The IASLC Lung Cancer Staging Project: Proposals for Revision of the M Descriptors in the Forthcoming (Seventh) Edition of the TNM Classification of Lung Cancer

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Purpose: To analyze all nonlymphatic metastatic components (T4 and M1) of the current TNM system of lung cancer, with the objective of providing suggestions for the next edition of the TNM classification for lung cancer.

Material and Methods: Data on 100,809 patients were submitted to the International Association for the Study of Lung Cancer International Database. Of these, 5592 selected T4M0 and M1 patients fulfilled the inclusion criteria for the analysis. Specific categories of clinically staged T4 (lesions not continuous with the primary tumor) and M1 cases were compared with respect to overall survival using Kaplan–Meier survival estimates and comparisons via Cox regression analysis. Relevant findings were validated internally by geographic area and type of database and were validated externally by the North American Surveillance, Epidemiology and End Results Registries.

Results: Median survival for cT4M0 with malignant pleural effusion was significantly worse than that of other cT4M0 patients (8 months versus 13 months) and was more comparable with M1 cases with metastases to the contralateral lung only (10 months). M1 cases with metastases outside the lung/pleura had a significantly poorer prognosis than those with metastases confined to the lung, with a median survival of 6 months.

Conclusions: Revisions to the TNM classification system for lung cancer should include grouping cases with malignant pleural effusions and cases with nodules in the contralateral lung in the M1a category, and cases with distant metastases should be designated M1b. In addition, cases with nodule(s) in the ipsilateral lung (nonprimary lobe), currently staged M1, should be reclassified as T4M0, in accordance with the recommendations of the T descriptor subcommittee of the IASLC international staging committee.

Key Words: NSCLC, Staging, Metastases.

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With changes in diagnostic capabilities, staging procedures, and treatment options, the TNM staging system for lung cancer[1] needs to be reexamined to optimize management and outcomes. With the current system, patients within the same stage group may have different prognoses; thus, clinicians have problems initiating the appropriate treatment.

It has become clear that an international database to inform future revisions of the TNM classification of lung cancer would be of tremendous benefit. Thus, the International Staging Project on Lung Cancer of the International Association for the Study of Lung Cancer (IASLC) was initiated.[2] The IASLC is uniquely positioned to take on this project because it is the only global organization dedicated to the study of lung cancer, with membership including representatives from all disciplines involved in lung cancer care. This staging project was approved by the board of the IASLC in 1998,[3] and by the end of 2005, data from 100,809 patients treated for primary lung cancer around the world from 1990 to 2000 had been submitted for review.

Detailed analyses of these data related to metastatic disease (M1) have been performed to determine whether a more uniform classification scheme based on outcome could be achieved. This analysis included all patients with a solitary metastasis. This included nodule(s) within the same lobe as the primary tumor (currently classified as T4), the pleura (currently classified as T4), nodule(s) within the same lung as the primary tumor (currently classified as M1), and nodule(s) in the other lung or extrathoracic sites of disease (currently all classified as M1). After analysis, the cases with nodule(s) in the same lobe or same lung will be discussed in a separate manuscript focusing on subclassifications of T.[4] Nevertheless, other cases initially classified as T4 on the basis of extension into the pleural cavity will be discussed here.

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MATERIALS AND METHODS

Study Population

A total of 100,809 lung cancer cases were submitted to the database. Of these, 81,021 cases had a new diagnosis of either SCLC or NSCLC, adequate follow-up for survival, and either a cTNM or pTNM designation at baseline. Of these cases, 67,731 had NSCLC, including 53,646 clinically staged cases and 33,933 pathologically staged cases. Twenty thousand six patients had both a clinical and pathological stage recorded. For the analyses concerning M stage, 5592 clinically staged cases in categories T4 and M1 were selected. An additional 1004 cases were included in secondary analyses of best stage, where *best stage* is defined as the pathological stage if available, and clinical otherwise. Table 1 shows the distribution of stage information and treatment modalities for all cases included in M category analyses.

The 6596 cases originated from four global regions: Europe with 52% of cases, North America with 34%, Asia with 11%, and Australia with 3%. For the 5592 cases in the analysis of cases requiring a clinical stage (the primary focus), the Asian contribution, composed entirely of surgical cases, was reduced relative to the others (4%). Types of contributing databases included clinical trial groups, registries, and surgical series (Table 2). A complete listing of data contributors has been given in a previous paper.[5]

In accordance with recommended changes to the T category,[4] for this analysis the T4 group included cases with additional nodule(s) in an ipsilateral lobe (formerly staged as M1) and excluded cases that were staged T4 by virtue of additional nodule(s) in the same lobe as the primary tumor. These additional nodule(s) in the same lobe are now proposed to be included in T3. For T4 cases, at least one T4 descriptor had to be documented to be included in this analysis; likewise, metastatic site was required for M1 cases. Unless we had explicit information to the contrary, nodule(s) reported in the contralateral lung that had the same histology and timing as the primary were assumed to be metastases (provided the cases were staged M1). Any nodules proven to have a different histology were considered synchronous primaries, in which cases we included only the highest-staged primary. Additional nodule(s) in a separate ipsilateral lobe were similarly treated, although the vast majority of these cases were from the surgical databases.

Validation Analyses

Internal validation

Internal validation was performed by comparing the results of interest between types of databases (consortium/surgical series versus clinical trials versus series/registries) and among geographic regions (North America versus Asia/Australia versus Europe). If the effects were relatively consistent within these subgroups, the results were considered validated.

External validation

For external validation of T4 and M1, cases of non-small cell lung cancer with similar features were selected from the Surveillance, Epidemiology and End Results Registries database. The analysis used only those cases drawn from 1998 to 2000, because changes to the classification of certain characteristics (enacted in 1998) enabled the creation of categories that matched those under the current study.[6]

Statistical Analysis

Survival was measured from the date of entry (date of diagnosis for registries, date of registration for protocols) and was estimated by the Kaplan–Meier method. Prognostic groups were formally compared by unadjusted Cox regression analysis, with individual disease categories represented by indicator variables. The SAS System for Windows version 9.0 was used for all analyses.

TABLE 1. Treatment Modality (Surgical versus Not) and Type of Stage Data Provided (Clinical versus Path) for 6596 Cases Included in Analyses

		Modality		
Category	**Type of Stage Data**	**Nonsurgical**	**Surgical**	**Total**
T4 M0, any N[a]	Clinical	255	60	315
	Pathological	0	590	590
	Both	0	201	201
Pleural dissemination	Clinical	478	6	484
	Pathological	0	260	260
	Both	0	27	27
Contralateral lung nodules	Clinical	362	0	362
	Pathological	0	7	7
M1 distant	Clinical	4285	31	4316
	Pathological	0	4	4
	Both	0	30	30
Total		5380	1216	6596

A subset of these cases (any with clinical stage available) formed the group for primary analyses of clinical stage.

[a] This category (1) includes same-side nodules (International Union Against Cancer 6 stage M1 but recommended change to T4 in a separate paper[4]), and (2) excludes same-lobe nodules (International Union Against Cancer 6 stage T4 but recommended change to T3 in a separate paper[4]).

TABLE 2. Summary of Data Source Types for 6596 Cases Included in Analyses

	Group Type			
Category	**Clinical Trial**	**Consortium/Surgical Series**	**Registry/Series**	**Total**
T4 M0, any N[a]	148	782	176	1106
Pleural dissemination	253	330	188	771
Contralateral lung nodules	313	7	49	369
M1 distant	2012	742	1596	4350
Total	2726	1861	2009	6596

[a] This category (1) includes same-side nodules (International Union Against Cancer 6 stage M1 but recommended change to T4 in a separate paper[4]), and (2) excludes same-lobe nodules (International Union Against Cancer 6 stage T4 but recommended change to T3 in a separate paper[4]).

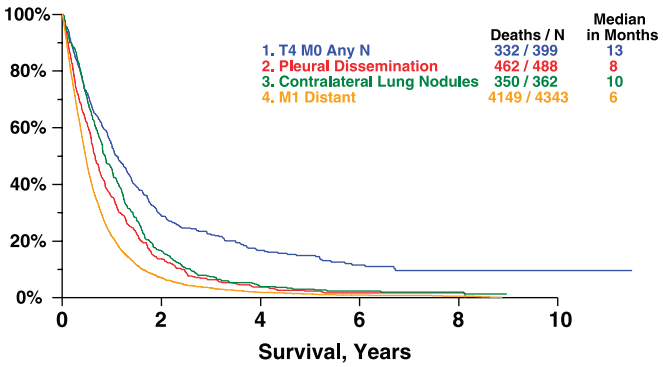

FIGURE 1. Overall survival comparisons for proposed clinical stage T4 (any N) N0 versus proposed categories M1a (pleural dissemination) and M1a (contralateral lung nodules) versus M1b (distant metastases). The T4 group includes cases with same-side nodules, in accordance with the proposal to move these cases to the T4. The T4 group excludes the cases with same-lobe nodules, in accordance with the proposal to move this group to the T3.

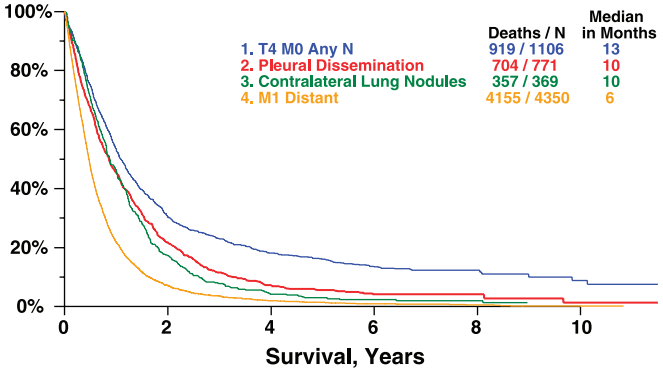

FIGURE 2. Overall survival comparisons for proposed best stage T4 (any N) versus proposed categories M1a (pleural dissemination) and M1a (contralateral lung nodules) versus M1b (distant metastases). The T4 group includes cases with same-side nodules, in accordance with the proposal to move these cases to the T4. The T4 group excludes the cases with same-lobe nodules, in accordance with the proposal to move this group to the T3.

RESULTS

Overall survival results for four subsets of T4 and M1 patients are shown in Figure 1 (clinical stage) and Figure 2 (best stage). They are summarized in Tables 3 and 4.

Malignant Pleural Effusion

Patients with a clinical finding of pleural dissemination (malignant pleural effusion or pleural nodules) and without other metastatic disease ($n = 488$) had a median overall survival of 8 months versus 13 months for other cT4 M0 (any N) patients ($p < 0.0001$), and the difference persisted over time. The 1- and 5-year survival rates for the pleural dissemination group were 36% and 2% versus 53% and 15% for the remaining cT4. Those with pleural metastases according to best stage had a median survival of 10 months versus 13 months for other T4 cases by best stage.

Additional Nodule(s) in the Contralateral Lung

Additional nodule(s) detected in the contralateral lung by imaging studies precludes surgery; therefore, results for this M1 subgroup are driven primarily by clinical stage. Median overall survival for this group was 10 months, with a 1-year survival rate of 45% and a 5-year survival rate of 3%. It was not possible to differentiate between single and multiple lesions in the contralateral lung. Although there was a statistically significant difference in survival on clinical staging between the pleural dissemination group versus the contralateral nodule(s) group ($p = 0.0235$, in favor of the contralateral nodule(s) group), the two groups are closer to each other in prognosis than they are to the proposed (new) T4, and they both differ significantly from the subset of M1 that have distant metastases ($p < 0.0001$ for both comparisons). Furthermore, in an analysis of best-stage categories, the group with additional nodules in the contralateral lung differs significantly from the group with nodule(s) in the ipsilateral lung in a different lobe than the primary ($p < 0.0001$) (Table 5).

Extrathoracic Metastases

As a group, patients with distant metastases had a poorer prognosis, with a 6-month median survival and 22% surviving at 1 year. Reported sites of extrathoracic metastases at presentation were as follows: multiple sites (43%), bone (24%), liver (10%), brain (9%), adrenal (6%), skin (<1%), and other single sites (7%). The median survival of patients with multiple distant metastatic sites was 5 months, which was slightly worse than the 6-month median for patients with

TABLE 3. Overall Survival Comparisons for Proposed Clinical Stage T4 (any N) versus Proposed Categories M1a (Pleural Dissemination) and M1a (Contralateral Lung Nodules) versus M1b (Distant Metastases)

	n	One-Year Survival Rate (%)	Five-Year Survival Rate (%)	Comparison	HR	*p*
T4 M0, any N	399	53	15			
Pleural dissemination	488	36	2	vs. T4	1.70	<0.0001
Contralateral lung nodules	362	45	3	vs. pleural dissemination	0.85	0.0235
M1 distant	4343	22	1	vs. contralateral lung nodules	1.61	<0.0001
				M1 distant vs. pleural dissemination	1.37	<0.0001

TABLE 4. Overall Survival Comparisons for Proposed Best Stage T4 (any N) versus Proposed Categories M1a (Pleural Dissemination) and M1a (Contralateral Lung Nodules) versus M1b (Distant Metastases)

	n	One- Year Survival Rate (%)	Five-Year Survival Rate (%)	Comparison	HR	*p*
T4 M0, any N	1106	53	16			
Pleural dissemination	771	45	6	vs. T4	1.91	<0.0001
Contralateral lung nodules	369	46	3	vs. pleural dissemination	1.06	0.3816
M1 distant	4350	22	1	vs. contralateral lung nodules	1.56	<0.0001
				M1 distant vs. pleural dissemination	1.65	<0.0001

TABLE 5. Comparison of Tumors with Nodule(s) in the Same Lobe, in the Same Lung, in the Opposite (Contralateral) Lung, and Other T4 Lesions

Category	*n*	One-Year Survival Rate (%)	Five-Year Survival Rate (%)	Comparison	HR	*p*
Same-lobe nodule(s)[a]	377	69	28			
T4 (extension), any N	906	51	15	T4 extension vs. same lobe	1.61	<0.0001
Same-side nodule(s)	200	61	21	Same side vs. T4 extension	0.75	0.0010
Contralateral lung nodules	369	46	3	Contralateral lung vs. same side	1.90	<0.0001

[a] The same-lobe nodule group consists of 377 cases, 375 of which were surgically managed. These cases were not included in the main analyses and are covered in more detail in a separate paper.[4]

a reported single distant metastatic site ($p = 0.006$). The 1-year survival rates for these two groups were 20% and 23%, respectively.

Patient survival with metastases to single sites of interest (with the brain as a primary focus) was not different and resulted in a 6-month median survival, with the exception of brain, which had a 5-month median. There was essentially no difference between single-site locations. Although a therapeutic decision to operate on single synchronous brain metastases in patients with otherwise resectable tumors is frequently necessary, it was impossible within the available cases in the database to evaluate possible prognostic differences between single and multiple brain metastases. In fact, it was not possible to analyze single versus multiple sites in any extrathoracic organ.[9–11]

Recommendations

- Reclassify pleural dissemination (malignant pleural effusions, pleural nodules) from T4 to M1a.
- Subclassify M1 by additional nodules in the contralateral lung as M1a.
- Subclassify M1 by distant metastases (outside the lung/pleura) as M1b.

Internal Validation

Figures 3 and 4 show the T4 and M1 categories within types of database submissions (Figure 3) and by geographic region (Figure 4) for clinically staged cases. We focused on the clinically assigned staging when we compared these groups, because surgery was rarely performed on these patients.

Although the majority of cases in the pleural dissemination group are from Europe and North America (primarily from clinical trials and registries), the prognosis of this category is consistently worse than other T4M0 cases and is consistently better than cases with distant metastases, across all regions and database types.

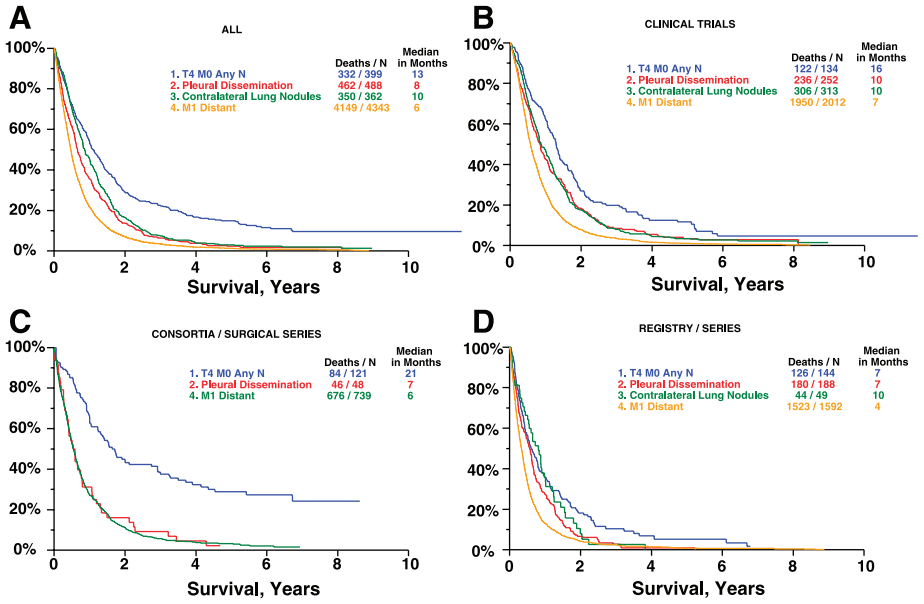

FIGURE 3. Comparisons of clinical T4/M1 within database types.

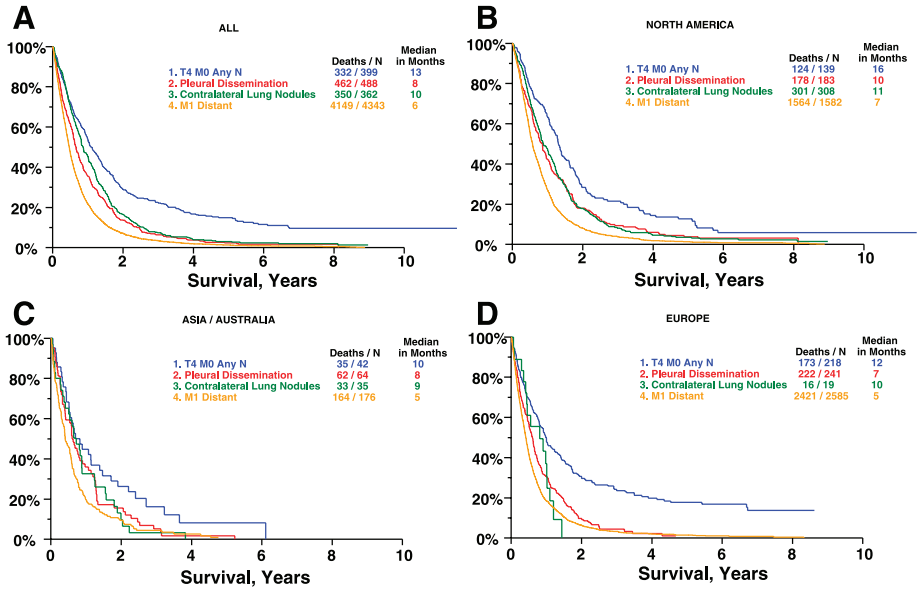

FIGURE 4. Comparisons of clinical T4/M1 within region.

Median survival across regions and database types for cases with metastases limited to the lung ranged from 9 to 11 months. For cases with distant metastases, median survival is from 4 to 7 months across regions and database types. The internal validation process supports the recommendations to move the cases with pleural dissemination to the M1 and to subdivide the M1 into M1a (lung and pleura) and M1b (distant metastases).

External Validation

The North American Surveillance, Epidemiology and End Results Registries population for external validation of M recommendations included 27,393 patients staged T4 (as previously described) or M1; overall survival for these cases is shown in Figure 5. Survival is generally poorer than in the IASLC database, but the ordering of categories supports the recommendations. Median survival for cases with pleural dissemination is 4 months, and the 1-year survival rate is 21% versus 10 months for other T4 cases (1-year survival rate, 40%). Cases with one or more nodules in the contralateral lung have a median survival of 6 months (1-year survival rate, 31%), and cases with extrathoracic metastases have a median survival of 3 months (1-year survival rate, 15%).

DISCUSSION

Accurate staging is essential for patient management, particularly when designating the M descriptor. Roughly speaking, this means initiating a therapy with a chance of

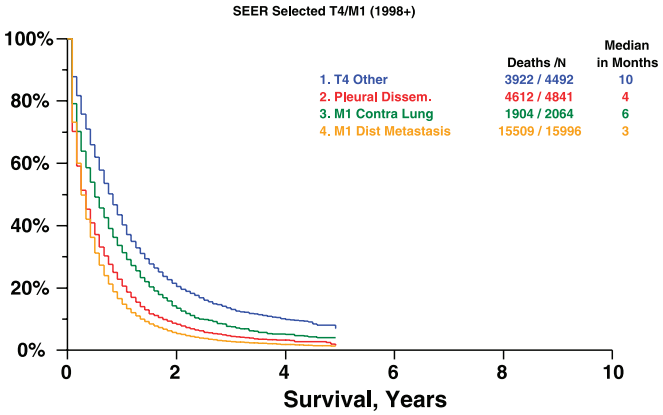

FIGURE 5. Comparison of T4/M1 cases from the North American Surveillance and End Results Registry.

long-term survival or cure, rather than palliative therapy, including chemotherapy.

The currently used staging system is based on a relatively small database without validation for individual T, N, and M descriptors in previous iterations. In addition, this database recruited from a limited geographic area and is composed predominantly of surgical cases.

The current analysis was performed to help redefine the current classification system on the basis of a large number of lung cancer cases from around the world. The database has extensive patient information, although no uniform staging protocol was available. The majority of patients were clinically staged with conventional imaging that included computed tomography of the chest and upper abdomen. Overall, the staging procedures were consistent for a relatively short period of 10 years. Additional studies were not systematically obtained if there was no clinical suspicion of metastases; examples of these are bone scintigraphy and brain computed tomography or magnetic resonance imaging.[7] We recognize that this nonuniform collection of imaging studies and pathological proof is a limitation of any large, multinational database.[8]

The results from this analysis are obtained from the largest lung cancer database ever accumulated and currently provide the best possible evidence to support changes in the TNM system. For instance, the M group within the database is four times larger than the one used for the previous revision. Now, for the first time, it is possible to properly evaluate the classification of additional pulmonary nodules introduced in the 1997 edition of the TNM classification for lung cancer. The specific recommendations focus on changes in the T4 and M categories. The recommendations as described above will reclassify malignant pleural disease from T4 to M1a. Regarding the M factor, better outcomes for patients with contralateral nodule(s) now grouped as M1a were found compared with distant extrathoracic metastases now designated as M1b.

It is unclear why there is a prognostic difference between distant metastases in the other lung (new M1a) versus other sites (new M1b). Unfortunately, from the database it is not possible to differentiate between cases with multiple lesions in the contralateral lung or a single nodule. For single M1 lesions in the lung, there is always a question of whether this is M1 disease or multiple primaries.[9,10,1112–15] Without comparing a tissue sample of both lesions, the question usually remains unanswered, and even if identical histology is found, this does not exclude two primaries.[16,17] Often, it is impossible to get tissue from the primary and possible metastases or second primary by means other than a thoracotomy. Therefore, a clinical decision is often made after evaluating other criteria such as radiological characteristics.[12] A spiculated or lobulated lesion often indicates a primary tumor, whereas a smooth border is more often seen in hematogeneic metastases. Potentially, a number of cases in the database might be operated as second primaries, thus improving the overall prognosis of the new M1a group. With this in mind, a clinician treating a patient with a single contralateral lung lesion still must decide whether this patient is a candidate for a "benefit of doubt" approach and should not be treated as disseminated disease (stage IV) by systemic treatment but as two primaries, which might both be candidates for treatment with curative intent. For these situations, new and promising treatments such as 4D high-dose radiotherapy might be indicated.[18,19]

This analysis has raised additional questions that cannot be addressed by the current database. A prospective collection of patient data will be essential for future TMN revisions. This will provide guidelines as to what information should be considered as minimal staging procedures and what, ideally, should be performed.[20,21]

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APPENDIX 1

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