ORIGINAL ARTICLE

# The International Association for the Study of Lung Cancer Mesothelioma Staging Project: Proposals for Revisions of the "T" Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Pleural Mesothelioma

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## ABSTRACT

**Introduction:** The primary tumor (T) component in the eighth edition of pleural mesothelioma (PM) staging system is based on pleural involvement and extent of invasion. Quantitative assessment of pleural tumor has been found to be prognostic. We explored quantitative and qualitative metrics to develop recommendations for T descriptors in the upcoming ninth edition of the PM staging system.

**Methods:** The International Association for the Study of Lung Cancer prospectively collected data on patients with PM. Sum of maximum pleural thickness (Psum) was recorded. Optimal combinations of Psum and eighth edition cT descriptors were assessed using recursive binary splitting algorithm, with bootstrap resampling to correct for the adaptive nature of the splitting algorithm, and validated in the eighth edition data. Overall survival (OS) was calculated by the Kaplan-Meier method and differences in OS assessed by the log-rank test.

**Results:** Of 7338 patients submitted, 3598 were eligible for cT analysis and 1790 had Psum measurements. Recursive partitioning identified optimal cutpoints of Psum at 12 and 30 mm, which, in combination with extent of invasion, yielded four prognostic groups for OS. Fmax greater than 5 mm indicated poor prognosis. cT4 category (based on invasion) revealed similar performance to eighth edition. Three eighth edition descriptors were eliminated based on

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low predictive accuracy. Eighth edition pT descriptors remained valid in ninth edition analyses.

**Conclusion:** Given reproducible prognostication by Psum, size criteria will be incorporated into cT1 to T3 categories in the ninth edition. Current cT4 category and all pT descriptors will be maintained, with reclassification of fissural invasion as pT2.



*Keywords:* Clinical stage; Pleural mesothelioma; Staging; T component

## Introduction

Clinical stage classification of patients with pleural mesothelioma (PM) in the eighth edition is based on a qualitative assessment of imaging using binary criteria identifying invasion of adjacent structures.[1] As such, it is prone to interobserver and intraobserver variability resulting in inconsistent clinical staging and unclear prognostic accuracy.[2–4] The use of the TNM stage classification in clinical trials for PM is low. Large randomized trials in PM revealing the benefit of platinum and antifolate chemotherapy, and more recently, the benefit of dual-agent immune checkpoint inhibitor therapy, did not include clinical stage as a stratification factor, unlike other solid thoracic malignancies.[5–7] The circumferential rind-like appearance of pleural tumor, with its ability to invade multiple structures and planes simultaneously, limited distinction from adjacent tissue planes on imaging studies, and the inability to quantify the overall tumor burden with a single measurement has made it difficult to develop a size-based descriptor for the primary tumor (T) categories of the staging system.[8,9]

The initial pathologic stage classification system for PM was developed from a single-institution surgical database[10] in 1976 and later modified using information from patients treated with extrapleural pneumonectomy (EPP) and trimodality therapy.[11–13] Nevertheless, these systems did not conform to a TNM classification system. In 1994, at a consensus workshop sponsored by the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG), international PM experts proposed a stage classification system based on the TNM format. This was subsequently accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) as the international PM staging system for the sixth and seventh editions of their stage classification manuals.[9,14] Pleural thickness measurements were collected for the first time as a potential T category descriptor in the IASLC PM database used to develop the eighth edition of the TNM staging system.[1,15] Exploratory analyses revealed that pleural thickness measurements had prognostic significance, and a plan was formulated to collect more comprehensive data to support developing the ninth edition stage classification system.

Tumor volume, assessed from three-dimensional segmentation of the whole tumor on computed tomography (CT), has been explored as a surrogate of tumor size, and several centers of excellence use tumor volume to stratify patients.[15–18] The feasibility of incorporating tumor volume as a T descriptor was explored in a North American multi-institutional pilot study and found to be promising.[3,4] Nevertheless, not all centers have the appropriate software or technical expertise for volumetric measurement of mesothelioma. For ubiquitous applicability, a simpler approach to assessment of tumor size in PM that can provide prognostic information is needed. Therefore, for the ninth edition of the PM stage classification, both pleural thickness measurements on CT and the existing clinical T (cT) descriptors were analyzed to refine cT categories. CT was the imaging modality selected because it is available worldwide and is widely acknowledged as pivotal for clinical stage assessment.[19,20]

## Methods

### *Patient Cohort*

The target population included patients with pathologically proven PM diagnosed between July 2013 and 2022, with extent of disease classified according to the AJCC UICC eighth edition TNM classification system. Data contribution was solicited from investigators from centers across the world treating patients with PM. Demographic and clinical information, clinical and pathologic stage (TNM eighth edition UICC AJCC), treatment, and survival data were collected. Data entry through an electronic data capture (EDC) system designed by the Cancer Research And Biostatistics (CRAB) was the preferred method of data submission; alternatively, the transfer of external institutional data, termed "batch" data, was also permitted.[21]

Inclusion criteria for the initial cT category analysis included histologically or cytologically confirmed PM classified as M0 by the eighth edition of TNM. Participants were eligible for the pathologic T (pT) category analysis if they had undergone surgical resection, were M0, did not receive neoadjuvant therapy, had information regarding fissure involvement if pT1, and had a pT category by eighth edition, which matched any pT descriptors provided (Fig. 1).

### *Selection of T Descriptors and Categories*

PM has several inherent characteristics that affected the decision-making process of the mesothelioma

domain. Experience has revealed that qualitative assessment of imaging poorly correlates with tissue invasion (unless it is quite extensive); hence, a quantitative method of categorizing tumor extent for clinical stage is needed. Quantification of tumor thickness or volume at resection (on pathologic specimens), however, has proven to be problematic, because en bloc removal of tumor is often not feasible. Therefore, for PM, there is an inherent difference between clinical assessment of tumor burden and pathologic assessment. Many patients are managed without surgery; hence, the major focus was on the definition of clinical T descriptors and categories.

Possible definitions of T category were explored, including factors suggested by previously published literature and defined by analysis of the IASLC database. Practical considerations included evidence regarding consistency of measurements and feasibility across regions of the world. A candidate T classification system was required to reveal stepwise ordering, discrimination between adjacent categories, and consistency across regions and histologic types of PM.

### *Quantitative Imaging Assessment*

For the ninth edition analyses, data elements were refined as informed by the eighth edition and revised to incorporate information from the published studies including maximum diaphragmatic (Dmax) and fissure thickness (Fmax) measurements in addition to maximum pleural thickness measurements at the upper, middle, and lower hemithorax (Psum = pmax1 + pmax2 + pmax3).[1,15,22]

Pleural thickness measurements were collected from CT scans by participating institutional investigators. The site radiologists helped capture the quantitative metrics. The chest was divided into three compartments with a virtual demarcation at the level of the top of the arch of the aorta and the first image at or below the level of the left atrium, dividing the chest into three relatively equal parts (Fig. 2*A–C*). The maximum pleural thickness measurements were assessed on axial images perpendicular to the chest wall or mediastinum in the area of maximal pleural thickness in each third of the hemithorax (pmax1, pmax2, and pmax3) and combined to estimate the sum of the maximal pleural thickness at the three levels (Psum = pmax1 + pmax2 + pmax3). Maximal pleural thickness was also measured along the fissures (Fmax) and diaphragm (Dmax) on sagittal images at sites of maximum thickness (Fig. 2*A–C*).

Involvement of the fissure was defined as maximum pleural thickness along the fissures (Fmax) measuring

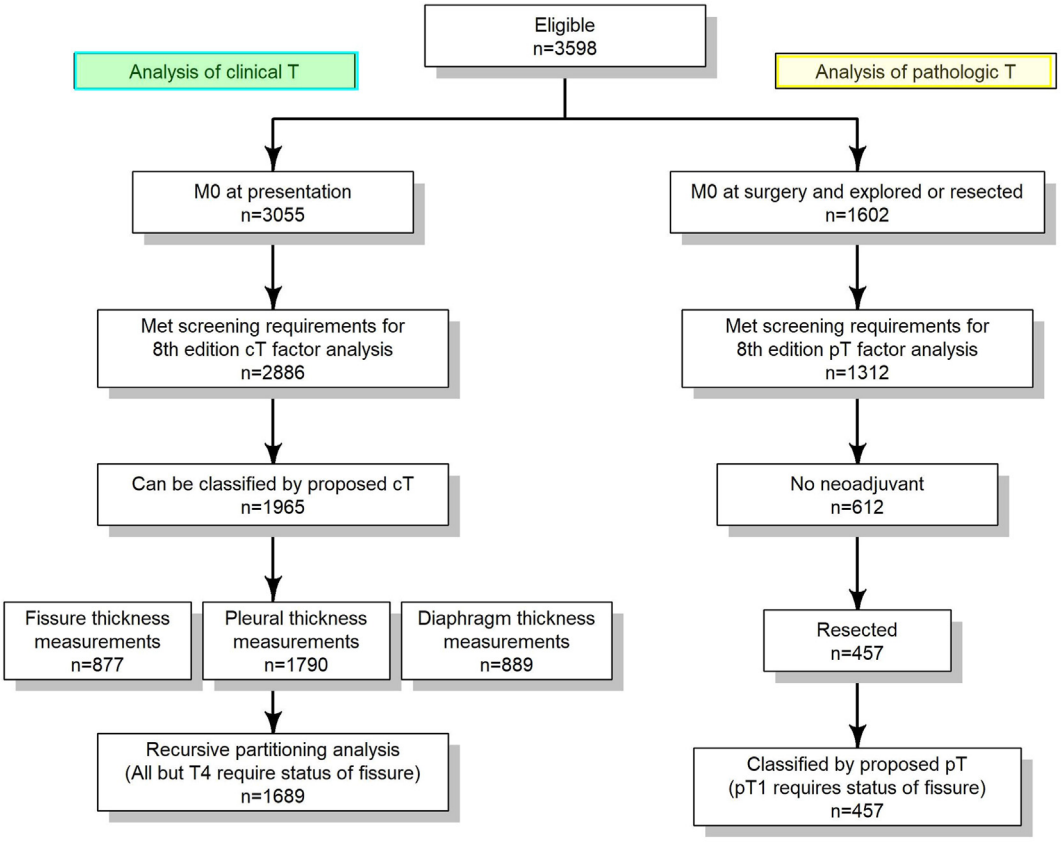


**Figure 1.** Consort diagram for patient selection.

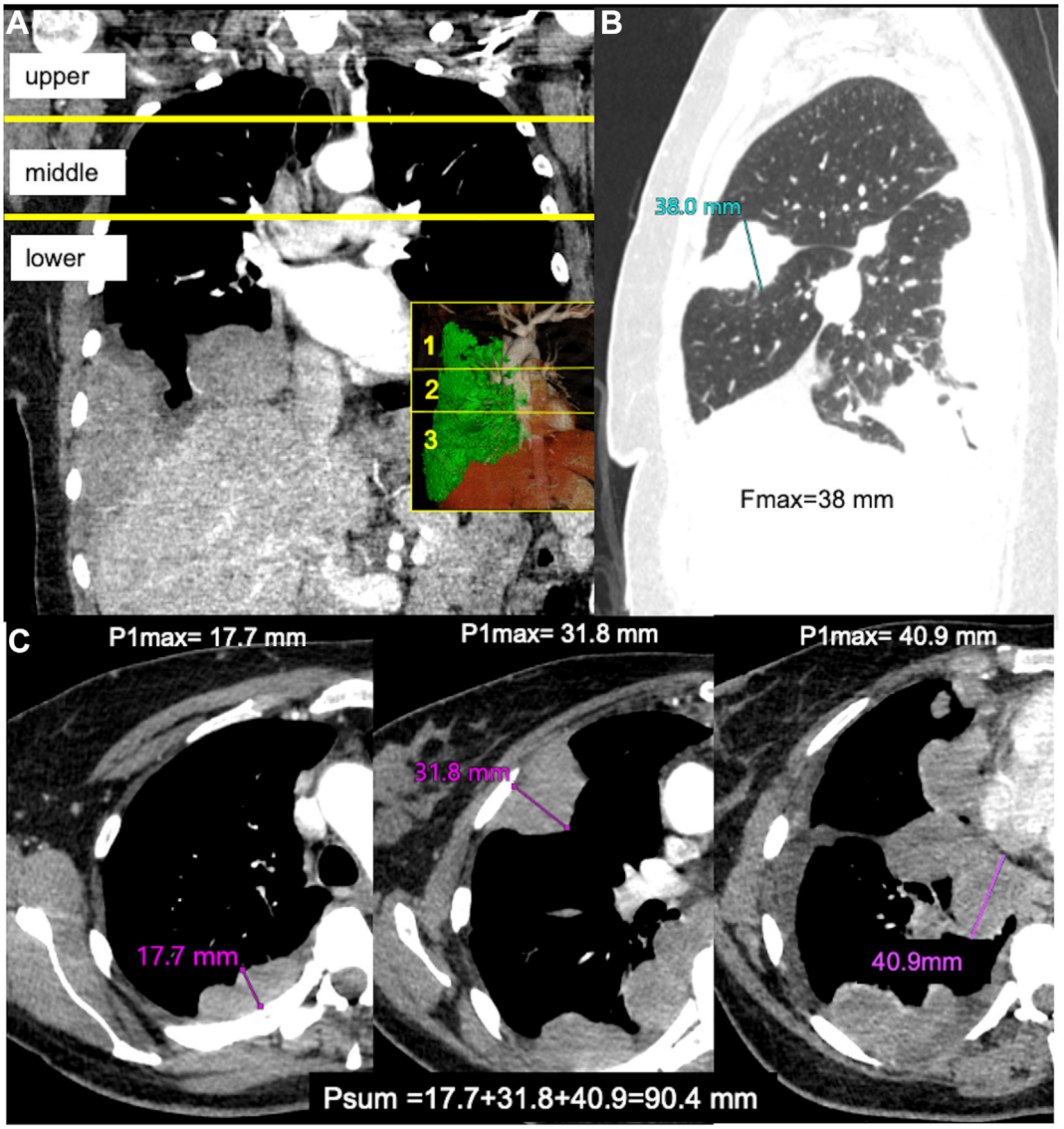


**Figure 2.** (*A*) Coronal and sagittal images of patients with pleural mesothelioma illustrating division of the chest into approximate thirds by a line drawn at the level of the aortic arch and a second line at the top of the left atrium, dividing the chest into three relatively equal parts of upper, middle, and lower levels. The maximum pleural thickness on each of these levels (pmax1, pmax2, and pmax3) is measured and combined to derive a sum of maximum pleural thickness (Psum = pmax1 + pmax2 + pmax3). (*B*) Sagittal image revealing fissure involvement by tumor; maximal fissure thickness Fmax = 38 mm. (*C*) Axial images with maximal pleural thickness measurement at each of the three levels; p1max = 17.7 mm; p2max = 31.8 mm and p3max = 40.9 mm, and Psum = 17.7 + 31.8 + 40.9 = 90.4 mm.

more than 5 mm or documented as "present" in the absence of measured thickness. This cutpoint for fissure thickness was based on previous published work and was also close to the optimal cutpoint of 8 mm ($p$ = 0.007) in the ninth edition IASLC database.[15] The relationship between Dmax and nontransmural invasion of the diaphragm is less well understood. In a univariate analysis of overall survival (OS), an optimal cutpoint of 6.8 mm was identified in the 889 patients with Dmax measurements. Nevertheless, due to the lack of Dmax measurements in approximately half of the samples prevented inclusion of Dmax in the multivariable analyses. The decision to not include Dmax was also influenced by the inability to validate it within the eighth edition IASLC database.

### *Qualitative Imaging Assessment*

The TNM descriptors scored in a binary fashion for invasion of the adjacent planes, structures, and organs for each patient were collected based on the eighth edition AJCC/UICC TNM staging system. Because published studies have now revealed that nontransmural invasion of the diaphragm (cT2), invasion of lung

parenchyma by tumor (cT2), and endothoracic fascia (cT3) invasion cannot be accurately determined based on CT imaging, therefore the qualitative measure of tumor extent based on eighth edition cT categories was assessed after removal of these three descriptors.[15] With these T descriptors eliminated, there was no longer a distinction between the eighth edition T1 tumors, T2 tumors, or T3 solely by endothoracic fascia invasion in the simplified, qualitative component.

## Statistical Considerations

The primary end point was OS, measured from the date of diagnosis for clinical stage or from the date of operation for pathologic stage to the date of death, censored on the date of last known follow-up, if alive. After screening for eligibility and data completeness, the relationship between T categories and OS was assessed by the Kaplan-Meier method.[23] Reproducibility of findings was assessed in subgroup analyses including histologic type, geographic region, sex, and data source (batch versus EDC). Findings were further validated by replication of the analysis in the eighth edition data set. Pairwise differences in OS between adjacent T categories were tested for statistical significance using the log-rank test.[24]

A recursive partitioning and amalgamation-generated survival tree was fitted to the data to produce groupings that maximized differences in OS among subsets defined by the covariates of Psum and the simplified qualitative measure of T. Terminal nodes of the tree containing patients with tumors with similar survival outcomes were compared through log-rank statistics, with bootstrap resampling to correct for the adaptive nature of the splitting algorithm.[25] Pairwise differences in OS between adjacent T categories were tested for statistical significance using the log-rank test[24] within the SAS system for Windows version 9.4 LIFETEST procedure.

Data management and analysis were provided by CRAB in Seattle, Washington. All analyses were conducted using the SAS statistical software package (SAS Institute, Cary, NC) or R (R Foundation for Statistical Computing, Vienna, Austria; version 4.2.1).

## Results

Of the 3598 patients who met the general screening requirements for the project, 3055 patients were M0 at presentation and 2886 met the initial inclusion criteria for cT category analysis. Of these, 1965 patients comprised the final cohort analyzed for proposed cT and 457 patients were eligible for analysis of pT (Fig. 1). Most patients were treated in Asia, North America, and Europe, with smaller cohorts from Australia and South America. Patient demographics for both cohorts cT and pT are listed in Table 1. Psum was available for 1790 patients and ranged from 0.4 to 462.7 mm with an average of 45.5 mm. Dmax measurements were available for 889 patients with an average measurement of 11.3 mm (0–96 mm). Fmax measurements were available for 877 patients with an average measurement of 9.6 mm (0–64.8 mm).

Initial evaluation of the cT data revealed that both Psum and extent of the primary tumor (involvement of anatomic structures) were useful in constructing distinct T categories with respect to OS. The OS for patients deemed to have T1 tumors but accompanied by fissure thickness greater than 5 mm was similar to eighth edition T2 category, suggesting the presence of fissure involvement as an independent predictor of worse prognosis irrespective of Psum (Supplementary Fig. 1).

In the exploratory analyses performed for the eighth edition, Psum cutpoints of less than 13 mm, 13 to 60 mm, and more than 60 mm were identified.[1] These Psum cutpoints separated the ninth edition data into three distinct groups as well (Supplementary Fig. 2), although a side-by-side comparison of survival by cutpoint groups by the ninth edition versus by the eighth edition T (modified by removing the three descriptors—endothoracic fascia, lung parenchyma, and nontransmural diaphragm) suggested that patients with T4 disease represented a risk group with particularly poor prognosis that was not identified based on pleural thickness cutpoints alone. The qualitative component of T was thus divided into the following three groups: Group 1. “Low,” that is, T1 or T2 tumors with no involvement of the fissure or T3 solely by invasion of the endothoracic fascia. Group 2. “Medium,” that is, all other T1 to T3 tumors. Group 3. “High,” that is, T4 tumors.

Recursive partitioning applied to the ninth edition data suggested that OS for patients with “High T” (T4) tumors was distinct irrespective of pleural thickness. The optimal cutpoints of less than 12.2 mm, greater than or equal to 12.2 mm, and less than 31 mm and greater than or equal to 31 mm for Psum were useful in reclassifying the remaining tumors into proposed T1, T2, or T3 categories (Fig. 3*A–C*). In accordance with the convention of placing the equal sign on the upper bound, the boundary of less than 12.2 mm was changed to less than or equal to 12 mm, and the boundary less than 31 mm was changed to less than or equal to 30 mm.

The proposed definitions for cT for the ninth edition are summarized in Table 2 (Supplementary Fig. 1). Comparison of the proposed definitions for cT and pT with the eighth edition is summarized in Supplementary Table 1. Using these definitions, median OS for patients with T1 tumors was 49.8 months, 27.5 months for T2, 21.1 months for T3, and 12.6 months for T4. All comparisons of OS between proposed T categories were statistically significant, whereas OS was not significantly

**Table 1.** Demographics of Analyzed Patients

| Category | Clinically Staged T Cohort (cT) (N = 1965) | | Pathologically Staged T Cohort (pT) (Resected, No Neoadjuvant Treatment) (N = 457) | |
|---|---|---|---|---|
| Age (y) | | | | |
| Mean | 69.7 | | 67.0 | |
| Range | 18.4 | 99.0 | 22.0 | 91.6 |
| Sex, n (%) | | | | |
| Female | 471 | (24%) | 120 | (26%) |
| Male | 1494 | (76%) | 337 | (74%) |
| Performance status, n (%) | | | | |
| 0 | 1001 | (51%) | 242 | (53%) |
| 1 | 694 | (35%) | 120 | (26%) |
| 2 | 111 | (6%) | 14 | (3%) |
| 3–4 | 25 | (1%) | 5 | (1%) |
| No data | 134 | (7%) | 76 | (17%) |
| Region, n (%) | | | | |
| Asia | 494 | (25%) | 44 | (10%) |
| Australia | 54 | (3%) | 39 | (9%) |
| Europe | 513 | (26%) | 136 | (30%) |
| North America | 904 | (45%) | 238 | (52%) |
| South America | 38 | (2%) | 0 | (0%) |
| Histologic type/subtype, n (%) | | | | |
| Epithelioid mesothelioma | 1551 | (79%) | 376 | (82%) |
| Biphasic mesothelioma | 225 | (11%) | 66 | (14%) |
| Sarcomatoid mesothelioma | 166 | (8%) | 12 | (3%) |
| Desmoplastic mesothelioma | 23 | (1%) | 3 | (1%) |
| Treatment, n (%) | | | | |
| Not explored or resected | 924 | (47%) | 0 | (0%) |
| Neoadjuvant treatment followed by exploration/resection | 492 | (25%) | 0 | (0%) |
| Exploration/resection, no neoadjuvant treatment | 549 | (28%) | 457 | (100%) |
| Curative resection attempt, n (%) | | | | |
| Pleurectomy/decortication | 322 | (16%) | 226 | (49%) |
| Extended pleurectomy/decortication | 258 | (13%) | 154 | (34%) |
| Extrapleural pneumonectomy | 158 | (8%) | 77 | (17%) |
| None or no data | 1227 | (62%) | 0 | (0%) |

different for eighth edition T2 versus T3 (Table 3). The proposed ninth edition cT was validated in the eighth edition data set, again revealing better separation of the curves for the proposed new T categories in the eighth edition data set when compared with the eighth edition T categories (Fig. 4*A*–*D*).

The pT category was analyzed in 457 patients with data available for assessment by the proposed cT (ninth edition) (Fig. 1). The OS curves for the proposed pT (ninth edition) among the 457 patients revealed similar separation between the pT categories when compared with the eighth edition, as only nine patients were reclassified from pT1 by the eighth edition to pT2 by the proposed ninth edition (Fig. 4*E* and *F*; Table 3). Given the lack of anatomic structural orientation in most pleural resection specimens, particularly when resections are performed by some form of pleurectomy/decortication (P/D), it is not possible to correlate pathologic size of pleural thickening to CT estimation of pleural thickness within each of the three levels. Therefore, the qualitative pT descriptors used in the eighth edition are maintained in the proposed ninth edition of the staging system, with the exception of fissure involvement designating T2 rather than T1 category.

Consistency was assessed through further analyses which confirmed that discrimination between the proposed new clinical T categories was upheld in all geographical regions and for both epithelioid and non-epithelioid tumors, although the numbers of non-epithelioid tumors were small (Supplementary Figs. 3–7).

## Discussion

This proposal for the ninth edition of TNM stage classification system for PM is the first to incorporate

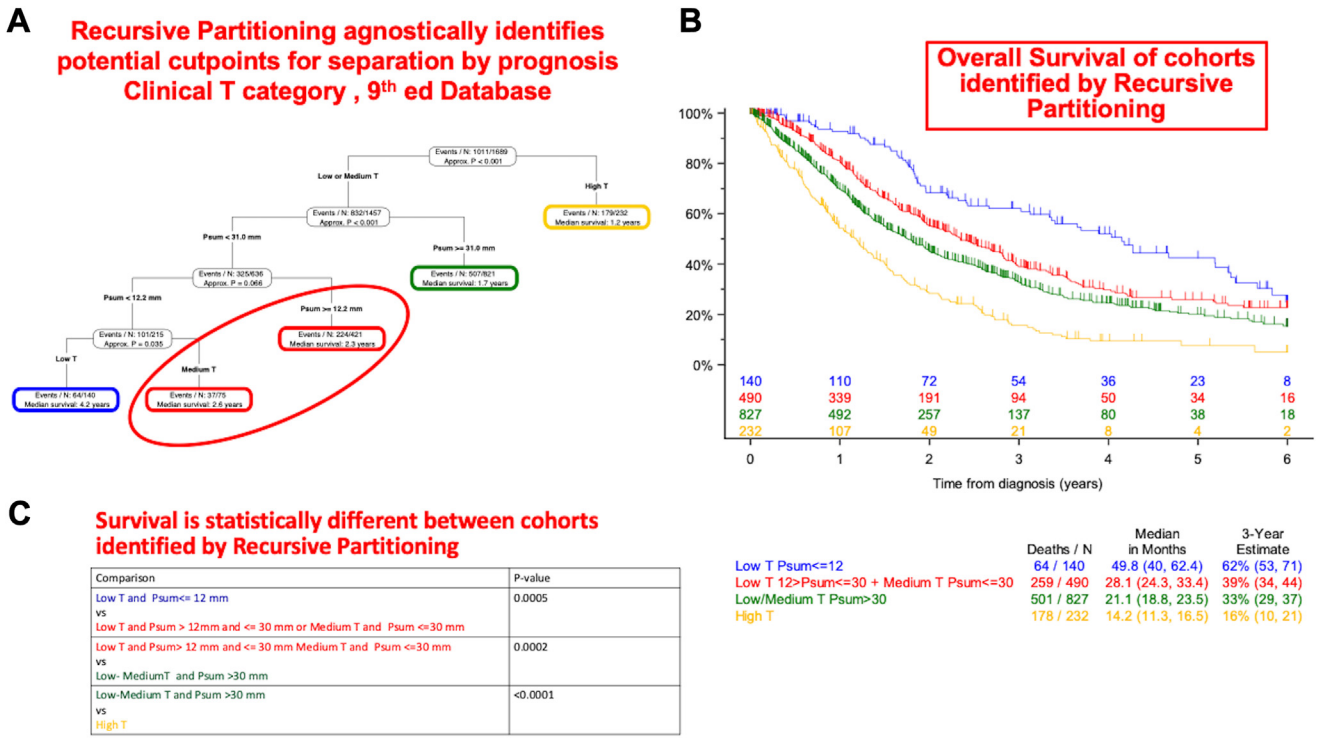


**Figure 3.** Recursive partitioning applied to ninth edition data based on predictor variables of quantitative T (low versus medium versus high) and Pmax (N = 1689); (*A*) survival tree, (*B*) overall survival by terminal nodes,* and (*C*) pairwise comparisons of survival between adjacent groups. *According to conventions for placement of the equal sign, the upper bounds for Psum were changed from less than 12.2 mm to less than or equal to 12 mm and from less than 31.0 mm to less than or equal to 30 mm. In panel (*C*), low T, T1 or T2 with no involvement of the fissure or T3 solely by invasion of the endothoracic fascia; medium T, all other T1 to T3; high T, T4; Psum, sum of maximum pleural thickness at three levels; *p* value, significance value from log-rank test comparing overall survival between adjacent T categories.

size criteria into the cT descriptors, in combination with the presence or absence of fissural invasion on imaging. Implicit in this proposal is the acknowledgment that some of the previous T descriptors of anatomical invasion, developed through surgical databases, do not lend themselves to assessment using CT imaging. Thus, these proposed ninth edition clinical T descriptors and categories are a major step toward clinical applicability. Implementation of the proposed cT categories will require education of the radiology and the oncology communities about how staging measurements should be performed, what imaging findings constitute fissural invasion, and a worldwide change of practice in radiologic reporting of the initial CT scan for patients with PM.

The proposed pT category remains similar to the eighth edition, although pathologic involvement of the fissure has been moved to pT2 category to align with the cT category. Surgical/pathologic pleural tumor thickness was not collected for this data set. Although there was considerable discussion about the potential applicability of tumor thickness measurements to patients with PM undergoing resection, this cannot be applied in routine practice. Tumor is rarely removed as an intact single specimen, thereby precluding reliable measurement of a "maximal pleural thickness" at prespecified locations in surgical specimens. Alternative metrics such as surgical tumor volume or weight would be similarly challenging, as different surgical procedures may remove adjacent organs (pericardium, diaphragm, lung parenchyma) and may not be amenable to complete gross tumor removal, making it difficult to compare across different procedures. Hence, the practical approach is to have distinct rules for the assessment of cT and pT, as with several other malignancies.

For cancers of the lip, oral cavity, and skin, cN and pN categories differ according to the quantification of nodal disease.[26] For cancers of the breast, penis, testes, and urinary system, the number of involved lymph nodes is a pathologic descriptor, only, and not a clinical descriptor.[27,28] In tumors with complex morphology such as ovarian cancer and peritoneal mesothelioma in which exact size cannot be determined, the TNM systems have not been found to be useful, and alternate stage classification systems are more popular.[29,30]

The cT categories performed better than the pT categories in prognostication, which may be related to

**Table 2.** Distribution by Clinical T (cT) and Pathologic T (pT) Descriptors for the Proposed Ninth Edition T Category for Pleural Mesothelioma

Primary Tumor (T)

| Category | Clinical T (cT) | Pathologic T (pT) |
|---|---|---|
| Tx | Tumor cannot be assessed | |
| T0 | No tumor is present | |
| T1 | Tumor limited to the ipsilateral pleura with **Psum**[a] **≤ 12 mm** with no involvement of the fissure (**Fmax**[b] **≤ 5 mm**) | Tumor limited to the ipsilateral pleura with no involvement of the fissure |
| T2 | Tumor involving the ipsilateral pleura with **Psum**[a] **≤ 12 mm** and with any of the following:<br>• involvement of the fissure (**Fmax**[b] **> 5 mm**)<br>• mediastinal fat invasion<br>• solitary area of chest wall soft tissue invasion; or Tumor involving the ipsilateral pleura with **Psum**[a] **> 12 mm but ≤30 mm**, with or without:<br>• involvement of the fissure (**Fmax**[b] **> 5 mm**)<br>• mediastinal fat invasion<br>• solitary area of chest wall soft tissue invasion | Tumor involving the ipsilateral pleura and with any of the following:<br>• involvement of the fissure<br>• ipsilateral lung parenchyma invasion<br>• diaphragm (nontransmural) invasion |
| T3 | Tumor involving the ipsilateral pleura with **Psum**[a] **> 30 mm**; with or without:<br>• involvement of the fissure (**Fmax**[b] **> 5 mm**)<br>• mediastinal fat invasion<br>• solitary area of chest wall soft tissue invasion | Tumor limited to the ipsilateral pleura (with or without fissure involvement) and with invasion of any of the following:<br>• mediastinal fat<br>• surface of pericardium<br>• endothoracic fascia<br>• solitary area of chest wall soft tissue |
| T4 | Tumor with invasion of any of the following (any **Psum**[a]):<br>• chest wall bony invasion (rib)<br>• mediastinal organs (heart, spine, esophagus, trachea, great vessels)<br>• diffuse chest wall invasion<br>• direct tumor extension through the diaphragm or pericardium<br>• direct extension to the contralateral pleura<br>• presence of malignant pericardial effusion | Tumor with invasion of any of the following:<br>• chest wall bony invasion (rib)<br>• mediastinal organs (heart, spine, esophagus, trachea, great vessels)<br>• diffuse chest wall invasion<br>• transmural invasion of the diaphragm or pericardium<br>• direct extension to the contralateral pleura<br>• presence of malignant pericardial effusion |

[a]Psum = pmax1 + pmax2 + pmax3 (sum of three measurements of maximal pleural thickness measured on axial images along the chest wall or mediastinum in each of the three divisions of the chest—upper, middle, and lower divided by two lines; one at the top of the aortic arch and the second drawn at the top the left atrium).
[b]Fmax = maximal thickness of pleural tumor along the fissures measured on sagittal images.

**Table 3.** Statistical Assessment of Differences Between Adjacent T Categories

| Comparison | Eighth Edition *p* Value | Proposed Ninth Edition *p* Value |
|---|---|---|
| Clinical T, ninth edition data, n = 1965 | | |
| T1 vs. T2 | <0.0001 | <0.0001 |
| T2 vs. T3 | 0.3841 | 0.0007 |
| T3 vs. T4 | <0.0001 | <0.0001 |
| Pathologic T, ninth edition data, n = 457 | | |
| T1 vs. T2 | 0.0056 | 0.0277 |
| T2 vs. T3 | 0.2335 | 0.1153 |
| T3 vs. T4 | 0.2880 | 0.2880 |
| Clinical T, eighth edition data, n = 567 | | |
| T1 vs. T2 | 0.1056 | 0.0240 |
| T2 vs. T3 | 0.9460 | 0.1068 |
| T3 vs. T4 | 0.0032 | 0.0077 |

*Note:* The table depicts *p* values for log-rank comparisons of overall survival of adjacent T categories by eighth edition and proposed ninth edition definitions and in the eighth edition and the ninth edition databases.

several factors. First, the recursive partitioning model was fitted to the ninth edition cT data, and therefore, the proposal can be expected to perform optimally in that context. Importantly, the proposal also performed better than eighth edition cT when applied to the eighth edition data, revealing a significant difference in OS for T1 versus T2 and better separation of T2 versus T3. Another factor may be related to the trend in the last decade of proportionately fewer surgical patients undergoing EPP, with only 158 (15%) of patients in the current study, thus providing less complete information regarding pathologic stage than historic data sets involving more of such specimens. With a relatively higher proportion of surgical patients undergoing P/D, key pathologic information such as invasion of mediastinal fat, endothoracic fascia invasion, presence of pericardial effusion, and orientation of pleural tumor may not be available from surgical

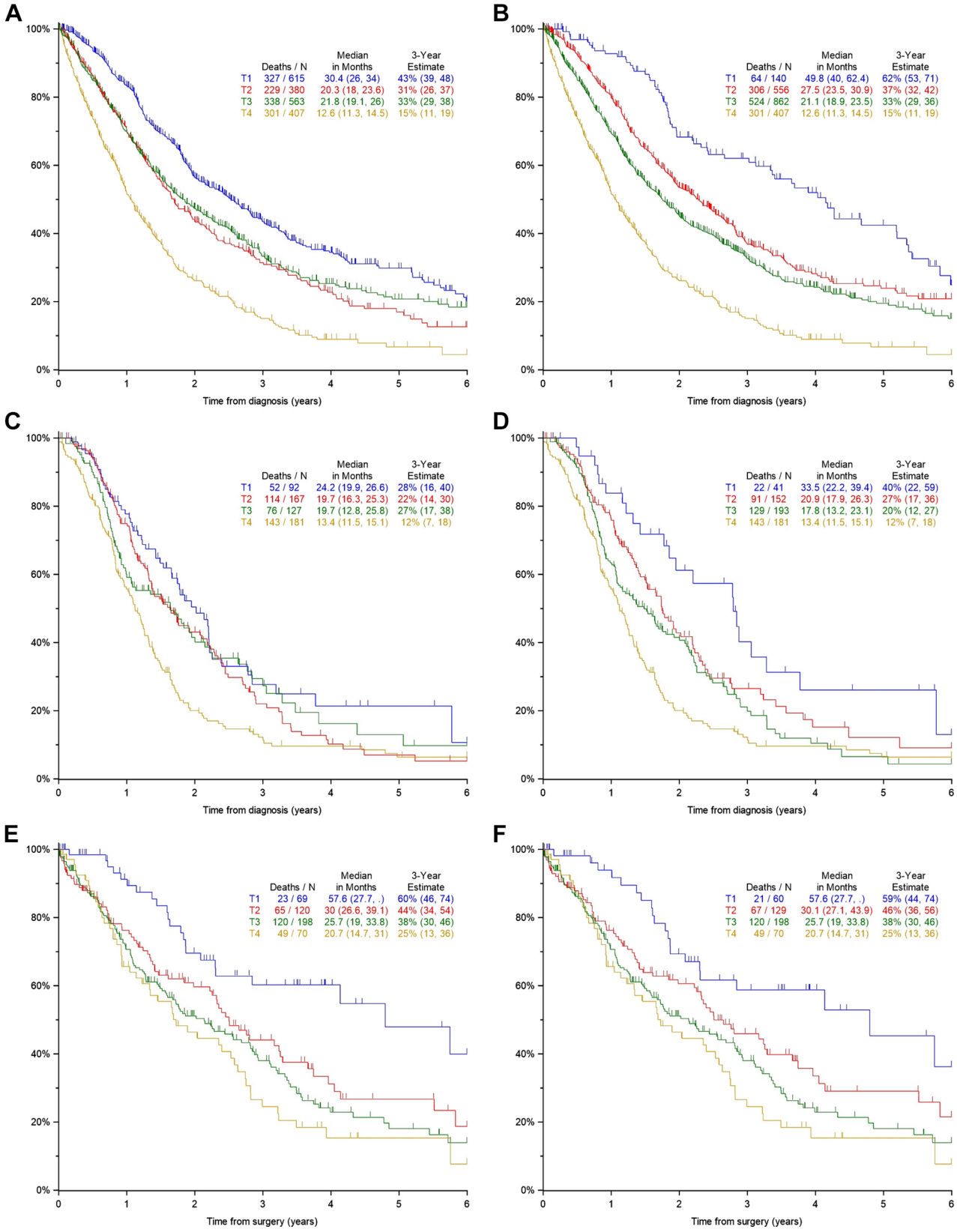


**Figure 4.** Overall survival by (*A*) eighth edition clinical T applied to the ninth edition data, (*B*) proposed ninth edition clinical T applied to the ninth edition data, (*C*) eighth edition clinical T applied to the eighth edition data, (*D*) proposed ninth edition clinical T applied to the eighth edition data, (*E*) eighth edition pathologic T applied to the ninth edition data, and (*F*) proposed ninth edition pathologic T applied to the ninth edition data.

specimens. In comparison, overall tumor bulk or tumor volume can be assessed from imaging, especially using the simplified approach of dividing the chest into three equal parts and measuring pleural thickness at three sites generating a maximum pleural thickness, which is a surrogate for tumor size.

Tumor volume, a surrogate for tumor burden, has been found to be prognostic in a number of studies and has revealed to predict survival and time to recurrence[4,15,16,31–33] in both surgical and nonsurgical patients, and thus confirming the need for a size descriptor for the T category. Although tumor volume measurements have potential as a more accurate predictor of survival, as yet there is neither standardization of volumetric techniques nor can all sites measure volume on CT scan. Therefore, in order for widespread use in a stage classification system, a simple approach that has potential for widespread adoption is needed. Unidimensional pleural thickness measurements were initially explored during the eight edition revision and found to be promising. An international collaborative effort to collect pleural thickness measurements has now confirmed the initial findings in the eighth edition data, and we conclude that tumor size category in addition to fissural invasion is the best current clinical T category descriptor.

Mesothelioma in situ (potentially cTis/pTis) has recently been recognized as a distinct entity and is regarded as a precursor to invasive mesothelioma.[34] The diagnosis can be challenging and requires multidisciplinary correlation among histologic, immunohistochemical, and/or molecular, clinical, and radiologic findings. It is usually characterized by the presence of effusion in the absence of pleural thickening, minimal changes in pleural appearance on video thoracoscopy, and subtle pathologic abnormalities, characterized by BAP1, MTAP loss by immunohistochemistry or homozygous deletion CDKN2*a* in the absence of invasion.[35] This data set was not designed to collect information about this category. Future investigations for the tenth edition of the stage classification system may elucidate this proposed category further.

In conclusion, for the ninth edition of the stage classification system, we propose a cT category based on a combination of both unidimensional measurements of pleural thickness and invasion of adjacent planes and organs. This improves prognostic stratification across cT categories substantially, relative to the eighth edition AJCC/UICC cT categories. Thus, it will improve stratification of patients entering clinical trials and may improve the selection of treatment for patients in routine practice.

## CRedit Authorship Contribution Statement

**Ritu R. Gill:** Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing.

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## Disclosure

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## Appendix 2. Chairpersons and Members of the Subcommittees of the Lung Cancer, Thymic Epithelial Tumors, Pleural Mesothelioma and Esophageal Cancer Domains of the IASLC Staging and Prognostic Factors Committee

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**Lung Cancer Domain Neuroendocrine Tumors Subcommittee.** Ming S. Tsao (chair), Andrew G. Nicholson (co-chair), Ricardo Beyruti, Frank Detterbeck, Wilfried Eberhardt, Pier Luigi Filosso, Yolande Lievens, Eric Lim, Geoffrey Liu, José-María Matilla, Natasha Rekhtman, William D. Travis, Jeff Yang, Yasushi Yatabe.

**Lung Cancer Domain Stage Group Subcommittee.** Hisao Asamura (chair), Giuseppe Cardillo, Frank Detterbeck, John Edwards, Kwun Fong, Meredith Giuliani, James Huang, Kemp H. Kernstine, Edith M. Marom, Andrew G. Nicholson, Ramón Rami-Porta, William D. Travis, Ming S. Tsao, Paul Van Schil, Shun-ichi Watanabe.

**Lung Cancer Domain Lymph Node Chart Subcommittee.** Shun-ichi Watanabe (chair), Jin Mo Goo (co-chair), Hisao Asamura, Hans Hoffman, James Huang, Kemp H. Kernstine, Yolanda Lievens, Raymond U. Osarogiagbon, Paul Martin Putora, Ramón Rami-Porta, Valerie Rusch, Paul Van Schil, Jeff Yang.

**Lung Cancer Domain Validation and Methodology Subcommittee.** Frank Detterbeck (chair), Alyson Mahar

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**Lung Cancer Domain Prognostic Factors Subcommittee.** Frank Detterbeck (chair), Raymond U. Osarogiagbon (co-chair), Alex Brunelli, Kwun Fong, Meredith Giuliani, James Huang, Young Tae Kim, Mark Krasnik, Hiu Liu, Jan van Meerbeeck, Luis M. Montuenga, Andrew G. Nicholson, Paul Martin Putora, Valerie Rusch, Robert Samstein, Navneet Singh, Martin Tammemägi, Ricardo Terra, Ming S. Tsao, Akif Turna, Terence Williams.

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**Lung Cancer Domain Molecular Subcommittee.** David Carbone (co-chair), Fred Hirsch (co-chair), Luiz Henrique Araujo, Hisao Asamura, Elisabeth Brambilla, Jason Chang, Frank Detterbeck, Oliver Gautschi, Nagla Karim, Keith Kerr, Peter Kneuertz, Eric Lim, Philip Mack, José-María Matilla, Luis M. Montuenga, Andrew G. Nicholson, Raymond U. Osarogiagbon, Harvey Pass, Carolyn J Presley, Ramón Rami-Porta, Natasha Rekhtman, Harry Ren, Robert Samstein, Kenichi Suda, Ricardo M. Terra, William D. Travis, Ming S. Tsao, Terence Williams, Ignacio Wistuba, Dawei Yang, Yasushi Yatabe.

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### *Pleural Mesothelioma Domain*

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### *Esophageal Cancer Domain*

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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 https://doi.org/10.1016/j.jtho.2024.03.007.

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