle zone and 10.9 mm in the lower zone. Pleural thickness correlated with 7th 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 the sum of the three pleural measurements was analysed 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 Figure 2a), with a median survival of 23.4 months for the lowest quartile tumor thickness (<16.0 mm) compared to a median survival of 13.2 months for the highest quartile (>50.0 mm). (P=.005 by log-rank test testing equality across quartiles). When two data-driven cut points were derived, these were at 13mm and 60mm total pleural thickness (Supplementary Figure 2b, p<.0001 by log-rank test). Increasing thickness sum according to these cutpoints was significantly associated with cT categories (p<.0001), node positivity (p<.0001), and overall stage (p<.0001) by a Chi-square test of

association. Analysing survival by a single measurement of maximum pleural thickness from all three levels, a single data-driven cut point was identified at 5.1mm, 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 above 5.1 mm (p=0.0014 by log-rank test; Supplementary Figure 2c). Investigators were also asked to classify the pattern of pleural involvement as 'minimal', 'nodular', and 'rind-like'. A minimal pattern of pleural thickening had the best prognosis, with a median survival of 23.4 months, whilst patients with nodular or rind-like patterns of pleural involvement had less favourable outcomes (median survival of 18.2 and 14.5 months, respectively; Supplementary Figure 2d) (P=.004 for nodular thickening versus minimal thickening, and P=.001 for rind-like thickening versus minimal thickening.) Survival was not significantly different between patients with nodular thickening and patients with rind-like 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 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, 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 was unable to identify any which may have been misclassified or to improve separation of survival curves between T categories, resulting in a recommendation that the key elements of T component remain unchanged for the 8th 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 EPP being better placed to identify some T4 descriptors, in particular. We hypothesise that there may also be confounding through 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 context of effective surgical debulking. Although many cases were upstaged from clinical to pathological staging, it is unclear whether the use of the most sensitive imaging procedures for pericardial, diaphragmatic or chest wall invasion, such as MRI, were utilised 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, aligned with the concept of maximal tumor dimension used in staging of many other malignancies, and with the RECIST criteria modified for mesothelioma.[13] Also, unlike volumetric CT scanning it does not require use of software or technology which 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 manuscript). However, additional validation and increased numbers of patients with measurements would be needed before proposing to incorporate tumor measurements into the staging system. Firstly, 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. Secondly, 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 dataset 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, semi-automated, computer-aided measurements.[14] Although measurements of tumor thickness in MPM are highly correlated between observers, absolute differences may be up to +/- 2mm even when a fixed outer measurement point is provided.[15] Even with a fixed initial measurement point, there is substantial inter-observer variability at measurements below 7.5mm, which may impact on the reproducibility of staging criteria incorporating unidimensional measurement, arguing against the use of the potential dichotomous cut point of around 5mm derived from our data.[16] We also acknowledge that prior pleurodesis is a potential confounder when measuring pleural thickness, and that although initial pre-treatment 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, 17, 18] Although tumor volume can be measured on CT, there are a number of different methodologies in use, requiring variable user input.[17, 19, 20] However, there has been no cross-platform validation and no single software fulfils the requirements for widespread adoption in a staging system: being widely available, cheap, simple to use, and requiring minimal user time. Similar considerations surround the use of 18F-FDG-PET for tumor volume estimation, 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, diminishing the selection bias of previous institutional datasets. Whilst this is the largest database of pleural mesothelioma staging created to date, numbers remain small in comparison to 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 assessing many descriptors on CT imaging.

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

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Figure captions

Figure 1a. Maximal tumor thickness perpendicular to the chest wall or mediastinum was measured for each of three levels, on axial imaging.

Figure 1b. 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: Upper level extends from the apex of the lung to the inferior margin of the arch of the aorta; middle level includes the pleura between the upper and lower levels; lower level is pleural including and inferior to the first image on which the left atrium is seen.

Figure 2. Kaplan Meier curve for survival by 7th edition UICC/AJCC T category in cases with T descriptor support. a. clinical staging b. pathological staging.

Figure 3. Kaplan Meier curve for survival by proposed 8th edition T category in cases with T descriptor support. a. clinical staging b. pathological staging c. 'best' staging.

Supplementary Figure 1. Cases analysed and reasons for exclusion.

Supplementary Figure 2. Kaplan Meier curves for survival by tumor thickness measurements a. by quartile (lowest to highest) of sum of tumor thickness. b. by sum of tumor thickness when two data-driven cut points were derived. c. by maximum tumor thickness when one data-driven cut point was derived. d. by

investigator-classified description of the pattern of pleural involvement as ‘minimal’, ‘nodular’, or ‘rind like’.

APPENDIX

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Supplemental data

Supplementary Tables.docx

Supplementary Figures.pptx

TABLES

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		Pathologic	
	ALL	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%)
HISTOLOGY							
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%)

Table 2: Formal comparisons between adjacent T-component categories for existing 7th edition. Cox regression model adjusted for sex and region.

	Clinical Stage		Pathologic Stage	
Comparison	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

Table 3: Overall outcomes with categories T1a and T1b combined. Clinical, pathological and best stage, M0 cases only for proposed 8th edition staging nomenclature.

	Clinical Stage				Pathologic Stage				Best Stage			
T categories	**N**	**Median OS(Mos.)**	**24 Month OS Rate**	**60 Month OS Rate**	**N**	**Median OS (Mos.)**	**24 Month OS Rate**	**60 Month OS Rate**	**N**	**Median OS (Mos.)**	**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%

Table 4: Formal comparisons between adjacent T-component categories after combining categories T1a and T1b. Cox regression model adjusted for sex and region.

	Clinical Stage		Pathologic Stage	
Comparison	**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

Table 5: Final recommendations for T descriptors for the 8th Edition of the AJCC/IUCC 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 ▸ non-transmural 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

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