ORIGINAL ARTICLE

The IASLC Mesothelioma Staging Project: Proposals for the M Descriptors and for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Mesothelioma

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ABSTRACT

Introduction: The M component and TNM stage groupings for malignant pleural mesothelioma (MPM) have been empirical. The International Association for the Study of Lung Cancer developed a multinational database to propose evidence-based revisions for the eighth edition of the TNM classification of MPM.

Methods: Data from 29 centers were submitted either electronically or by transfer of existing institutional databases. The M component as it currently stands was validated by confirming sufficient discrimination (by Kaplan-Meier analysis) with respect to overall survival (OS) between the clinical M0 (cM0) and cM1 categories. Candidate stage groups were developed by using a recursive partitioning and amalgamation algorithm applied to all cM0 cases.

Results: Of 3519 submitted cases, 2414 were analyzable and 84 were cM1 cases. Median OS for cM1 cases was 9.7 months versus 13.4 months ($p = 0.0013$) for the locally advanced (T4 or N3) cM0 cases, supporting inclusion of only cM1 in the stage IV group. Exploratory analyses suggest a possible difference in OS for single- versus multiple-site cM1 cases. A recursive partitioning and amalgamation–generated survival tree on the OS outcomes restricted to cM0 cases with the newly proposed (eighth edition) T and N components indicates that optimal stage groupings for the eighth edition will be as follows: stage IA (T1N0), stage IB (T2–3N0), stage II (T1–2N1), stage IIIA (T3N1), stage IIIB (T1–3N2 or any T4), and stage IV (any M1).

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****See Appendix for the members of the IASLC Staging and Prognostic Factors Committee, advisory boards, and participating institutions.**

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Conclusions: This first evidence-based revision of the TNM classification for MPM leads to substantial changes in the T and N components and the stage groupings.

Keywords: Mesothelioma; Staging; Staging system; TNM stage groupings

Introduction

The current staging system for malignant pleural mesothelioma (MPM) was developed in 1994 at a workshop sponsored by the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG), during which MPM investigators analyzed reported surgical databases and the available small clinical trials in this disease. The resulting TNM-based system was potentially applicable to the clinical, surgical and pathologic staging of MPM,[1] and it was subsequently accepted by the Union for International Cancer Control (UICC) and the American Joint Commission on Cancer (AJCC) as the first international MPM staging system for the sixth edition of their staging manuals. Although this system was thereafter widely used in retrospective studies and in clinical trials, it has been criticized for being insufficiently evidence based and difficult to apply to clinical staging.

To identify potential deficits in the MPM staging system, the IASLC Staging and Prognostic Factors Committee, in collaboration with members of the IMIG, initiated a large international database in 2009. This approach was modeled on the methods used by the IASLC to revise the lung cancer staging system. Data were solicited from surgeons around the world known to care for a high volume of patients with MPM and were transmitted to the statistical center, Cancer Research And Biostatistics (CRAB) in Seattle, Washington, without identifiable private patient information. Common data elements were established after review of institutional databases, and the time frame chosen for the initial analysis was 1995 to 2009. Data were submitted on 3101 patients from 15 centers on four continents, and a first analysis was published in 2012.[2] Although overall survival data largely supported continued use of the original IMIG system for the seventh editions of the staging manuals, several important areas for improvement were identified, particularly for the T and N components.

To address controversies raised by the initial analysis, an expansion of the IASLC MPM database was started in July 2013 in anticipation of the eighth editions of the AJCC and UICC staging systems. The data dictionary was revised to provide more granular information for the T, N, and M descriptors, and a new electronic data capture (EDC) system, housed at CRAB, was developed. Additional investigators who could provide valid information on patients with tumors staged clinically and managed non-surgically were recruited.[3] The proposals for changes to the T and N components have been published previously.[4,5] Here we present the proposals for the M component and for the resultant TNM stage groupings.

Methods

This was an international, multi-institutional cohort study. The study population included 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 seventh edition of the UICC/AJCC staging system for MPM.[6,7] Biostatistical support was provided by CRAB.

Data to inform this effort originated from 29 centers on four continents (see Appendix). Some of the cases from the initial surgically managed database[2] 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 electronic database. Cases with complete anatomical stage information, complete survival information, and a diagnosis of MPM between January 1995 and June 30, 2013, were eligible. All data were collected in compliance with applicable local legislation, and only coded, deidentified data were submitted 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.

For this analysis, clinical stage and pathologic stage were considered along with best stage, which was defined as pathologic stage when available and clinical stage otherwise. For cases in which chemotherapy was received before surgery (usually denoted as ypTNM), only clinical stage was considered. For analyses of the T component, which is described elsewhere,[4] anatomical tumor descriptors were required. For analyses of the N component,[5] nodal station data were required. The M component of TNM classification as it currently stands was validated by confirming sufficient discrimination with respect to overall survival between the clinical M0 (cM0) and cM1 stage groups. Analyses regarding sites of metastasis and number of metastatic sites and lesions were restricted to exploratory examinations of overall survival prognosis (Kaplan-Meier survival estimates) owing to the small number of M1 cases in this data set. The requirements for

Table 1. Patient Characteristics

Characteristic	Total	"Best" Stage Only		Available TNM Staging					
				Clinical + Pathologic		Clinical		Pathologic	
		n	(%)	N	(%)	N	(%)	N	(%)
Region									
Asia	224	0	0	85	(37%)	133	(59%)	6	(2%)
Australia	221	1	(<1%)	0	(0%)	112	(50%)	108	(48%)
Europe	804	4	(<1%)	131	(16%)	361	(44%)	308	(38%)
North America	807	0	(0%)	395	(48%)	304	(37%)	108	(13%)
Turkey	358	0	0	46	(12%)	8	(2%)	304	(84%)
Sex									
Female	532	1	(0%)	145	(27%)	166	(31%)	220	(41%)
Male	1882	4	(0%)	512	(27%)	752	(39%)	614	(32%)
Histologic type									
Biphasic	349	0	(0%)	103	(29%)	103	(29%)	143	(40%)
Epithelioid	1765	3	(<1%)	513	(29%)	643	(36%)	606	(33%)
Other/NOS	187	2	(1%)	30	(16%)	100	(53%)	55	(30%)
Sarcomatoid	113	0	(0%)	11	(9%)	72	(63%)	30	(26%)
Total	2414	5	(<1%)	657	(27%)	918	(38%)	834	(34%)

Note: Best stage only refers to a composite of available clinical and pathologic TNM components.
NOS, not otherwise specified.

inclusion in primary analyses of overall TNM stage groups were as follows: complete T, N, and M components; known survival status at last follow-up; presentation within the specified time frame; and complete agreement between anatomical descriptors and assigned TNM category.

Candidate proposals for overall TNM stage groups were developed by incorporating proposed changes to the T and N components that have been reported elsewhere.[4,5] Briefly, they are to combine T1a and T1b to form a T1 category, combine N1 and N2 to form a new N1 category, and rename N3 as N2. Candidate stage group schemes were developed for consideration by using a recursive partitioning and amalgamation algorithm[8] applied to all M0 cases. Survival was measured from the date of diagnosis and was calculated by the Kaplan-Meier method. The analysis utilized the R version 3.1.2 RPART and RLSPLIT packages.[9–11] The algorithm generated a tree-based model for the survival data by using log-rank test statistics for recursive partitioning, and for selection of the important groupings, bootstrap was used to correct for the adaptive nature of the splitting algorithm. The primary tree-based analysis grouped 2307 cases on the basis of ordered representations of "best" T category (pathologic if available, otherwise clinical) and best N category restricted to M0 cases. An ordered list of groupings was constructed from the terminal nodes of the survival tree. With this as a guide, several stage grouping schemes were proposed by combining adjacent groups. Candidate TNM stage grouping schemes were evaluated in part by assessing overall survival in clinical, pathologic, and best stage. Contrasts between adjacent stage groupings were evaluated by using Cox proportional hazards regression (version 9.4 of the SAS System for Windows [SAS Institute, Inc., Cary, NC]), with stage group modeled by indicator variables and adjustment for sex and cell type (epithelioid versus nonepithelioid). Consensus for a final stage grouping proposal from among the candidates was based not only on the statistical results but also on relevance to clinical practice and implementation.

Results

As of January 2014, the combined databases of the EDC and individual submissions totaled 3519 cases, of which 2460 passed the initial eligibility screen. Cases

Table 2. Location of Metastatic Sites in 84 Patients with M1 Disease Identified before Any Treatment

Site	n
Contralateral pleura	6
Contralateral lung	13
Peritoneum	9
Intra-abdominal	22
Bone	8
Liver	7
Brain	2
Distant lymph node[a]	23
Other site	7
No descriptors	14

Note: Some patients had multiple sites of disease (see text).
[a]Includes all extrathoracic lymph nodes other than supraclavicular nodes. Specific information regarding these lymph node sites is not available in the database.

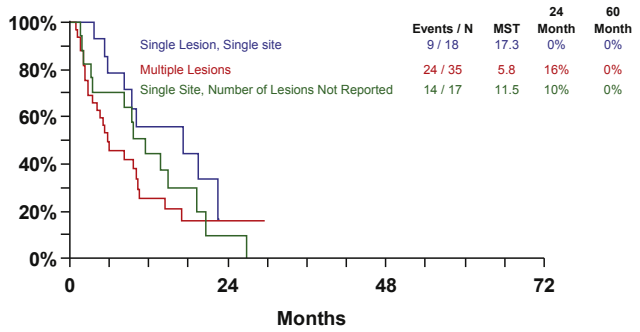

Figure 1. Overall survival according to site/number of metastatic lesions, clinical M1 cases. MST, median survival time.

that were stage I NOS (not otherwise specified), TXN3, or T4NX were then also excluded, leaving a total of 2414 cases. Screened cases presented within the prescribed time frame, with MPM histologic or cytologic features, with clinical and/or pathologic stage provided, and with known survival status at last contact. Additional requirements for inclusion were specific to the analyses conducted regarding the T component, N component, M component, and overall stage groupings. For the primary analyses of overall clinical and pathologic stage groups, anatomical descriptors were required in support of the T category, and cases staged T1 without indication of a subcategory of T1a versus T1b were generally excluded. Median follow-up in living patients for the entire group was 16 months. Full clinical stage was available in 1575 of these cases, and pathologic stage was available for 1491. Best stage was derived from all of these cases plus five additional cases in which neither full clinical nor full pathologic stage components were reported but a mix of clinical and pathologic components were available. Best stage took the pathologic stage component as the accepted standard when this was available. Patient characteristics are shown in Table 1. Surgical patients comprised 81% of cases, although 21% of these surgical cases were explored only and not resected.

There were 84 patients with clinically staged M1 tumors at diagnosis. Location(s) of metastatic lesions were given in 70 of 84 cases (Table 2). Eighteen had a single lesion, 14 had multiple lesions in a single metastatic site, 21 had multiple sites of metastatic disease, and 17 had a single site but with an unspecified number of lesions. An exploratory analysis examining categories

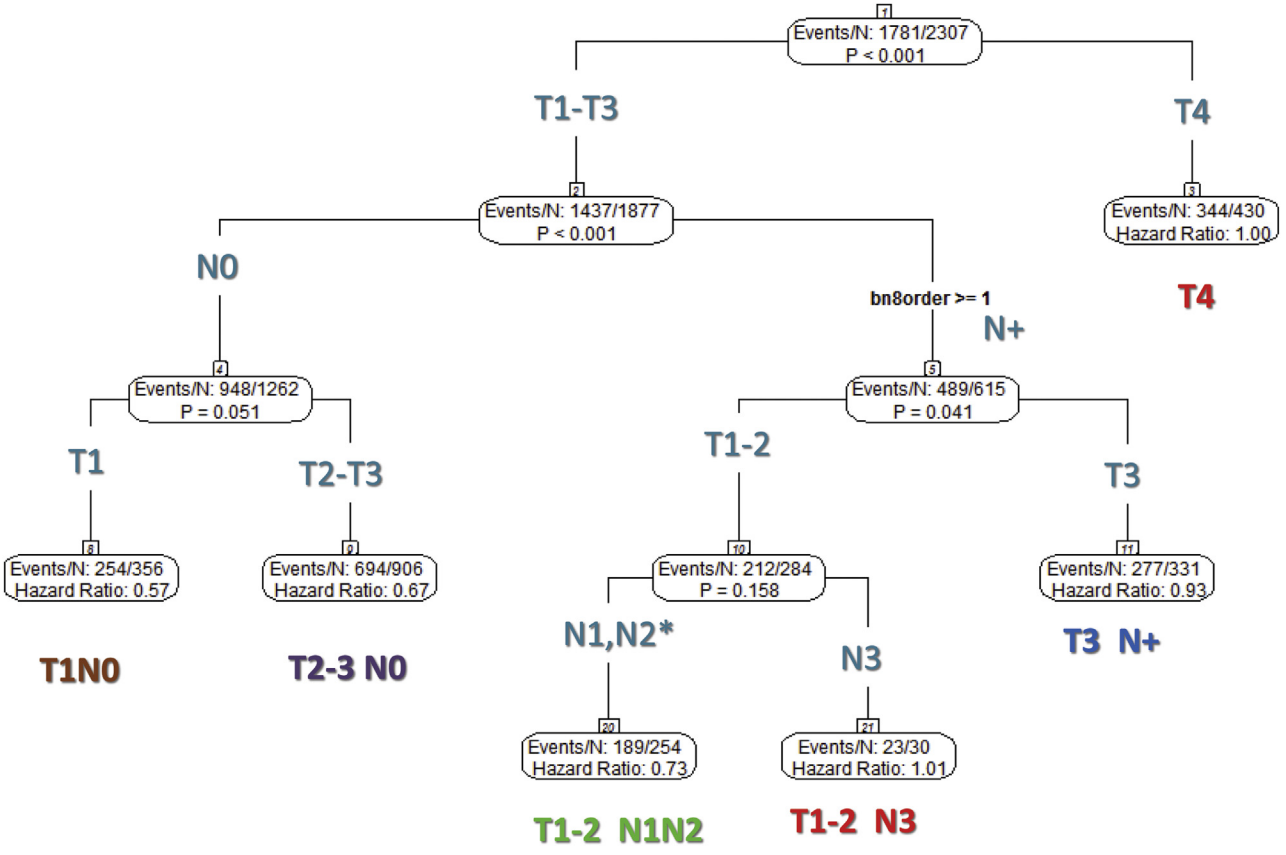

Figure 2. Recursive partitioning and amalgamation-generated survival tree based on best stage for 2307 M0 cases. T and N categories are modeled as ordered variables. Stratified hazard ratios are given relative to the right-most terminal node, T4 any N. The N definitions refer to those used in the seventh edition of the malignant pleural mesothelioma staging classification.

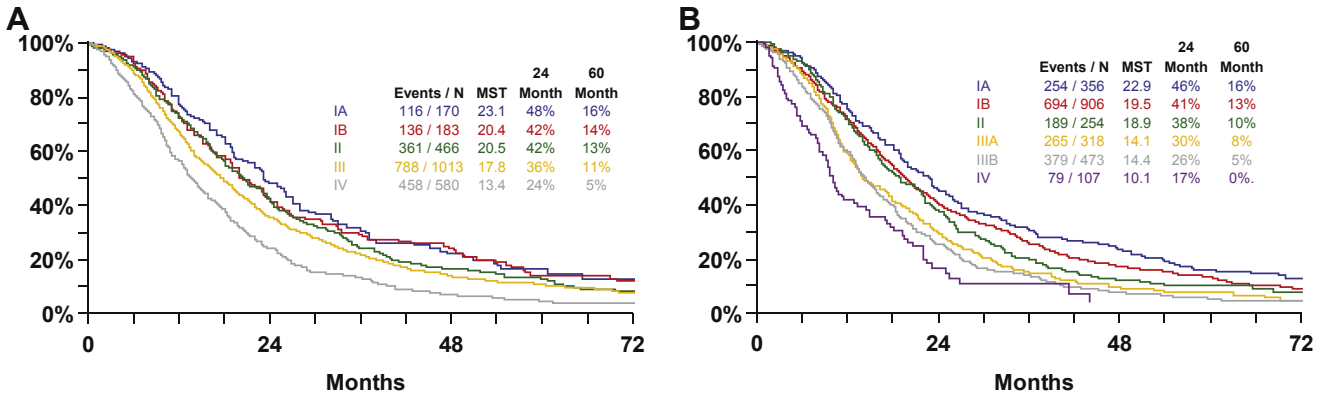

Figure 3. (*A*) Overall survival according to best stage, seventh edition. (Two stage I NOS cases are excluded.) (*B*) Overall survival according to best stage (proposed eighth edition).

analogous to those proposed for extrathoracic metastases in lung cancer suggests a better prognosis in cases in which there is only a single lesion (Fig. 1). Median overall survival in the entire group of clinical stage M1 cases was 9.7 months, which contrasts with the median survival of the proposed eighth edition stage IIIB (T4 or N3, M0) of 13.4 months. The difference is significant (hazard ratio = 1.64, $p = 0.0013$), supporting the proposal to include only the M1 cases in stage IV.

A recursive partitioning and amalgamation–generated survival tree on the overall survival outcome restricted to M0 cases with the newly proposed T category and N category entered as ordered variables is shown in Figure 2. Terminal nodes, indicating subgroups with the specified survival prognosis, are shown. Hazard ratios are relative to the right-most terminal node, the T4 (any N) cases. There was no statistical difference between T4N0 and T4N+ (OS for T4N0 = 14.9 months versus T4N+ = 13.9 months, $p = 0.94$ by log-rank test), and thus there is no branching below the T4 node. The T1–T2, N3 group has a similar prognosis. Others are sufficiently different from one another to potentially warrant their own classification.

Overall survival according to TNM best stage group in the seventh edition and proposed eighth edition is shown in Figure 3*A* and *B*. The seventh edition stages IB and II have similar prognoses and are not significantly different. For the eighth edition best stage, the IIIA and IIIB groups are similar in prognosis, with no separation before 12 months. For clinical stage, however, the stage IIIB cases have a median survival of 13.4 months, which is considerably poorer than the median survival of 17.3 months in stage IIIA (Supplementary Fig. 1*A* and *B*). Survival according to pathologic seventh edition and eighth edition stage is shown in Supplementary Figure 2*A* and *B*. Formal comparisons of all adjacent stage groupings for clinical, pathologic, and best stage are shown in Table 3. On the basis of these data, the stage groupings recommended for the eighth edition of the MPM staging system include the following: T1N0M0 as stage IA, T2–3N0M0 as stage IB, T1–2N1M0 as stage II, T3N1M0 as stage IIIA, T1–3N2M0 and T4anyNM0 as stage IIIB, and anyTanyNM1 as stage IV. The proposed eighth edition descriptors for T, N, and M and the overall stage groupings are shown in Tables 4 and 5. In some comparisons, OS differences are either small or significant for clinical but not for pathologic stage (or vice versa). The new stage groupings are fundamentally guided by statistical analyses but also informed by relevance to clinical practice. Future additional data may lead to either expansion or consolidation of these stage groupings. Overall, the proposed revisions represent substantial changes from the stage groupings used in the sixth and seventh editions of the staging system.

Discussion

This is the first evidence-based revision of the TNM staging system for MPM. The original TNM classification developed in 1994 was based on the modest amount of data available at that time, predominantly from retrospective surgical series. Alternative proposed staging

Table 3. Formal Comparisons between Adjacent TNM Stage Groups Proposed for the Eighth Edition and Based on a Cox Regression Model Adjusted for Sex and Cell Type (Epithelioid versus Nonepithelioid)

	Clinical Stage		Pathologic Stage		Best Stage	
Comparison	HR	*p* Value	HR	*p* Value	HR	*p* Value
IB vs. IA	1.67	<0.0001	1.05	0.60	1.19	0.02
II vs. IB	1.13	0.22	1.11	0.32	1.14	0.11
IIIA vs. II	0.92	0.54	1.35	0.0083	1.19	0.072
IIIB vs. IIIA	1.36	0.02	0.97	0.77	1.12	0.17
IV vs. IIIB	1.64	0.0013	1.06	0.80	1.42	0.0047

HR, hazard ratio.

Table 4. Definitions of TNM

Stage	Definition
Primary tumor (T)	
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
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) lymph nodes
N2	Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present

systems have been either not TNM based or derived from single-institution surgical data.[3] The current analyses leading to substantial proposed revisions for the eighth edition of the UICC/AJCC staging system benefit from data that are multicenter and international, are submitted from high-volume centers treating this rare malignancy, are detailed with respect to T and N components, and are derived from patients managed both surgically and nonsurgically.

Although the current proposed revisions are based on the most robust staging and survival data yet available for MPM, they also emphasize the need for continued data collection and additional analyses to inform revisions for the ninth edition of the staging system of this rare cancer. As noted in our previous reports,[4,5] additional data may ultimately lead to further revisions of the T and N components of the staging system, which could then influence stage groupings. In particular, both the IASLC MPM database analyses and other studies correlating tumor volume to outcomes in MPM[12,13] suggest that either pleural thickness measurements or computed tomography–based calculations of tumor volume may provide a more accurate assessment of T category than the current T descriptors.

Table 5. TNM Stage Groupings Proposed for the Eighth Edition of MPM Staging System Relative to Those Used in the Seventh Edition

	N0		N1/N2	N1	N3	N2
Stage	Seventh Edition	Eighth Edition	Seventh Edition	Eighth Edition	Seventh Edition	Eighth Edition
T1	I (A, B)	IA	III	II	IV	IIIB
T2	II	IB	III	II	IV	IIIB
T3	II	IB	III	IIIA	IV	IIIB
T4	IV	IIIB	IV	IIIB	IV	IIIB
M1	IV	IV	IV	IV	IV	IV

Additional studies addressing this issue could lead to substantially different T categories. Likewise, additional detailed data correlating pathologic involvement of specific nodal stations with outcome could alter the current recommendation to consider all ipsilateral intrathoracic lymph nodes as N1. The M1 data reported here are hypothesis-generating in that a single metastasis or single site of metastatic disease appears to be associated with an overall survival that is different from that seen with multiple lesions or sites. Much more data are needed to confirm these initial results and will involve continued efforts to accrue more nonsurgically treated patients to the database.

The current proposed revisions for the stage groupings provide a better estimation of outcomes than have previously been shown. However, in the future, additional data collected from patients managed both surgically and nonsurgically will also help refine these stage groupings, potentially providing a more consistent separation of overall survival curves and resolving some of the differences found between clinical and pathologic staging.

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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.2016.09.124.

Appendix

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