The IASLC Lung Cancer Staging Project

Proposals for the Revision of the M Descriptors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer

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Introduction: The aim of this study is to analyze all metastatic (M) categories of the current tumor, node, and metastasis (TNM) classification of lung cancer with the objective of providing suggestions for modifications of the M component in the next edition of the TNM classification for lung cancer.

Methods: The new International Association for the Study of Lung Cancer lung cancer database was created from 94,708 patients diagnosed as having lung cancer between 1999 and 2010. Including further patients submitted through the electronic data capture system to Cancer Research and Biostatistics until 2012, all together 1059 non–small-cell lung cancer cases were available for a detailed analysis of the clinical M categories. Overall survival was calculated using the Kaplan–Meier method, and prognosis was assessed using a Cox proportional hazards regression analysis.

Results: No significant differences were found among the M1a (metastases within the chest cavity) descriptors. However, when M1b (distant metastases outside the chest cavity) were assessed according to the number of metastases, tumors with a single metastasis in a single organ had significantly better prognosis than those with multiple metastases in one or several organs.

Conclusions: In this revision of the TNM classification, cases with pleural/pericardial effusions, contralateral/bilateral lung nodules, contralateral/bilateral pleural nodules, or a combination of multiple of these parameters should continue to be grouped as M1a category. Single metastatic lesions in a single distant organ should be newly designated to the M1b category. Multiple lesions in a single organ or multiple lesions in multiple organs should be reclassified as M1c category. This new division can serve as a first step into providing rational definitions for an oligometastatic disease stage in non–small-cell lung cancer in the future.

Key Words: Lung cancer, Non–small-cell lung cancer, Staging, Metastases.

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The baseline objective of this investigation was to explore if the M categories developed for the 7th edition of the tumor, node, and metastasis (TNM) classification for lung cancer, and proposed by the International Association for the Study of Lung Cancer (IASLC) accurately reflect patient prognosis in the data set prospectively submitted to form the new IASLC TNM staging classification database.[1,2] Since the 7th edition TNM staging classification for non–small-cell lung cancer (NSCLC) was proposed in 2007, several innovative developments in diagnosis, imaging, and treatment of NSCLC have been added to our general lung cancer management portfolio.[1,2] Especially, since the last database was derived from patients diagnosed and treated between 1990 and 2000, positron emission tomography (PET) staging has entered into common diagnostic practice (as opposed to the database for the 7th edition, which was based on patients diagnosed and treated between 1990 and 2000).[3] Minimally invasive endoscopic and surgical methods for handling small pleural and pulmonary lesions both diagnostically and therapeutically have found

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their way into staging and treatment algorithms.[4,5] Significant improvements have been made in precision radiotherapy techniques such as brain or body stereotactic radiotherapy.[6,7] Systemic treatments including molecular-targeted agents in selected adenocarcinoma patients with a driver mutation and maintenance chemotherapy strategies have significantly improved systemic control in some of the patients.[8,9] With this in mind, we may have to reconsider some of the existing staging and therapeutic algorithms for several of the disease stages in NSCLC in the future.[10–12] But the metastatic disease status has to be redefined keeping in mind ongoing stage migration (PET, brain computed tomography [CT], and magnetic resonance imaging) and new possibilities for definitive treatment of single metastatic lesions (surgery, stereotactic body radiation therapy).[13] This is the general scenario based on which we should critically analyze the new prospectively collected IASLC staging database for the development of proposals for the new M descriptors of the 8th TNM classification.[1] Based on early expert recommendations coming from input of the IASLC Staging and Prognostic Factor Committee, documentation for the prospective data set had included several parameters to work on a potentially relevant revision of the M category.[1] This information exceeded that available for the generation of the 7th edition of the lung cancer TNM staging classification. Here, we will report the overall findings generated from this existing database and propose possible lines of future developments based on prospective documentation of parameters for the next database to come.

MATERIAL AND METHODS

Population Analyzed for the M Descriptors

The process for data acquisition and analysis of the IASLC lung cancer database has already been described in detail in the introduction manuscript to the new staging initiative and the manuscripts covering the proposals for the T and the N descriptors of the 8th edition of the TNM classification.[2,14–16] The analysis population of this manuscript includes a subset of patients from the IASLC database diagnosed with lung cancer between 1999 and 2010. Additional patients were submitted to Cancer Research and Biostatistics (CRAB) from 2010 to 2012 through the electronic data capture (EDC) system and were added to this investigation. After restricting to nonresected M1 subjects, 2411 NSCLC cases were available for analysis (Table 1). This includes 1059 cases submitted to CRAB through the EDC, 1296 cases submitted from the Turkish Thoracic Society, and 56 cases from an Institutional Registry at Prince Charles Hospital. Specific data elements needed to address the objectives set out by the IASLC were primarily available in CRAB's EDC. Final analyses were, therefore, restricted to the EDC cases to avoid confounding. The number of cases used in a particular analysis is based on the availability of data to address the analysis question. Median follow-up for both M1a and M1b cases in the EDC was 29.3 months.

Statistical Methods

General statistical methodology was similar to that used for the analysis of the T and the N components of the classification. Overall survival was measured from the date of diagnosis for clinically staged patients. Survival was estimated using the Kaplan–Meier method.[17] Prognosis was assessed using Cox proportional hazards regression analysis.[18] All survival and regression analyses were performed using SAS version 9.4.[19]

RESULTS

Prognostic Impact of M1a Descriptors from the 7th Edition TNM Classification

This analysis was meant to validate the prognostic impact of the M1a descriptors from the current 7th TNM staging classification when looked at within the data set from the 1999 to 2010 prospective staging database.[1] This included (a) pleural/pericardial effusions, (b) contralateral/bilateral tumor nodules, (c) pleural/pericardial nodules, or (d) the presence of multiple M1a descriptors. Because of the lack of information on thoracic tumor nodules in the Turkish data, these 81 cases with pleural effusion were excluded from the final analysis. Complete data information was available for this analysis in 324 patients from the EDC. Prognosis for the different M1a descriptors turned out to be similar (Table 2; Fig. 1). In addition, no prognostic effect of single versus multiple M1a descriptors was determined.

Prognostic Impact of 7th Edition M1b Cases

Prospectively collected information in the EDC for the metastatic status of the patients was available on single metastatic lesions in a single organ site (225 patients), multiple metastatic lesions in a single organ (229 patients), and multiple lesions in multiple organs (247 patients). Overall, the site of the metastasis was not prognostic for single or multiple lesions within a single organ (Figs. 2 and 3). The aggregated data suggested that adrenal metastases might be associated with a worse prognosis, but comparisons between data sources were not consistent. When the two largest contributors were separated out, the negative effect of adrenal metastasis was no longer apparent (Figs. 4 and 5). This also held true for multiple lesions within a single site (Fig. 6 and 7). Additional data from more data sources would certainly be necessary to adequately address this important issue. The data suggested that the number of metastatic lesions may be more prognostic than the number of organs involved. In addition, prognosis based on a single distant metastatic lesion is more similar to M1a (Table 3).

Comparison of the 7th Edition M Categories with the Proposed 8th Edition M Categories

The 7th edition M1a and M1b categories separated out tumors with different prognosis (Fig. 8). Median survival in the M1a category was 11.5 months. For the proposed 8th edition of the TNM staging system, we reclassified M1 categories as M1a, M1b (single metastatic lesion in one organ), and M1c (multiple metastases in either single organ or multiple organs). When the proposed 8th edition M1a disease, single extrathoracic metastasis and multiple extrathoracic metastases were evaluated, patients with a single metastatic lesion in one organ site (new M1b) showed a prognosis more similar to that of patients in the M1a category with a median

TABLE 1. Subject Counts by Data Source and 7th edition M Category

			7th Edition M Category	
Database Type	**Country**	**Institution**	**M1a**	**M1b**
EDC	Argentina	Hospital Británico de Buenos Aires	2	4
		Hospital Universitario Austral	2	2
		Hospital Universitario-Fundación Favalor		7
		Hospital de Rehabilitación Respiratoria	3	1
	Australia	Peter MacCallum Cancer Institute		2
	Belgium	University Hospital Antwerp	15	51
		University Hospital Ghent	6	18
	Brazil	University of Sao Paulo Medical School		2
	China	Guangdong General Hospital	83	188
	France	L'Institut Mutualiste Montsouris	3	5
	Greece	Athens School of Medicine	6	15
	Spain	Complejo Hospitalario de Ourense	41	83
		Complejo Hospitalario La Mancha Centro	9	31
		Fundación Jiménez Díaz	18	45
		Htal. de la Plana Vila-Real	12	28
		Htal. General Universitario de Valencia	1	
		Htal. General Universitario Gregorio Mar	1	
		Htal. General Universitario de Albacete	14	42
		Htal. Meixoeiro	3	26
		Htal. Nuestra Señora de Sonsoles	2	8
		Htal. San Pedro Alcántara	12	24
		Htal. Severo Ochoa	10	13
		Htal. Sierrallana, Sección de Neumología	9	23
		Htal. Universitari Joan XXIII	13	10
		Htal. Universitario Central de Asturias	6	5
		Htal. Universitario La Fe	12	28
		Htal. Universitario de Canarias	10	15
		Htal. de Sagunto		4
	United States	Mayo Clinic Rochester		13
		NYU Langone Medical Center and Cancer Center	29	37
		Penrose Cancer Center	2	5
Subtotal—EDC cases by 7th edition M category			324	735
Subtotal—EDC cases			1059	
Consortium	Turkey	Turkish Thoracic Society	81	1215
Institutional registry	Australia	Prince Charles Hospital	2	54
Subtotal—All institutions by 7th edition M category			407	2004
Total			2411	

EDC, electronic data capture.

survival of 11.4 months (Fig. 8). In addition, patients with single extrathoracic metastasis had better prognosis than those with multiple metastatic lesions in one organ or multiple organs involved (new M1c).

DISCUSSION

The 7th edition of the TNM classification for lung cancer laid a specific focus on separating potentially curative IIIB stages without proven metastatic M1 disease from categories with positive M1 descriptors—M1a and M1b—where there was little chance of achieving relevant rates of 5-year survival.[1,2] Pragmatically, these staging categories were meant to address the fundamental differences in curatively intended treatments—still possible for stages IIIA and IIIB—from palliative—purely systemic—treatments necessary for stage IV.[2] The prospectively generated database from 1999 until 2012 employed for studying the M component and presented in this analysis resulted from patients submitted to the IASLC/CRAB through the EDC.[1,2] First of all, the value of the former M1a descriptor

TABLE 2. Prognostic Impact of M1a Descriptors

	Overall Survival		
Variable	**n/N (%)**	**HR (95% CI)**	***P* Value**
Multiple M1a descriptors	95/324 (29)	Reference level	
Contra/bilateral tumor nodules	94/324 (29)	0.87 (0.62, 1.24)	0.446
Pleural/pericardial nodules	52/324 (16)	0.81 (0.53, 1.22)	0.314
Pleural/pericardial effusion	83/324 (26)	1.00 (0.70, 1.43)	0.997

P value from score χ^2 test in Cox regression.
HR, hazard ratio; 95% CI, 95% confidence interval.

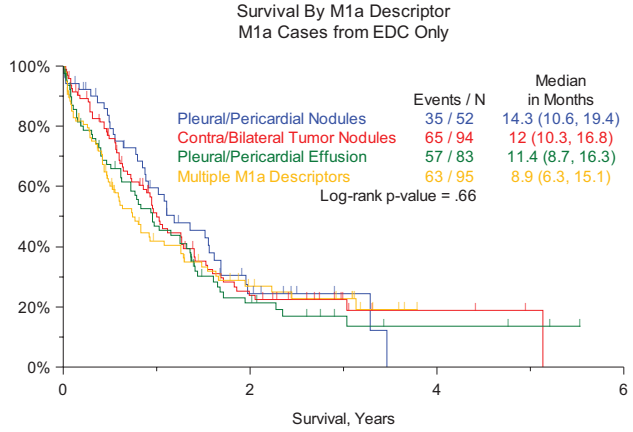

FIGURE 1. Prognostic impact of M1a descriptors.

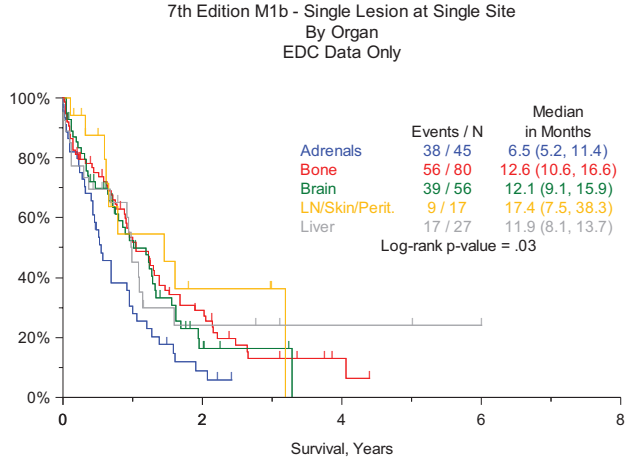

FIGURE 2. Single lesion at single site by organ.

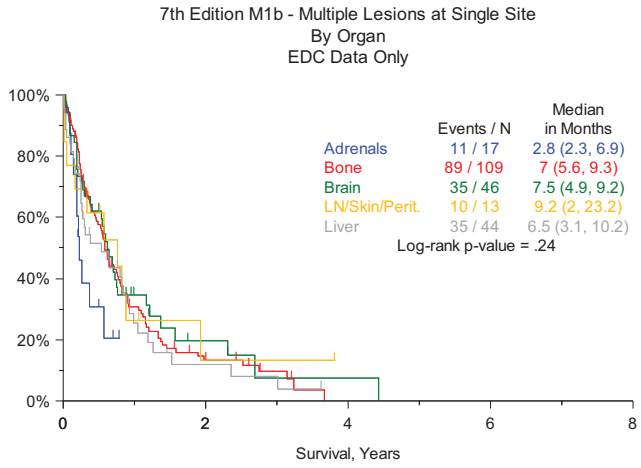

FIGURE 3. Multiple lesions at single site by organ.

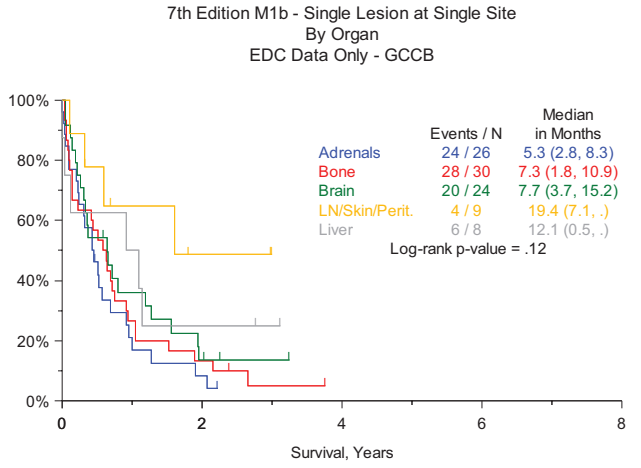

FIGURE 4. Single lesion at single site by organ—GCCB.

definition could be confirmed, including patients with pleural or pericardial effusions, contralateral or bilateral lung nodules, or pleural/pericardial nodules into this category.[20] No significant differences were noted between the different groups defined by these M1a descriptors, and there was also no effect noted of single versus multiple descriptors in a given cohort. It is not clear, whether these positive findings from clinical staging (e.g., the obviously increased landmark survival rates at 1 or 2 years) in comparison with the results of the previous edition of the TNM classification can be explained by stage migration effects based on modern imaging methods (PET-CT at least in some of the patients, modern CT-scanners or brain magnetic resonance imaging—identifying those with small brain lesions) or can be attributed to the possibility that some lesions identified on clinical grounds are not actual sites of malignant involvement.[20–22] Future documentation of these parameters should in detail register the employed imaging technology in a given patient and the necessary cytological/histological confirmation of clinical results from any imaging investigation.

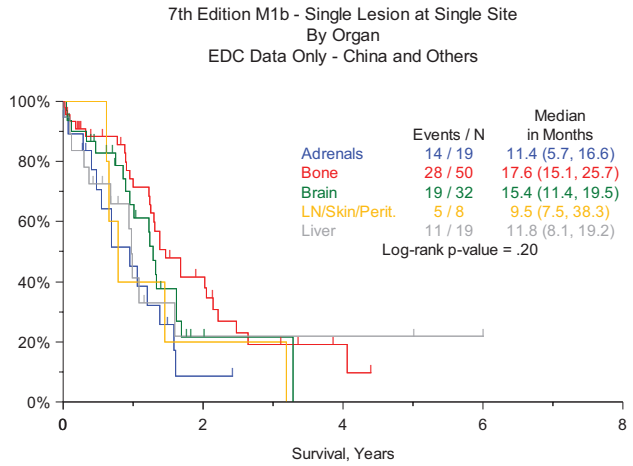

FIGURE 5. Single lesion at single site by organ—China and others.

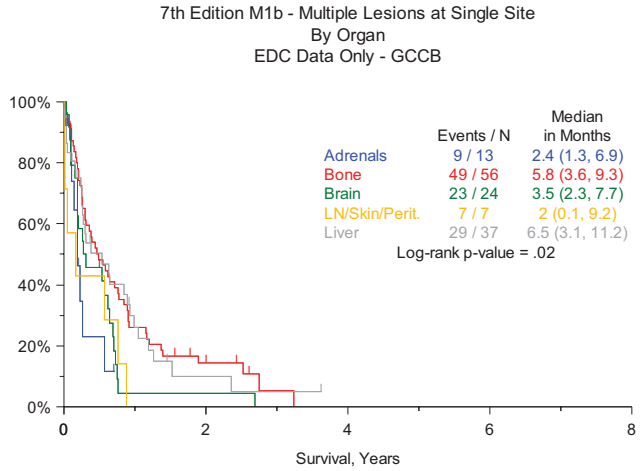

FIGURE 6. Multiple lesions at single site by organ—GCCB.

In recent years, more and more retrospective analyses have suggested that there are patients with an "oligometastatic disease" status, but these findings were based primarily on retrospective series of selected patients with single metastatic lesions in organ sites such as brain, adrenals, or bone, most of them from retrospective surgical series.[23–29] The current EDC database was able to generate analyses on single metastatic lesion in a single organ site, multiple metastases in a single organ, and multiple metastases in multiple organs.[1,2,20] Interestingly, the group with single metastatic lesions in one organ site stood out significantly from the rest of the population and showed results more comparable with those of the M1a descriptor cohort. A detailed analysis could not substantiate any organ system that showed a significantly different prognosis once a single metastatic lesion was noted. There were, however, some signals that single metastatic lesions in the adrenals were a group of significantly poor prognosis, but this finding could not be confirmed in all patient groups analyzed. Therefore, currently a single metastatic lesion in (a) brain, (b) liver, (c) bone, (d) distant lymph node or peritoneum, (e) skin, and (f) adrenal should all be grouped together under the M1b descriptor. It may be wise

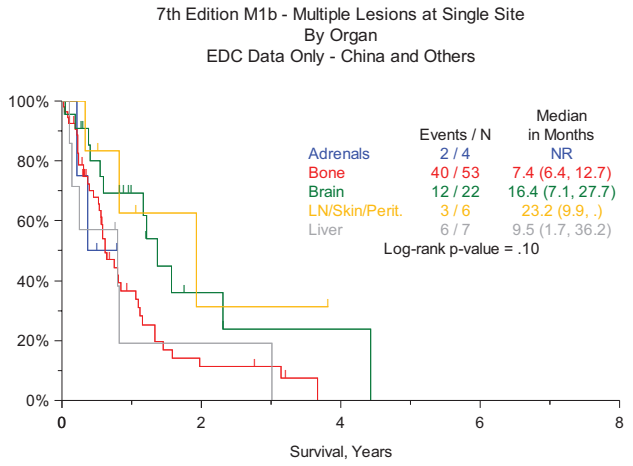

FIGURE 7. Multiple lesions at single site by organ—China and others.

in the future for the development of the next revision of the TNM classification to rigidly document also (a) PET positivity (if available) or (b) pathological confirmation of imaging-based suspicion of single metastatic lesions. Considering the volume effect on prognosis for T descriptors, the diameter of the single metastasis and also those of multiple metastases should further be prospectively documented.[15]

The separation of distant metastases into two categories was based on the prognostic differences for subjects with a single metastatic lesion in a single organ (M1b) versus all other patient groups including those with multiple metastatic lesions in a single organ and multiple lesions in multiple organs (subsumed under M1c). This is based for the first time on a prospective data set to enter the era of rational definitions for an "oligometastatic disease subset" in NSCLC.[28,29] Retrospective data sets had already speculated that prognostic differences exist between patients with single metastatic lesions and those with multiple lesions or even those with multiple organs involved in the metastatic process.[24–29] However, the retrospective nature of most of these investigations and the differences in the individual definitions of "oligometastatic disease" (spanning between one lesion and five lesions based on the individual report) as well as resulting different study-related decisions on individualized local treatment approaches (surgery, body stereotactic radiotherapy, radiotherapy, radiofrequency ablation, etc.) created a heterogeneity that did not result in a clear consensus on this important issue, so far.[24–30] With the findings presented here from the analysis for the proposed 8th edition M categories, we clearly have a rational approach to this unsolved issue at hand. Here, again, it may be wise for future prospective analyses of patients for the next TNM classification to document (a) number of metastatic lesions, (b) diameter of individual metastatic lesions, and (c) number of involved organs with metastatic lesions. In the next staging classification, this could then potentially develop further subsets of patients with individualized more favorable prognosis and in whom curative local treatments could be worthwhile testing.

In conclusion, based on the analyses from the given prospective dataset for this revision for the 8th TNM classification, we can give the following recommendations.

TABLE 3. Prognostic Impact of Single and Multiple Metastatic Lesions in a Single Organ versus Multiple Metastatic Sites

		Overall Survival		
Proposed Category	**Variable**	**n/N (%)**	**HR (95% CI)**	***P* Value**
M1a	M1a	324/1025 (32)	Reference level	
M1b	M1b, single organ/lesion	225/1025 (22)	1.11 (0.91, 1.36)	0.308
M1c	M1b, single organ/multiple lesions	229/1025 (22)	1.63 (1.34, 1.99)	<0.001
	M1b, multiple organs	247/1025 (24)	1.85 (1.52, 2.24)	<0.001

P value from score χ^2 test in Cox regression.
HR, hazard ratio; 95% CI, 95% confidence interval.

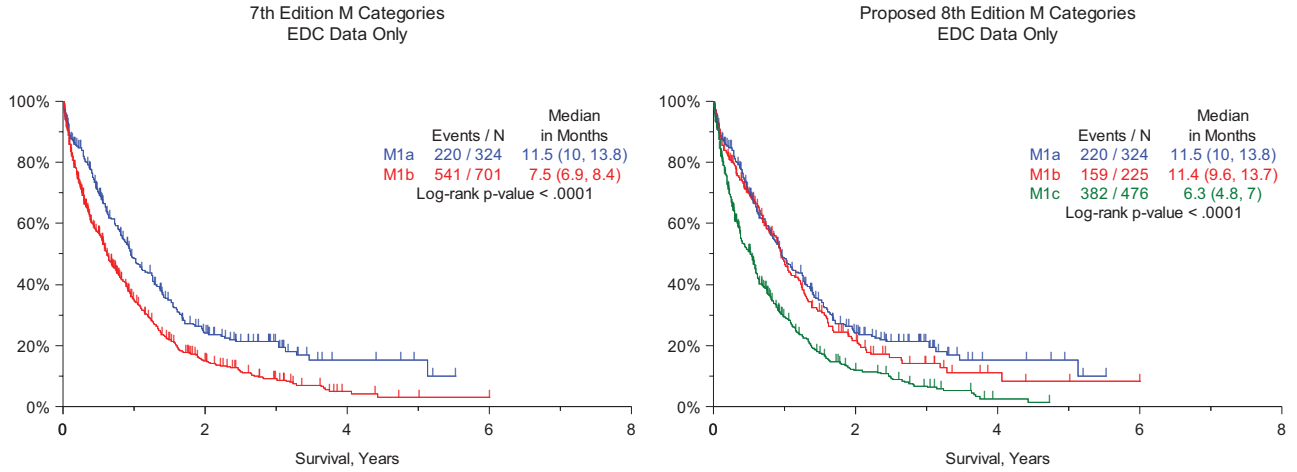

FIGURE 8. The 7th edition and proposed 8th edition M categories.

Recommendations

1. Maintain the use of the current M1a category, including any of the following descriptors: (a) pleural/pericardial effusion, (b) contralateral/bilateral tumor nodules, (c) pleural/pericardial nodules, and (d) multiple M1a descriptors.
2. Reclassify the current M1b category for patients with a single metastatic lesion in a single organ site, for example: (a) brain, (b) liver, (c) bone, (d) distant lymph node/skin/peritoneum, and (e) adrenal gland. Categorization of localization of single lesions in a single organ should be prospectively tested based on the individually involved organ.
3. Introduce the new M1c category for patients with (a) multiple lesions in a single organ or (b) multiple lesions in multiple organs. Comparable with the data now available for the influence of tumor volume in the T descriptors,[2] it is recommended to prospectively register in detail (a) the number of metastatic lesions and (b) the number of involved organs.

The proposed changes in the M descriptors maintain the compatibility with the M descriptors of the previous edition, help to better define "oligometastatic disease," and improve our capacity to indicate prognosis, which is an important objective of the TNM classification in lung cancer.

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APPENDIX

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