

# Do we need a revised staging system for malignant pleural mesothelioma? Analysis of the IASLC database

Valerie W. Rusch<sup>1</sup>, Dorothy Giroux<sup>2</sup>

<sup>1</sup>Memorial Sloan-Kettering Cancer Center, New York, NY, USA; <sup>2</sup>Cancer Research and Biostatistics, Seattle, WA, USA

*Corresponding to:* Valerie W. Rusch, M.D, Chief, Thoracic Service. Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Email: ruschv@mskcc.org.

**Introduction:** A number of staging systems have been proposed for malignant pleural mesothelioma (MPM) in the past, but few have utilized a TNM (tumor, node, metastasis) system. The International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG) previously developed a TNM-staging system which has been accepted by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC). The present study examines this staging system by analysing the updated IASLC database for patients with MPM.

**Methods:** De-identified data from participating centres dated from 1995 to 2009 were submitted to the IASLC Statistical Center. Surgical procedures included those with a curative or palliative intent. Survival was measured from the date of pathologic diagnosis to the most recent contact or death. Endpoints included overall survival and analysis of potential prognostic factors.

**Results:** Data was available for 3,101 patients from 15 centers, mostly from North America and Europe. After a median follow-up of 15 months, a number of clinicopathological and treatment-related prognostic factors were found to significantly influence overall survival. These included overall tumor stage based on the proposed TNM staging system, T category, N category, tumor histology, gender, age, and type of operation.

**Conclusions:** The IASLC database represents the largest, multicenter and international database on MPM to date. Analyses demonstrate that the proposed TNM staging system effectively distinguishes the T and N categories, but also highlight areas for potential revision in the future.

**Key Words:** Pleural mesothelioma; extrapleural pneumonectomy; pleurectomy; decortication; trimodality therapy; multi-institutional database; survival; staging

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## Introduction

Despite recent advances in treatment for malignant pleural mesothelioma (MPM), long-term survivors of this difficult malignancy are rare. A well validated staging system is essential to evaluating new therapies for MPM. Until the mid-1990s no such staging system existed. At least 6 staging paradigms had been proposed, none evidence-based, and few utilizing a TNM (tumor, node, metastasis) system. In 1994, at a workshop sponsored by the International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group (IMIG), MPM investigators analyzed existing surgical databases to develop

a TNM-based staging system (1). This proposed staging system was accepted by the UICC (International Union Against Cancer) and the AJCC (American Joint Commission on Cancer) as the international MPM staging system for the 6<sup>th</sup> and 7<sup>th</sup> editions of their staging manuals (2,3). The IMIG staging system has since been widely used but questions about its validity persist because it is derived from analyses of small retrospective surgical series, can be difficult to apply to clinical staging and utilizes descriptors for lymph node involvement that may not be relevant to MPM. Therefore, in collaboration with IMIG, the IASLC decided to update the staging system for MPM by developing a large international

database, an effort modeled on the revisions that the IASLC proposed for lung cancer staging for the 7<sup>th</sup> editions of the UICC and AJCC manuals (4). Initial analyses of the international IASLC/IMIG database for MPM have been reported and identified areas in which the current staging system warrants modification. This article succinctly reviews information from analyses of the IASLC database presented in more detail in a recent publication in the *Journal of Thoracic Oncology* (5).

## Methods

Participation in the database was solicited from investigators active in the IASLC and/or IMIG. Initial analyses focused on MPM patients who had surgery as part of their care and therefore, presumably had earlier stage disease. Participating investigators submitted de-identified data from existing registries to the IASLC Statistical Center, Cancer Research and Biostatistics (CRAB) in Seattle, WA., USA. Common data elements were established after review of each institutional database at CRAB. The time frame chosen for data was from 1995 to 2009, considered a contemporary period for providing relevant staging information.

Surgical procedures were classified as either palliative or curative intent operations. The former included exploration without resection and partial pleurectomy while the latter included extrapleural pneumonectomy (EPP), pleurectomy/decortication for resection of all gross tumor (P/D) and P/D combined with anatomical lung resection other than pneumonectomy. Because of the diverse nature of the individual databases, details of chemotherapy and radiation were not available and were thus recorded only as modalities given or not given.

Survival was measured from date of pathologic diagnosis to the date of last contact or death due to any cause. Median survival was estimated using the Kaplan-Meier regression method. Prognostic groups were assessed by Cox regression analysis of survival. Significance values from pair-wise comparisons reflect the Wald test; those from joint model effects (e.g., comparing the full model to the null model) reflect the likelihood ratio test.

All covariates in regression analyses were modeled categorically using indicator variables, and the threshold for statistical significance was set at  $P=0.05$ . Covariates which met the criteria for statistical significance by univariate analysis were further evaluated for inclusion in multivariable regression models, using a stepwise algorithm with backward selection. Such models were considered “exploratory” in nature when

**Table 1** Patient demographics

	Number of patients	Percent total %	
<b>Source</b>			
USA	1,151	37.1	
Italy	549	17.7	
Australia	392	12.6	
Turkey	236	7.6	
Japan	180	5.8	
Great Britain	177	5.7	
Switzerland	158	5.1	
Germany	97	3.1	
Canada	82	2.6	
EORTC (Europe)	59	1.9	
France	20	0.6	
<b>Age</b>			
<40	83	2.7	Min 13
40–59	1,098	35.4	Max 94
60–79	1,807	58.3	Mean 62.1
80 or older	110	3.5	Median 63
No data	3	0.1	
<b>Sex</b>			
Female	621	20.0	
Male	2,451	79.0	
No data	1	0.0	
<b>Histology</b>			
Biphasic	483	15.6	
Epithelial	1,933	62.3	
Sarcomatoid	253	8.2	
Other mesothelioma	432	13.9	
<b>Asbestos exposure</b>			
No	558	18.0	
Probable	91	2.9	
Yes	1,495	48.2	
No data	957	30.9	

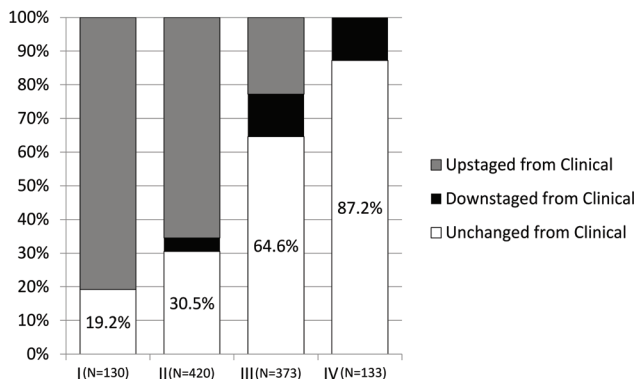
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33% or more of the sample had to be excluded from analysis due to missing data for any of the covariates being explored.

**Table 2** Information on surgical procedures performed for all 3,101 submitted cases that met initial screening requirements for date of diagnosis, date of last follow-up and age

	Total	Staged cases (percent total)
Surgery - palliative	1,250	729 (31.5%)
Exploration	1,172	669 (28.9%)
Palliative pleurectomy	78	60 (2.6%)
Surgery - curative	1,708	1,494 (64.5%)
Pleurectomy/decortication	479	299 (12.9%)
Extrapleural pneumonectomy	1,225	1,191 (51.4%)
Therapeutic lung*	4	4 (0.2%)
No surgery	84	70 (3.0%)
No data	59	20 (0.9%)
<b>Total</b>	<b>3,101</b>	<b>2,316</b>

\*Cases in which lung resection other than pneumonectomy with or without chest wall resection was performed with curative intent



**Figure 1** Differences between clinical (cTNM) and pathological (pTNM) staging in the 1056 patients for which such information was available. Reprinted from Rusch VW, Giroux D, Kennedy C, *et al.* Initial analysis of the International Association For the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7;1631-9. Permission is granted by Wolters Kluwer Health

## Results

Data were submitted on 3,101 patients from 15 centers on 4 continents with 82.6% of the patients emanating from North America and Europe (Table 1). Patients were predominantly male with a median age of 63 years. Asbestos exposure was recorded in nearly half of the patients but data on this were lacking in 30.9% of cases. Epithelioid histology was the most common MPM subtype reported (60% of cases). Both clinical and pathological staging data were not available on all patients and thus clinical (cTNM) and pathological (pTNM) staging information were combined

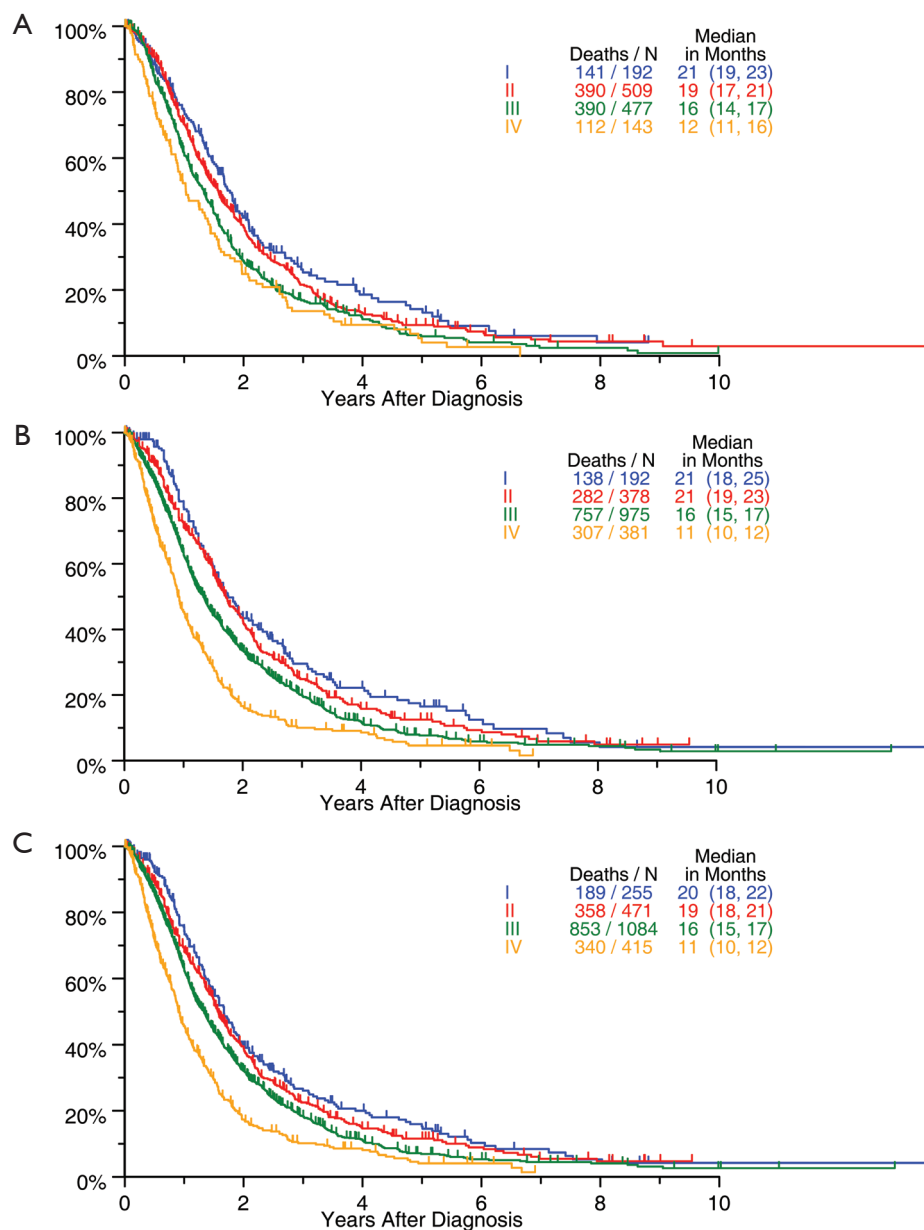
in 2,316 patients to provide “best” staging (bTNM) in accordance with AJCC and UICC guidelines. The majority of patients (64.5%) had curative intent procedures with approximately half undergoing EPP (Table 2). Upstaging based on final pTNM occurred in up to 80% of patients deemed to have clinical stages I or II disease but only in 22.8% of clinical Stage III tumors and not at all in Stage IV disease (Figure 1).

The median length of follow-up for all patients was 15 months. Survival by cTNM, pTNM and bTNM stage for all patients undergoing any type of surgical procedure is shown in Figure 2. Overall survival by bTNM for the patients undergoing surgery with curative intent demonstrates more obvious differences in median survival across all 4 tumor stages (Figure 3).

Survival by tumor T categories for all patients having non-metastatic disease managed by any type of surgical procedure and for those undergoing operations with curative intent is shown in Figure 4. Separation is seen among the median survivals for all 4 T categories but this is least apparent between T2 and T3. Survivals by tumor N categories for patients undergoing any type of surgical procedure and for those having curative intent operations are shown in Figure 5. Differences are seen for N0 versus N1 versus N2 but with the predominant difference being between N0 and N1/N2.

The relationship between histological subtype and survival for all patients undergoing surgery is shown in Figure 6. Pronounced differences in outcome were seen, with epithelioid histology being associated with the best outcome and sarcomatoid, the worst.

Survival was significantly different according to whether the surgical procedure was performed with curative versus

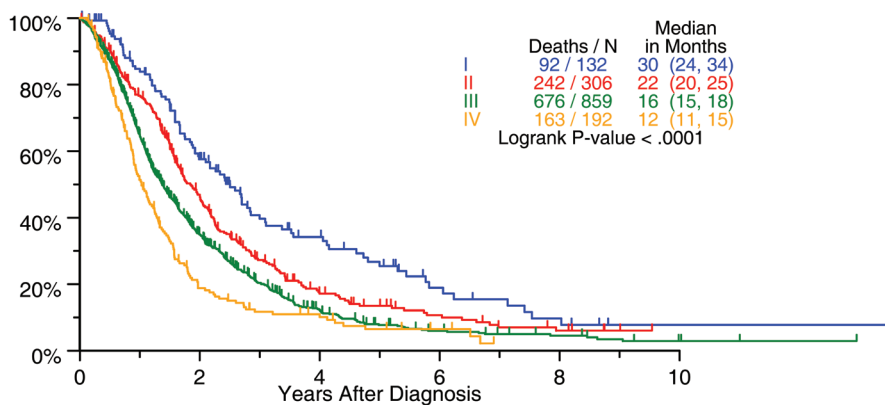


**Figure 2** Survival for all patients undergoing any type of surgical procedure, according to cTNM (Figure 2A), pTNM (Figure 2B) and bTNM (Figure 2C). The 95% confidence interval is shown in parentheses. Reprinted from Rusch VW, Giroux D, Kennedy C, *et al*. Initial analysis of the International Association For the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7;1631-9. Permission is granted by Wolters Kluwer Health

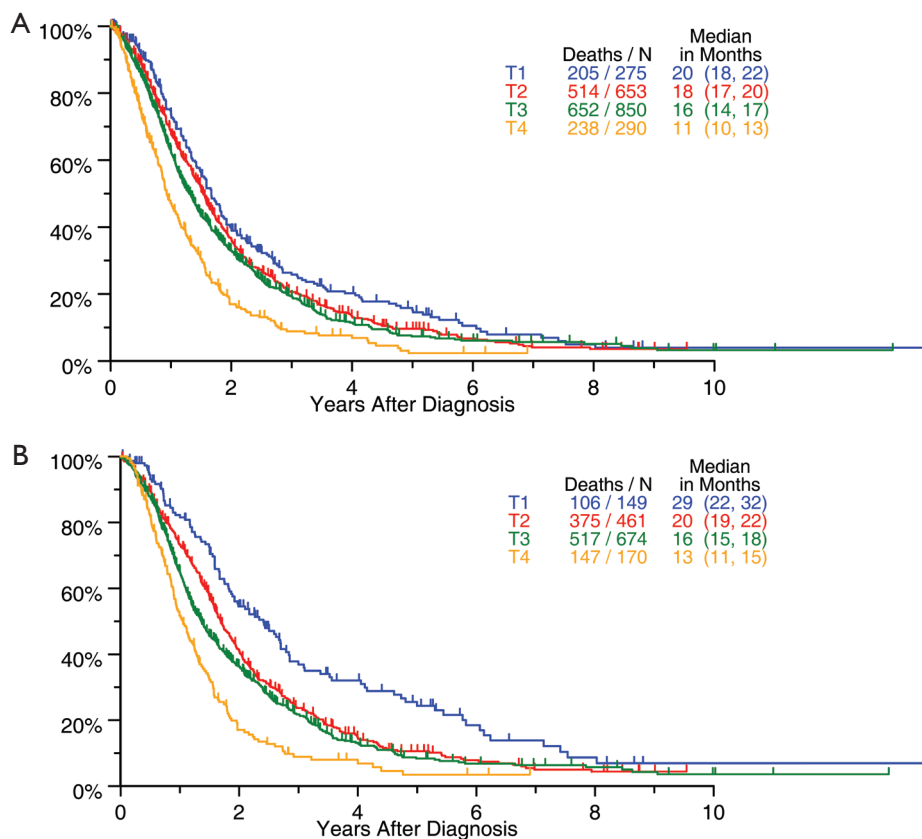
palliative intent (median survival 18 versus 12 months,  $P < 0.0001$ ). Prognostic groups defined by the type of curative intent procedure performed (EPP versus P/D) were examined in relationship to tumor stage. Stage I tumors resected by EPP were associated with a median survival of 40 months while those managed by P/D had a median survival of 23 months. No differences in survival between EPP and P/D were

identified in patients with higher stage disease.

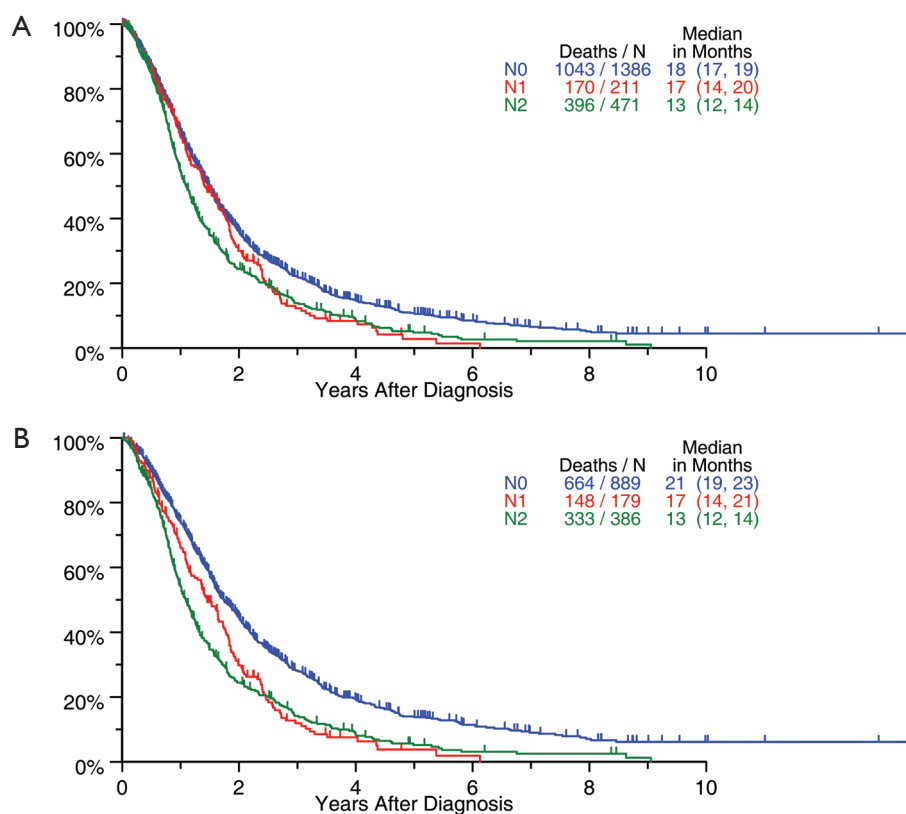
Among the patients undergoing curative intent operations, 1,162 received additional treatment, either chemotherapy or radiation or both. Relative to the 207 patients in this group who were managed with surgical resection alone, the patients receiving multimodality treatment had a significantly better outcome with median survivals of 20 versus 11 months



**Figure 3** Overall survival by bTNM for patients undergoing surgery with curative intent. The 95% confidence interval is shown in parentheses. Reprinted from Rusch VW, Giroux D, Kennedy C, *et al.* Initial analysis of the International Association For the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7;1631-9. Permission is granted by Wolters Kluwer Health



**Figure 4** Survival by tumor T stage for all patients with non-metastatic disease having any type of surgical procedure (*Figure 4A*) and for those undergoing operations with curative intent (*Figure 4B*). The 95% confidence interval is shown in parentheses. Reprinted from Rusch VW, Giroux D, Kennedy C, *et al.* Initial analysis of the International Association For the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7;1631-9. Permission is granted by Wolters Kluwer Health



**Figure 5** Survival by tumor N stage for patients undergoing any type of surgical procedure (Figure 5A) and for those having curative intent operations (Figure 5B). The 95% confidence interval is shown in parentheses. Reprinted from Rusch VW, Giroux D, Kennedy C, *et al.* Initial analysis of the International Association For the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7;1631-9. Permission is granted by Wolters Kluwer Health

( $P < 0.0001$ ).

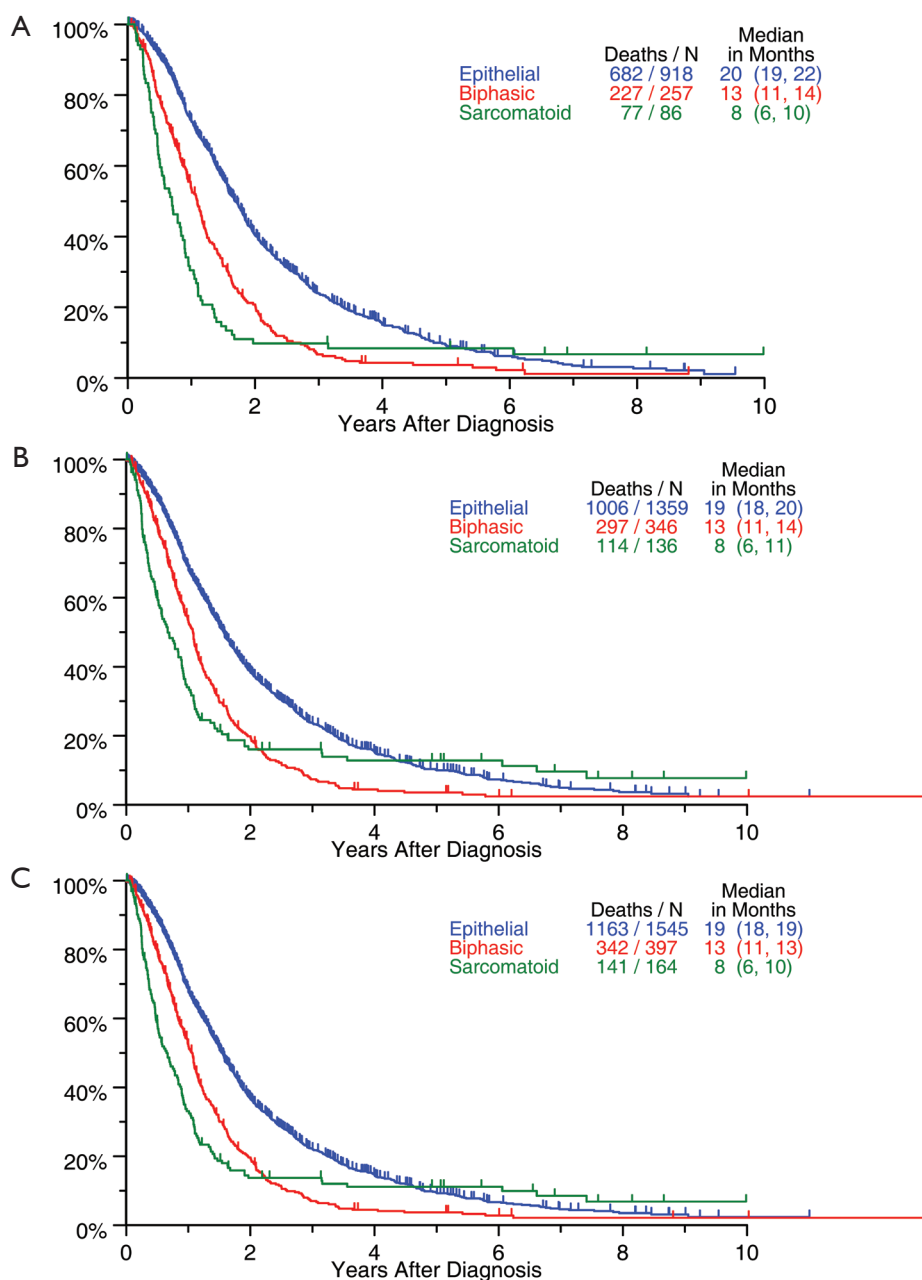
Several multivariable analyses (Tables 3,4) were performed for patients undergoing any type of surgical procedure. Overall tumor stage ( $P < 0.0001$ ), T category ( $P < 0.0001$ ), N category ( $P < 0.0001$ ), tumor histology ( $P < 0.0001$ ), patient gender ( $P = 0.0002$ ) and age ( $P = 0.0025$ ), and type of operation (curative versus palliative,  $P < 0.0001$ ) had a statistically significant impact on survival. Likewise, pairwise comparisons of adjacent stage groups, T, and N categories yielded statistically significant differences in survival, with the exception of stages I vs. II, T1 vs. T2, and N1 vs. N2.

## Discussion

Recent improvements in surgical treatment, chemotherapy and radiotherapy have led to an increasing use of multimodality therapy and to more clinical trials in MPM (6-12). An accurate staging system is essential in assessing the benefit of new

therapies for this difficult disease. The current staging system and reports suggesting possible revisions are based on small, retrospective surgical series (13-19). Though retrospective, this IASLC database is the largest multicenter and international database in MPM to date.

Analyses of the IASLC database show that the current staging system distinguishes among T and N categories and overall stages but also highlight areas for potential revision. Differences in survival among T categories and overall stage classifications are most apparent among patients undergoing resection with curative intent. Unlike many other cancers where the size and location of the primary tumor can be reproducibly measured, the extent of the tumor in MPM is not easily measured. The current T descriptors are qualitative and most applicable to surgical and pathological staging. In the future, volumetric tumor measurement on computed tomography (CT) could replace the current T descriptors (20-26). However, this approach requires further



**Figure 6** The relationship between histological subtype and survival according to cTNM (Figure 6A), pTNM (Figure 6B) and bTNM (Figure 6C) for all patients undergoing surgery. The 95% confidence interval is shown in parentheses. Reprinted from Rusch VW, Giroux D, Kennedy C, *et al.* Initial analysis of the International Association For the Study of Lung Cancer mesothelioma database. *J Thorac Oncol* 2012;7;1631-9. Permission is granted by Wolters Kluwer Health

study. For current purposes, revision of the descriptors for early stage disease (T1-3) is needed based on information regarding the anatomical extent of disease. Few participating institutions were able to provide information about the precise anatomical extent of tumor leading to the assignment

of T categories. This information will be necessary to recommend definitive revision of T categories.

The application of lung cancer N categories to MPM in the original IMIG staging system was empiric because no data were available at the time to suggest alternative

**Table 3** Cox Regression Model of Survival, including best stage, histology, sex, and age (n=2,107)

Variable	Hazard ratio	P-value
II vs. I	1.16	0.1153
III vs. I	1.47	<0.0001
III vs. II	1.27	0.0002
IV vs. I	1.86	<0.0001
IV vs. III	1.26	0.0008
Other histology vs. epithelial	1.70	<0.0001
Male vs. Female	1.28	0.0002
Age 50-45 vs. <50	1.23	0.0058
Age 65+ vs. <50	1.31	0.0006
Age 65+ vs. 50-64	1.07	0.2500
Palliative vs. curative surgery	1.71	<0.0001

options. The grouping of both N1 and N2 disease into stage III disease was also empiric because all that was known at the time was that *any* lymph node involvement was a poor prognostic factor. Subsequent surgical series suggested that the preferential pattern of lymphatic drainage in MPM is to N2 lymph nodes, including mediastinal regions such as peridiaphragmatic and internal mammary lymph nodes not usually involved in lung cancers (17,27-29). Involvement of N1 lymph nodes only was also reported to be associated with a better survival, and multiple N2 lymph node stations with a worse survival (17). By univariate analysis, our data suggest a difference in survival for N1 versus N2 disease (Figure 5), but these differences are not significant in multivariable analyses (Table 4). More information about the extent of lymph node involvement is needed to resolve this issue.

Stage groupings, especially for stages I and II disease, need to be reassessed. Univariate analyses of this database (Figures 2,3) suggest that the current stage groupings identify patient groups with distinctly different survivals. However, multivariable analyses taking into account known significant prognostic factors do not show a significant difference between stages I and II. Future analyses with more detailed information about T and N categories (as noted above) should readdress this since it is important that stage groupings be applicable across histological subtypes and patient age and sex. Although differences among stages II, III and IV remain significant in these analyses, stages III and IV define broad categories of disease, including both locally advanced tumors (T3 and T4), regionally advanced disease (N1 and N2) and metastatic disease (M1). In the

**Table 4** Cox regression model of survival, including T and N stage, intent of surgery, histology and sex (n=1,972)

Variable	Hazard ratio	P-value
Any surgical procedure		
T2 vs. T1	1.16	0.0907
T3 vs. T1	1.32	0.0011
T4 vs. T1	1.66	<0.0001
N1 vs. N0	1.26	0.0071
N2 vs. N0	1.40	<0.0001
Other histology vs. epithelial	1.70	<0.0001
Male vs. Female	1.25	0.001
Age 50-45 vs. <50	1.16	0.0483
Age 65+ vs. <50	1.24	0.008
Palliative vs. curative	1.77	<0.0001
Additional pairwise comparisons		
T2 vs. T1	1.16	0.0907
T3 vs. T2	1.14	0.0319
T4 vs. T3	1.26	0.0035
N1 vs. N0	1.26	0.0071
N2 vs. N1	1.11	0.2771
Age 65+ vs. 50-64	1.06	0.2769

future, the addition of a larger group of patients with more advanced disease, staged clinically and managed non-surgically, may help determine whether stages III and IV should be classified into “a” or “b” subcategories.

The primary purpose of this database is to determine whether and how the current TNM staging system should be revised. Given retrospective data, heterogeneous data sources and individualized treatment selection, evaluation of the effect of clinical interventions on survival can only be considered exploratory and hypothesis-generating. Other studies, both retrospective and prospective, have suggested a beneficial effect of both “curative intent” surgery and multimodality treatment on survival (9,11,30-33). Our data, absent details of adjuvant chemotherapy and radiotherapy, are consistent with previous reports. The role of EPP versus P/D remains highly controversial with impassioned views pro and con the use of EPP (34-47). In our data set, stage I patients treated with EPP survived longer than other patients. Why they survived longer cannot be determined without some understanding of how treatment was selected for these patients. Similar to lung cancer, different surgical procedures may be appropriate for different groups of patients. It is perhaps time to study this question



prospectively with more restricted stage and prognostic factor eligibility than has been done in the past.

In summary, analyses of this database suggest that the current MPM staging system does generally classify patients into groups with distinctly different outcomes but also highlights areas for potential revision. As IASLC and IMIG investigators continue to expand the database, more detailed information on T and N descriptors, as well as the addition of patients staged clinically and managed non-surgically, is required in order to propose revisions.

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