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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 metastasis (M) component and TNM stage groupings for malignant pleural mesothelioma (MPM) have been empiric. The International Association for the Study of Lung Cancer developed a multinational database to propose evidence-based revisions for the 8th editions of the tumor, node and metastases (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) with respect to overall survival (OS) between the clincal (c)M0 and cM1 categories. Candidate stage groups were developed using a recursive partitioning and amalgamation (RPA) algorithm applied to all cM0 cases.

Results: Of 3,519 submitted cases, 2,414 were analyzable and 84 cases were cM1. Median OS for cM1 was 9.7 months versus 13.4 months (p=.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. RPA generated survival tree on the OS outcomes restricted to cM0 with newly proposed (8th edition) T and N components, indicates that optimal stage groupings for the 8th edition will be: 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).

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.

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 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 6th 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 MPM patients and were transmitted to the statistical center, Cancer Research And Biostatistics (CRAB) in Seattle, Washington, USA, without identifiable private patient information. Common data elements were established after review of institutional databases and the timeframe chosen for the initial analysis was 1995 to 2009. Data were

submitted on 3,101 patients from 15 centers on 4 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 7th edition of the staging manuals, several important areas for improvement were identified, particularly for the T and N components.

In order to address controversies raised by the initial analysis, an expansion of the IASLC MPM database was started in July 2013, in anticipation of the 8th 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 7th 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 4 continents (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 malignant pleural mesothelioma between January 1995 and June 30, 2013 were eligible. All data were collected in compliance with applicable local legislation, and only coded, de-identified 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 (c) stage and pathological (p) stage were considered, along with best stage, defined as pathological stage when available, clinical stage -otherwise. For cases where chemotherapy was received prior to surgery (usually denoted as ypTNM), only clinical stage was considered. For analyses of the T component, 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 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) due to the small number of M1 cases in this dataset. Requirements for inclusion in primary analyses of overall TNM stage groups were: 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 incorporating proposed changes to the T and N components which have been reported elsewhere.[4,5] Briefly, they are: to combine T1a and T1b to form a T1 category; to combine N1 and N2 to form a new N1 category, and renaming N3 as N2. Candidate stage group schemes were developed for consideration using a recursive partitioning and amalgamation (RPA) 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 R Version 3.1.2, RPART and RLSPLIT packages.[9-11] The algorithm generated a tree-based model for the survival data using logrank test statistics for recursive partitioning and, for selection of the important groupings, bootstrap resampling to correct for the adaptive nature of the splitting algorithm. The primary tree-based analysis grouped 2,307 cases based on ordered representations of "best" T-category (pathological 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 using Cox proportional hazards regression (Version 9.4 of the SAS System for Windows. Copyright ©2002-2012 SAS Institute Inc., Cary NC,) with stage group modeled by indicator variables, adjusting for sex and cell type (epithelioid versus non-epithelioid). Consensus for a final stage grouping proposal from among the candidates was based not only upon 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 3,519 cases, of which 2,460 passed the initial eligibility screen. Cases that were Stage I NOS (not otherwise specified), TXN3 or T4NX were then also excluded leaving a total of 2,414 cases. Screened cases presented within the prescribed time frame, with MPM histology or cytology, with clinical and/or pathological stage provided, and 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 pathological stage groups, anatomic 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 1,575 of these cases, and pathologic stage was available for 1,491. Best stage was derived from all of these cases, plus 5 additional cases where neither full clinical nor full pathological stage components were reported, but a mix of clinical and pathologic components were available. Best stage took the pathological stage component as the gold standard where 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 M1tumors at diagnosis. Location(s) of metastatic lesions were given in 70 out 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, 17 had a single site but the number of lesions was not specified. An exploratory analysis examining

categories analogous to those proposed for extrathoracic metastases in lung cancer suggests a better prognosis in cases where there is only a single lesion (Figure 1). Median overall survival in the entire group of clinical stage M1 was 9.7 months, which contrasts with the median survival of the proposed 8th edition stage IIIB (T4 or N3, M0) of 13.4 months. The difference is significant (HR = 1.64, P=.0013), supporting the proposal to include only the M1 in stage IV.

An RPA-generated survival tree on the overall survival outcome, restricted to M0 cases, with 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 = .94 by logrank 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, 7th edition and proposed 8th edition, are shown in Figures 3a and 3b. Seventh edition stage IB and II have similar prognoses, and are not significantly different. For 8th edition "best stage," the IIIA and IIIB groups are similar in prognosis with no separation prior to 12 months. For clinical stage, however, the stage IIIB have a median survival of 13.4 months, considerably poorer than the median survival in the stage IIIA of 17.3 months (Supplementary Figures 1a and 1b). Survival according to pathological 7th edition and 8th edition stage are shown in Supplemental Figures 2a and 2b. Formal comparisons of all adjacent stage groupings for clinical, pathological, and best stage are shown in Table 3. Based on these data, the stage groupings recommended for the 8th edition of the MPM

staging system include: T1N0M0 as stage IA; T2-3N0M0 as stage IB; T1-2N1M0 as stage II; T3N1M0 as stage IIIA; T1-3N2M0 and T4any NM0 as stage IIIB; and anyTanyNM1 as stage IV. The proposed 8th edition descriptors for T, N and M, and the overall stage groupings, are shown in Tables4a and 4b. In some comparisons, OS differences are either small, or are significant for clinical but not for pathological 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 6th and 7th 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 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 8th 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 non-surgically.

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 9th 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 (CT) based calculations of tumor volume may provide a more accurate assessment of T category than the current T descriptors. Additional studies addressing this issue could lead to substantially different T categories. Likewise, additional detailed data correlating pathological 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 patients treated non-surgically 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 non-surgically 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 pathological staging.

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Table 1: Patient characteristics

				Available TNM Staging					
		"Best" Stage Only*		Clinical + Path		Clinical		Path	
	Total	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%)
N. 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%)
HISTOLOGY									
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%)

*Best stage only - a composite of available clinical and pathological TNM components

Table 2: Location of metastatic sites in 84 patients with M1 disease identified prior to any treatment

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

*Some patients had multiple sites of disease (see text)

**Includes all extrathoracic lymph nodes other than supraclavicular nodes. Specific information regarding these lymph node sites is not available in the database.

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Table 3: Formal comparisons between adjacent TNM stage groups, proposed 8th edition, based on a Cox regression model adjusted for sex and cell type (epithelioid versus non-epithelioid).

	Clinical Stage		Pathologic Stage		Best Stage	
Comparison	**HR**	**P**	**HR**	**P**	**HR**	**P**
IB vs. IA	1.67	<.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

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Table 4a: **DEFINITIONS OF TNM**

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 ▸ 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
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

Table 4b: TNM stage groupings proposed for 8th edition (v8) of MPM staging system relative to those used in 7th edition (v7)

	N0		N1/N2	N1	N3	N2
	v7	v8	v7	v8	v7	v8
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

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Figure Legends

Figure 1: Overall survival according to site/number of metastatic lesions, clinical M1 cases

Figure 2: Recursive partitioning and amalgamation-generated survival tree based on best stage for 2,307 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 7th edition of the MPM staging classification.

Figure 3a: Overall survival according to best stage, 7th edition. (2 cases stage I, NOS are excluded.)

Figure 3b: Overall survival according to best stage, proposed 8th edition.

Figure S1a: Overall survival according to clinical stage, 7th edition.

Figure S1b: Overall survival according to clinical stage, 8th edition.

Figure S2a: Overall survival according to pathological stage, 7th edition.

Figure S2b. Overall survival according to pathological stage, 8th edition.

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APPENDIX

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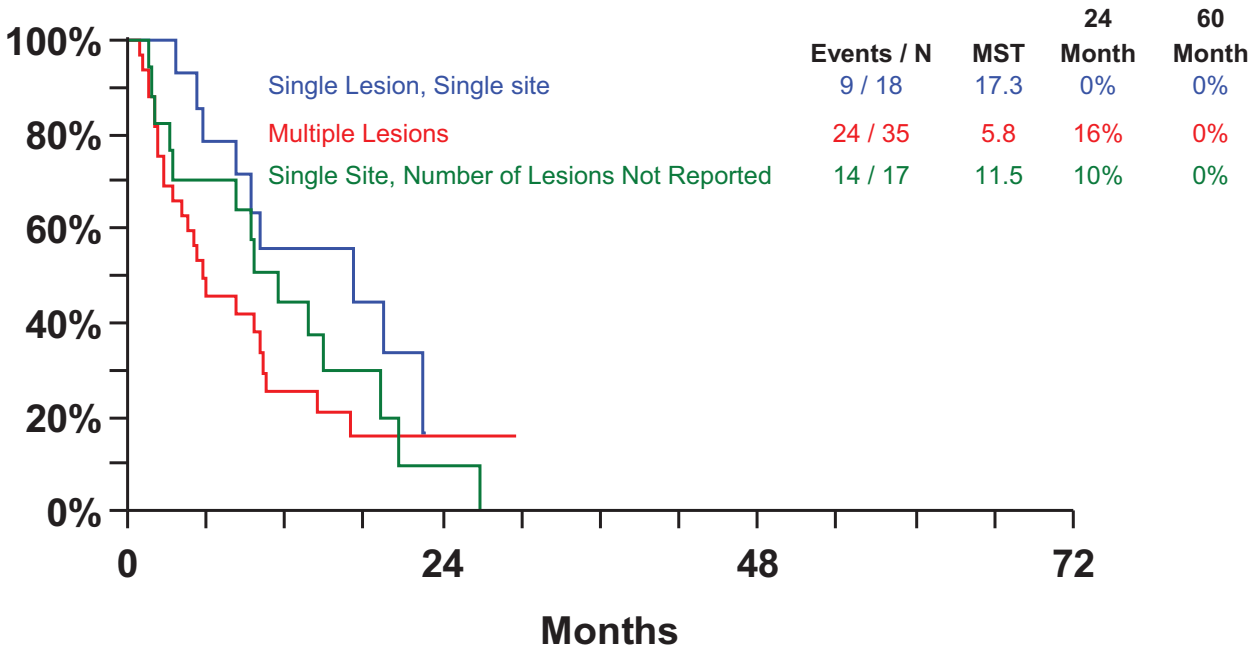

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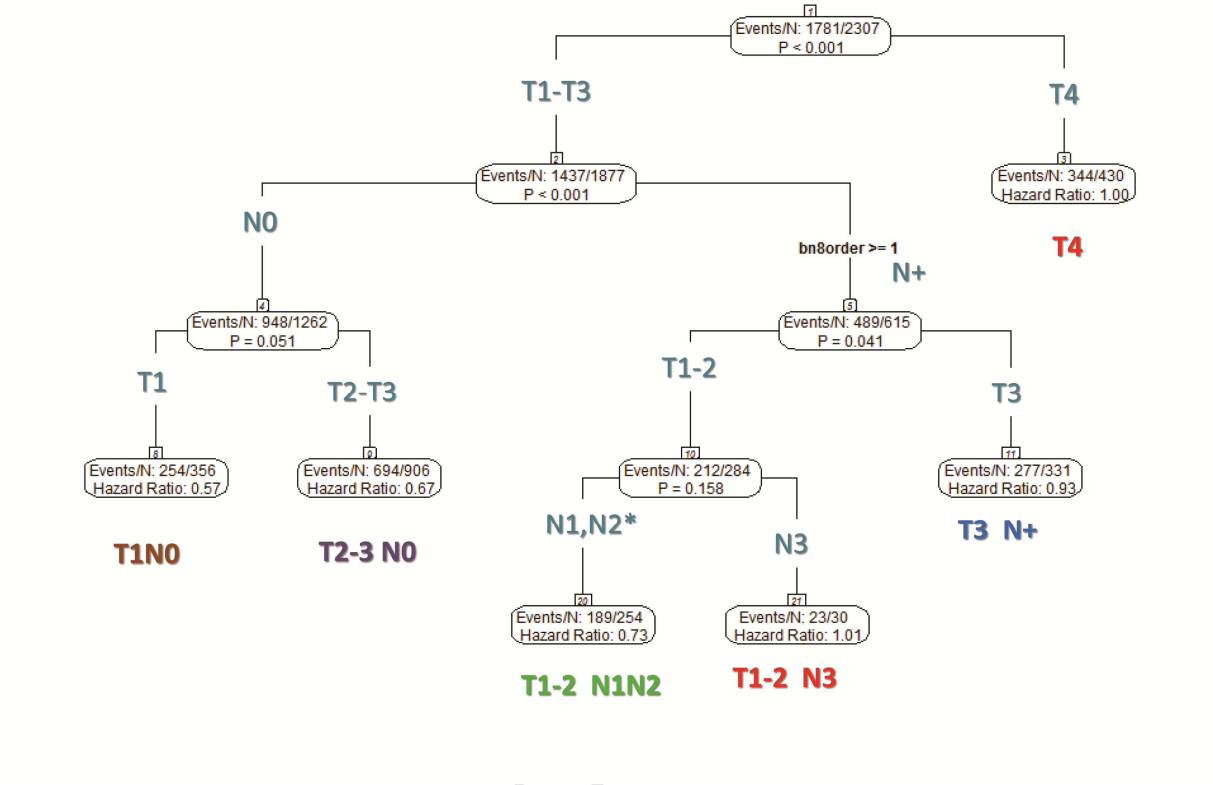
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T4
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N0
bn8order >= 1
N+
T4
Events/N: 948/1262
P = 0.051
Events/N: 489/615
P = 0.041
T1
T2-T3
T1-2
T3
Events/N: 254/356
Hazard Ratio: 0.57
Events/N: 694/906
Hazard Ratio: 0.67
Events/N: 212/284
P = 0.158
Events/N: 277/331
Hazard Ratio: 0.93
N1,N2*
N3
T3 N+
T1N0
T2-3 N0
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T1-2 N3

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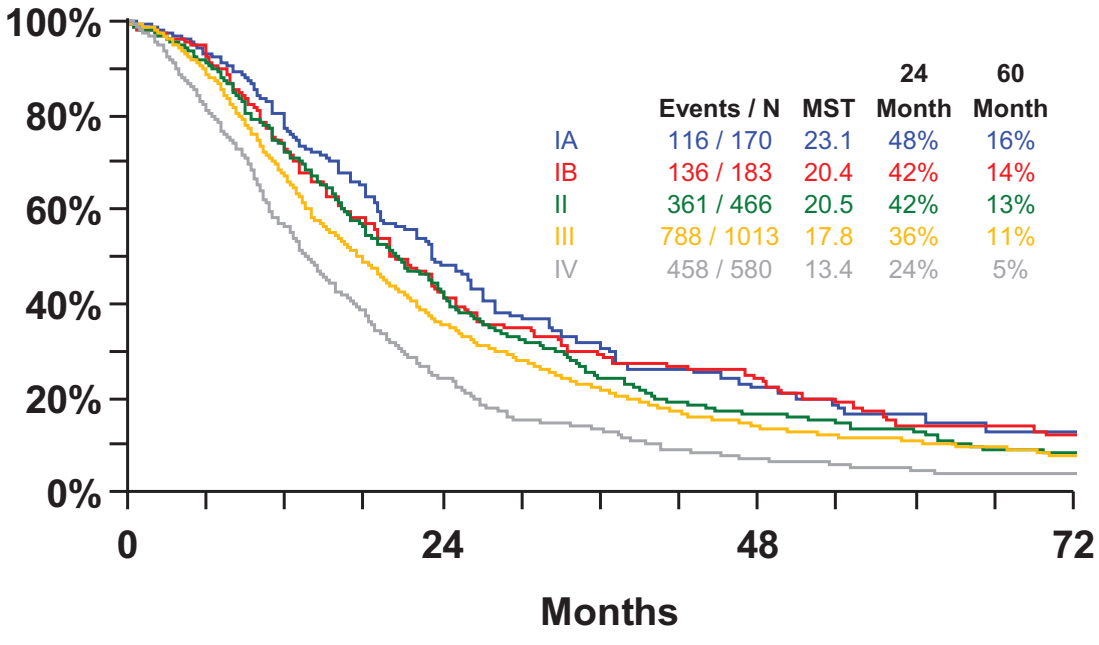

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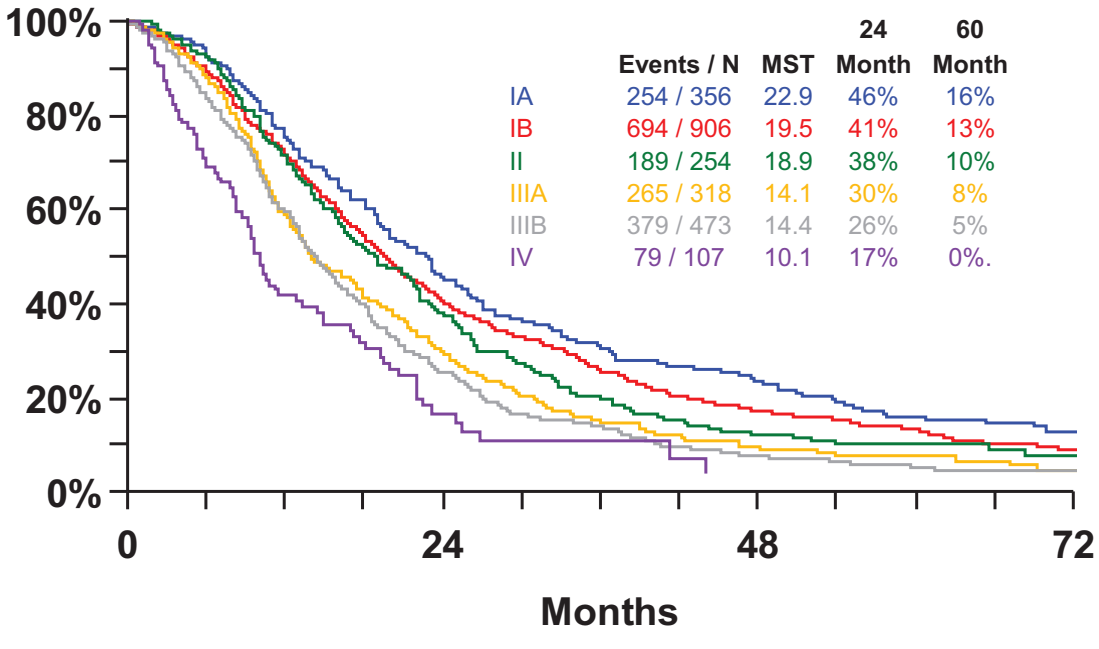

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