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

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Purpose: To propose changes in the seventh revision of the tumor, node, metastasis (TNM) classification for lung cancer.

Methods: Data on 100,869 patients were submitted to the international database, and data for 18,198 of these patients fulfilled the inclusion criteria for the T component analysis. Survival was calculated for clinical and pathologic T1, T2, T3, T4NOMO completely resected (R0), and for each T descriptor. A running log-rank test was used to assess cutpoints by tumor size. Results were internally and externally validated.

Results: On the basis of the optimal cutpoints, pT1NOR0 was divided into pT1a ≤2 cm (n = 1816) and pT1b >2 to 3 cm (n = 1653) with 5-year survival rates of 77 and 71% ($p < 0.0001$). The pT2NOR0 cutpoints resulted in pT2a >3 to 5 cm (n = 2822), pT2b >5 to 7 cm (n = 825), and pT2c >7 cm (n = 364). Their 5-year survival rates were 58, 49, and 35% ($p < 0.0001$). For clinically staged N0, 5-year survival was 53% for cT1a, 47% for cT1b, 43% for cT2a, 36% for cT2b, and 26% for cT2c. pT3NO (n = 711) and pT4 (any N) (n = 340) had 5-year survival rates of 38 and 22%. pT4 (additional nodule(s) in the same lobe) (n = 363) had a 5-year survival rate of 28%, similar to pT3 (p = 0.28) and better than other pT4 (p = 0.0029). For pM1 (ipsilateral pulmonary nodules) (n = 180), 5-year survival was 22%, similar to pT4. For cT4-malignant pleural effusion/nodules, 5-year survival was 2%.

Conclusion: Recommended changes in the T classification are to subclassify T1 into T1a and T1b, and T2 into T2a and T2b; and to reclassify T2c and additional nodule(s) in the same lobe as T3, nodule(s) in the ipsilateral nonprimary lobe as T4, and malignant pleural or pericardial effusions as M1.

Key Words: IASLC International Staging Committee, TNM classification of lung cancer, Lung cancer staging, Tumor size, Malignant pleural effusion, Complete resection.

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The sixth edition of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) has served as the current tumor, node, metastasis (TNM) staging system for lung cancer since 2002. A new staging project was initiated by the International Association for the Study of Lung Cancer (IASLC) in 1999, with the goal of providing data for the next revision of the international staging system.[1,2] The Cancer Research and Biostatistics office (CRAB) in Seattle, Washington, was selected to develop the database by collecting cases from around the world and to perform statistical analysis of TNM factors in the new dataset. Investigators were invited to share information from their local databases with CRAB. Data on a total of 100,869 patients treated for primary lung cancer from 1990 to 2000 were submitted to CRAB.[3] Subcommittees were formed from the parent IASLC International Staging Committee, to analyze the new international dataset and to propose appropriate changes for the next revision of the TNM classification for lung cancer. This manuscript provides an analysis of the T descriptors and recommends changes for the next revision of the UICC and AJCC staging system.

MATERIALS AND METHODS

Objectives

To study the prognostic impact of the different descriptors that define the T component of the TNM classification in patients with N0M0 tumors, and to see whether they are

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[a,b,c,d]See Appendix 1.

Eli Lilly and Company provided funding to support the International Association for the Study of Lung Cancer (IASLC) Staging Committee's work to establish a database and to suggest revisions to the sixth edition of the TNM classification for lung cancer (staging) through a restricted grant. Lilly had no input into the committee's analysis of the data or into their suggestions for revisions to the staging system. Dr. Jett has served on a Data Safety Monitoring Board for Phase III clinical trials for Pfizer and Astra Zeneca and on an advisory panel for Lilly, Inc. None of those drugs are discussed or mentioned in this manuscript.

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useful in classifying non-small cell lung cancer (NSCLC), the T descriptors subcommittee established the following issues as priorities:

- Clinical and pathologic tumor size in T1 and T2 tumors, excluding other T2 descriptors.
- Clinical and pathologic T2 descriptors, in general and stratified by tumor size: atelectasis/pneumonitis of less than the whole lung, visceral pleural involvement, and endobronchial location.
- Clinical and pathologic T3 descriptors: atelectasis/pneumonitis of the whole lung, parietal pleura invasion, chest wall invasion, diaphragmatic invasion, parietal pericardial invasion, mediastinal pleural invasion, endobronchial location, invasion of the phrenic nerve, and Pancoast tumor.
- Clinical and pathologic T4 descriptors: carinal invasion, invasion of mediastinal tissue, invasion of the great vessels, invasion of the heart, invasion of the recurrent laryngeal nerve, invasion of the esophagus, invasion of the trachea, invasion of the vertebral body, additional nodules in the same lobe as the primary tumor, and malignant pleural and pericardial effusion.
- Stratification of results by cell type.
- Stratification of results by completeness of resection.

Population

The total number of patients submitted to CRAB was 100,869,[3] of whom 18,018 patients met the T descriptors subcommittee's initial analytic requirements of M0 NSCLC, a complete set of either cTNM or pTNM, and sufficient T descriptor details to support the assigned T stage (Table 1). On the basis of recommendations by the M descriptors subcommittee, 180 patients with tumors staged as M1 because of additional nodules in an ipsilateral different lobe from the primary tumor were added to the T component analysis, bringing the total analyzed to 18,198. These 18,198 patients originated from four geographical areas, including Europe, North America, Asia, and Australia, and from a variety of data sources (see Table 2).

The NSCLC M0 population with complete cTN included 38,162 patients (Table 1). There was sufficient clinical T descriptor information for 5760 patients, including 339 treated preoperatively, distributed as follows: 68% cN0, 5% cN1, 21% cN2, 4% cN3, and 3% cT4Nx. As for the analysis of the pathologic T, the population excluded neoadjuvant treatment and consisted of 26,177 M0 patients with complete pTN (substitutions of cM for pM were permitted). In 15,234 of these patients, the tumors had sufficient pT descriptors and were distributed as follows: 64% pN0, 19% pN1, 17% pN2, 0.5% pN3, and 0.3% pT4Nx. Table 3 summarizes the distribution of histologic types according to clinical and pathologic T factors. Complete resection (R0) was achieved in 85% of tumors with any pN, and this rate increased to 89% in those with no nodal involvement (pN0) (Table 4).

Validation Analysis

The approach to validation was suggested by the validation and methodology subcommittee and is described in more detail elsewhere.[4] The validation analysis was performed in the general population and in the population of patients with no nodal disease. Complete and incomplete resections were included in the population for analysis of pathologic T.

Internal Validation

The internal validation approach was to compare results of interest among two descriptors, each divided into three strata: types of databases (consortium/surgical series versus clinical trials versus series/registries), and geographic regions (North America versus Asia/Australia versus Europe). If the direction and magnitude of effects were relatively consistent within these subgroups, the results were considered validated.

The population for internal validation of clinical T included 5760 patients. For the validation of pathologic T, the

TABLE 1. Number of M0 Non-small Cell Lung Cancer Cases Passing Initial Screening

	N0					Any N				
	Total	T1	T2	T3	T4	Total	T1	T2	T3	T4
Clinically staged										
Total	19,435	6331	8678	2484	1942	38,162	8066	16,794	6337	6965
No. analyzed#	3896	873	2234	486	303	5760	1066	3111	677	906
Clinically staged, surgically managed										
Total	15,347	5770	7317	1678	582	22,438	6698	11,341	3049	1350
No. analyzed#	3554	828	2160	456	110	4291	926	2642	554	169
Clinically staged, nonsurgically managed										
Total	4088	561	1361	806	1360	15,724	1368	5453	3288	5615
No. analyzed#	342	45	74	30	193	1469	140	469	123	737
Pathologically staged (surgically managed)										
Total	15,428	5011	8157	1654	606	26,177	6738	14,514	3361	1564
No. analyzed#	9724	3855	4797	711	361	15,234	4995	8067	1224	948

#Criteria for T factor analysis: cases must have had at least one T descriptor supporting the assigned T stage and no T descriptors suggesting a higher T stage.

TABLE 2. Number of Non-small Cell Lung Cancer Cases Analyzed by Type of Database, Continent, and Type of Staging (Clinical vs. Pathological)

		Clinically Staged			Pathologically Staged		
	Total	Total	cT1–cT4	*cM1	Total	pT1–pT4	*pM1
Total with sufficient T descriptors	18,198	5784	5760	24	15,414	15,234	180
Clinical trial							
Australia	58	58	58	0	0	0	0
Europe	67	67	67	0	0	0	0
North America	1552	1140	1140	0	446	446	0
Consortium/surgical series							
Asia	6307	0	0	0	6307	6183	124
Australia	1914	51	51	0	1869	1869	0
Europe	4122	3121	3118	3	3447	3404	43
North America	789	43	43	0	779	778	1
Registry/series							
Asia	465	414	394	20	278	266	12
Australia	123	123	122	1	0	0	0
Europe	2216	453	453	0	1777	1777	0
North America	585	314	314	0	511	511	0

*M1 attributable to additional nodules on the same side but on a different lobe from the primary tumor.

TABLE 3. Clinical and Pathologic T Stage by Histologic Type

	Clinical T						Pathologic T					
	Total	cT1	cT2	cT3	cT4	cM1*	Total	pT1	pT2	pT3	pT4	pM1*
Total	5784	1066	3111	677	906	24	15,414	4995	8067	1224	948	180
Adenocarcinoma NOS	1863	461	844	171	377	10	6999	2951	3101	347	471	129
Bronchioloalveolar	141	69	63	4	4	1	532	278	212	17	17	8
Squamous	2967	404	1814	385	353	11	6486	1473	3949	669	368	27
Adenosquamous	53	11	36	3	3	0	291	69	142	43	29	8
Large-cell neuroendocrine	7	2	5	0	0	0	29	8	21	0	0	0
Large-cell NOS	435	73	196	69	96	1	925	190	545	130	53	7
NSCLC, NOS	318	46	153	45	73	1	152	26	97	18	10	1

*M1 attributable to additional nodules on the same side but on a different lobe from the primary tumor. NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

population consisted of 15,234 patients. Table 2 shows the origins of these patients and their data sources in detail.

Additionally, in the analysis of tumor size, the sample pT1- and pT2 N0 R0 cases with size measurements by pathologic findings were divided into a learning set of approximately two thirds ($n = 4891$) and a validation set of the remaining third ($n = 2589$). The learning set was used to develop an optimal cutpoint for tumor size, which was confirmed in the validation set. Cases were selected for the learning versus validation sets at random after balancing on attributes of size, T status, N status, region, and type of database.

External Validation

For external validation of the T component analysis, cases of NSCLC diagnosed from 1990 to the end of 2000 were chosen from the Surveillance, Epidemiology and End Results (SEER) registry database.

Statistical Analysis

Survival was measured from the date of entry (date of diagnosis for registries, date of registration for protocols) for clinically staged data and from the date of surgery for pathologically staged data; it was calculated by the Kaplan-Meier method. Prognostic groups were assessed by Cox regression analysis, using the SAS System for Windows version 9.0 PHREG procedure.

In the derivation of tumor size cutpoints, the running log-rank statistic produced by each hypothetical cutpoint in the pN0 R0 learning set was graphed against tumor size, and the tumor size that coincided with the highest log-rank statistic was chosen as the optimal cutpoint, after rounding to the nearest whole centimeter.[5] The chosen cutpoint was then tested in the pN0 R0 validation set and explored in incompletely resected cases and in all the other nodal stage groups, and also in clinically obtained measurements of tumor size.

TABLE 4. Summary of Non-small Cell Lung Cancer Cases Analyzed by Pathologic T and Completeness of Resection

	Pathologic T					
	Total	**pT1**	**pT2**	**pT3**	**pT4**	**pM1***
Any pN						
Sufficient T information	15,414	4995	8067	1224	948	180
R0	13,167	4548	6936	1018	556	109
Non-R0	1009	102	314	179	351	63
R1	412	43	122	108	129	10
R2	327	23	41	38	173	52
R1/R2**	270	36	151	33	49	1
No information on completeness of resection	1238	345	817	27	41	8
pN0						
Sufficient T information	9778	3855	4797	711	361	54
R0	8727	3564	4267	619	238	39
Non-R0	331	39	91	78	111	12
R1	129	16	31	47	34	1
R2	103	3	9	21	59	11
R1/R2**	99	20	51	10	18	0
No information on completeness of resection	720	252	439	14	12	3

*M1 attributable to additional nodules on the same side but on a different lobe from the primary tumor. **No additional clarification was provided. R0, no residual disease; R1, microscopic residual disease; R2, macroscopic residual disease.

S-Plus version 7.0 was the software used to generate the log-rank statistics.

RESULTS

Tumor Size Cutpoints in Clinical and Pathologic T1 and T2

When comparing overall survival between groups of patients defined by tumor size, we found that survival differences were optimized at size cutpoints of 2, 3, 5, and 7 cm. These tumor size cutpoints were chosen on the basis of pathologic measurements from completely resected cases in the learning set and were then tested in the remaining pathologic and clinical data. In the learning set of 2284 R0 patients with pT1 N0 tumors (two thirds of all such patients), the highest log-rank statistic coincided with a pathologic tumor measurement of 2.0 cm (Figure 1). For the learning set for 2607 R0 patients with pT2 N0 tumors, the highest log-rank statistic occurred at a pathologic tumor measurement of 7.3 cm, with the second-highest split at 5.0 cm (Figure 2). These four tumor size cutpoints were confirmed in the validation set of 2589 pT1- and pT2 N0 R0 cases with p values of 0.0017, <0.0001, <0.0001, and 0.0125 for each comparison between the resulting five adjacent tumor size groups, starting with the smallest tumors. In both the learning set and the validation set, tumor sizes were distributed as follows: 23% smaller than or equal to 2 cm; 23% larger than 2 cm but smaller than 3 cm; 37% larger than 3 cm but smaller than 5 cm; 11% larger than 5 cm but smaller than 7 cm; and 5% larger than 7 cm. Figure 3.

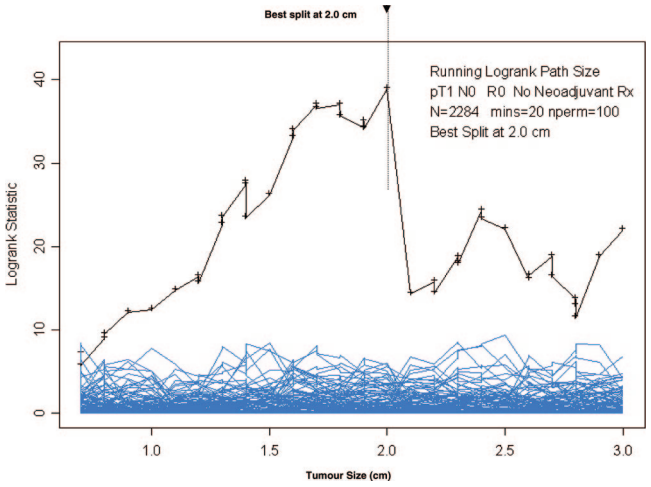

FIGURE 1. Running log-rank statistic for pathologically measured tumor size cutpoints, according to the T1 learning set ($n = 2284$; two thirds of patients with R0 pT1 tumors, by UICC6 classification). A running log-rank statistic is calculated and plotted on the y-axis for each possible cutpoint on the basis of pathologically measured tumor size (x-axis). The *blue lines* show log-rank statistics calculated on 100 random permutations of the data. The *black line* shows log-rank statistics for the actual data.

In all pathologically staged N0 R0 cases (learning and validation sets combined), for patients with tumors no larger than 2 cm ($n = 1816$), median survival was not reached. For those larger than 2 cm but smaller than 3 cm ($n = 1653$),

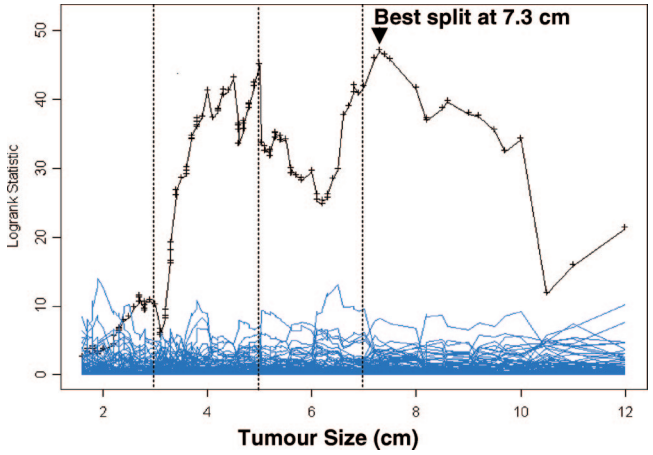

FIGURE 2. Running log-rank statistic for pathologically measured tumor size cutpoints, according to the T2 learning set (n = 2607; two thirds of patients with R0 pT2 tumors, by UICC6 classification). A running log-rank statistic is calculated and plotted on the y-axis for each possible cutpoint on the basis of pathologically measured tumor size (x-axis). The *blue lines* show log-rank statistics calculated on 100 random permutations of the data. The *black line* shows log-rank statistics for the actual data.

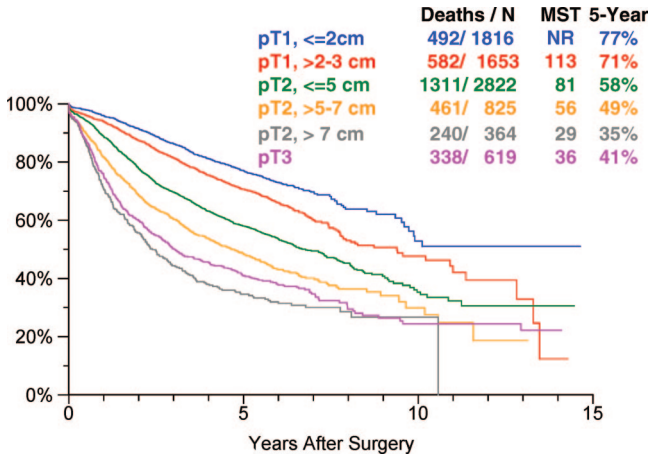

FIGURE 3. Overall survival by tumor size for patients with pT1-, pT2-, or pT3 pN0 R0 tumors, using UICC6 classification.

survival was 113 months. For those with tumors larger than 3 cm but smaller than 5 cm (n = 2822), survival dropped to 81 months. For those with tumors larger than 5 cm but smaller than 7 cm (n = 825), survival was 56 months. For those with tumors larger than 7 cm (n =364), survival was 29 months. See Figures 1, 2, and 3 and Table 5 and 6 for details; the tables also summarize results for N0 cases irrespective of completeness of resection, and for any N status.

When clinically staged N0 cases were grouped into the five size categories as above, median survival was not significantly different between the smallest two size groups (68 vs 52 months, p = 0.09); nevertheless, comparisons between adjacent groups yielded significant survival differences at the 3-cm cutpoint (43 vs 30 months, p = 0.001) and at the 5-cm cutpoint (30 vs 17 months, p = 0.008). Survival for patients with tumors larger than 7 cm was not significantly different from cT3 tumors (17 versus 19 months, p = 0.61) (Table 6, Figure 4).

Subgroup analyses of these tumor size cutpoints within different histologic types of NSCLC yielded similar results. The differences between size categories diminished as nodal disease advanced.

Pathologic T3, T4, and M1 by Ipsilateral Pulmonary Nodules

In our analyses of overall survival among pathologically staged cases categorized by UICC sixth edition as T3, T4, and M1 by additional nodule (same side, different lobe), the following prognostic groups emerged: T3 (n = 1224), with median survival of 24 months; T4 exclusively by same-side nodules (n = 363), with survival of 21 months; T4 by pleural dissemination, including malignant pleural effusion or pleural nodules (n = 245), with survival of 18 months; other T4 (n = 340), with survival of 15 months; and M1 by same side/different lobe (n = 180), with survival of 18 months. In contrast to the analysis of tumor size, the primary comparisons of survival described below and shown in Figure 5 for these later-stage cases include all pathologically staged cases, irrespective of completeness of resection or nodal status. Comparisons are summarized in Table 7 for various populations (N0 R0; any R N0; and any R, any N).

Pathologic T4 by Ipsilateral Pulmonary Nodules

Among patients with T4 tumors by additional nodules in the same lobe, 210 (58%) were adenocarcinomas, 109 (30%) were squamous cell carcinomas, and the remaining 44 (12%) were adenosquamous, bronchioloalveolar, or unspecified NSCLC. These patients were observed to have survival similar to T3 patients (p = 0.2838). They had markedly better survival than patients staged T4 for "other" reasons (p = 0.0029)—that is, invasion of mediastinal structures and excluding pleural dissemination.

Pathologic M1 by Ipsilateral Pulmonary Nodules in a Different Lobe from the Primary Tumor

Survival for the 180 patients whose tumors were staged M1 by ipsilateral separate-lobe pulmonary nodules was similar to the comparator T4 group (p = 0.41), with 5-year survival rates of 22% for both groups. Their histological types were adenocarcinoma in 129 (72%) and squamous cell carcinoma in 27 (15%); the remaining 24 (13%) were adenosquamous, bronchioloalveolar carcinoma, or unspecified NSCLC.

Clinical T4

In practice, the discovery of same-side and, especially, same-lobe nodules is primarily a surgical rather than a clinical finding; thus, there were few patients with tumors staged cT4 (n = 17) or cM1 (n = 24) on the basis of same-side pulmonary nodules. For this reason, comparisons involving same-side nodules were not explored in detail in the clinically staged data. Conversely, malignant pleural effusions are more commonly diagnosed clinically and preclude surgery as an option. Five-year and median survival rates for the 471 patients with pleural dissemination were 2% and 8 months

TABLE 5. Comparisons of Overall Survival between Tumor Size Groups for Patients with pT1, pT2, or pT3 Tumors, Using UICC6 Classification

	R0 pN0				Any R pN0				Any R, Any pN			
	n	Median Survival (mo)	5-Year Survival (%)	*p**	*n*	Median Survival (mo)	5-Year Survival (%)	*p**	*n*	Median Survival (mo)	5-Year Survival (%)	*p**
pT1												
≤2 cm	1816	NR	77		1959	124	76		2389	118	71	
>2–3 cm	1653	113	71	<0.0001	1800	105	70	<0.0001	2484	91	62	<0.0001
pT2												
>3–5 cm	2822	81	58	<0.0001	3175	80	58	<0.0001	5242	56	49	<0.0001
>5–7 cm	825	56	49	<0.0001	936	57	49	<0.0001	1615	37	40	<0.0001
>7 cm	364	29	35	<0.0001	426	30	35	<0.0001	788	22	28	<0.0001
pT3	619	36	41	0.0176	711	32	38	0.2739	1224	24	31	0.1597
Total	8099				9007				13742			

*Significance value from log-rank test of equality of survival hazard functions, relative to preceding row. NR, median survival not reached.

TABLE 6. Comparisons of Overall Survival between Tumor Size Groups for Patients with cT1, cT2, or cT3 Tumors, Using UICC6 Classification

	cN0				Any cN			
	n	Median Survival (mo)	5-Year Survival (%)	*p**	*n*	Median Survival (mo)	5-Year Survival (%)	*p**
cT1								
≤2 cm	423	68	53		518	54	48	
>2 to ≤3 cm	445	52	47	0.0932	543	44	43	0.1400
cT2								
>3 to ≤5 cm	1345	43	43	0.1032	1793	35	39	0.0388
>5 to ≤7 cm	411	30	36	0.0010	572	25	32	0.0001
>7 cm	173	17	26	0.0076	258	17	24	0.0182
cT3	486	19	29	0.6111	677	19	27	0.6482
Total	3283				4361			

*Significance value from log-rank test of equality of survival hazard functions, relative to preceding row.

versus 14% and 13 months for the 418 in the comparator cT4 group (excluding same-side nodules), and survival between these two groups was statistically significantly different ($p < 0.0001$) (Table 8, Figure 6).

Other T Descriptors

Other T2 descriptors (visceral pleural invasion and partial atelectasis), and the different T3- and T4 descriptors (except for the additional pulmonary nodule(s) in the lobe of the primary tumor) could not be evaluated, either because of the small number of patients, the inconsistent clinical and pathologic results, or lack of validation.

Validation of Results

Complete details of the internal and external validations of these findings are published elsewhere.[4] In summary, the subclassification of T1 and T2 into T1a and T1b, and T2a and T2b, respectively, driven by Asian data for pathologic size and by European data for clinical size, showed distinct differences in survival for both clinical and pathologic subgroups. These findings were consistent in most databases and in the SEER external validation, both in the overall population and in the surgical subset.

The finding that T2 tumors larger than 7 cm were more like T3 than other T2 was observed to be both internally and externally valid. The population-based SEER data indicated more of a risk continuum by size than was seen in the project dataset, but the >7-cm group's prognosis was closer to the T3 group than it was to the rest of the T2 group.

The influence of histologic type on the prognostic impact of tumor size was also evaluated, and the cutpoints of 2, 3, 5, and 7 cm were valid within all major cell types.

Cases with additional nodules in the primary lobe consistently experienced better survival than other T4 cases. Nevertheless, we were not able to look at this issue using cTNM, because this T descriptor was generally only documented in the surgical data. When restricted to those treated with surgery in the SEER data, the additional nodule group's survival was better than those even with T3 disease.

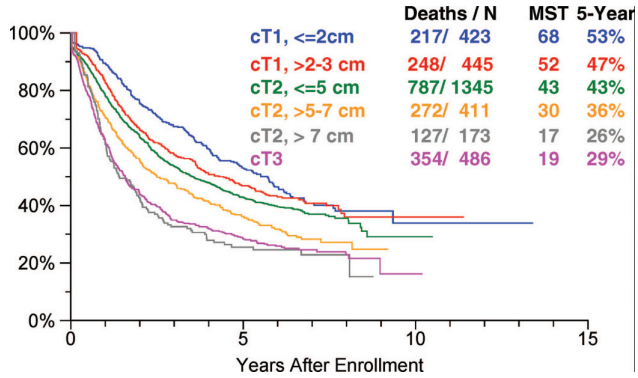

FIGURE 4. Overall survival by tumor size for patients with cT1-, cT2, or cT3 cN0 tumors, using UICC6 classification.

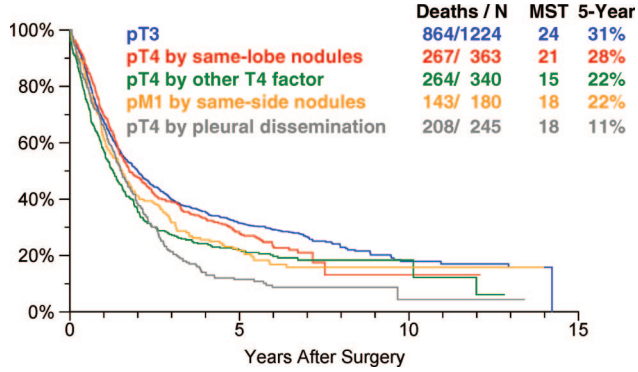

FIGURE 5. Overall survival for patients with pT3 tumors versus same-lobe nodules versus pleural dissemination by pathological finding versus other pT4 factor versus pM1 by same-side nodule, using UICC6 classification.

The finding that additional nodules in a different lobe of the ipsilateral lung had better prognosis than the present classification (M1) would indicate (and similar to that of T4) was driven by consortia/surgical series pathologic data that were almost all from the Asia/Australia region. This finding was also supported by the European pathologic data and the SEER registry.

Data supporting the reclassification of pleural dissemination from T4 to M1 were driven by the European and North American series in the clinically staged analyses and by pathologic series from consortium/surgical series. These findings also were supported by the SEER data.

DISCUSSION

Lung cancer is responsible for more cancer deaths than any other cancer worldwide, both in men and women. Complete resection gives the highest probability of long-term remission and even cure, but only about 25% of patients are candidates for surgical treatment at the time of diagnosis. Poor performance status, comorbidity, and either locally advanced or metastatic disease exclude the rest from surgical intervention. Lung cancer classification and staging assess the anatomical extension of the tumor; this is critical to choosing a therapy and provides information on prognosis. The latest (i.e., the sixth) edition of the TNM classification of lung cancer[6,7] was based on 5319 patients treated for primary lung cancer at The University of Texas–MD Anderson Cancer Center (4351 patients) from 1975 to 1988 or by the National Cancer Institute Cooperative Lung Cancer Study Group (968 patients) from 1977 to 1982.[8] Thus, the international system for staging lung cancer is based on a national database of patients who were treated mainly in one institution. Realizing that this database was becoming relatively old and that new technology was being applied to lung cancer staging, the IASLC established an international staging committee with the purpose of collecting a large international database of patients treated for primary lung cancer, to formulate, with the agreement of the UICC and the AJCC, a new revision of the TNM classification of lung cancer, to be published in 2009. More than 100,000 patients were submitted to CRAB, the data-managing center, and more than 81,000 met all inclusion criteria.[3] These patients had been treated from 1990 to 2000. This period was chosen because no major changes had been introduced in clinical practice regarding lung cancer staging, and computed tomography scans had been widely used all over the world to stage lung cancer.

The analyses conducted on the population of patients with information on the T descriptors revealed several find-

TABLE 7. Comparisons of Overall Survival between Patients with pT3 Tumors vs. same-lobe nodules vs. Pleural Dissemination by Pathological Finding vs. Other pT4 Factor vs. pM1 by Same-Side Nodule, Using UICC6 Classification

	R0 pN0				Any R pN0				Any R, Any pN			
	n	Median Survival (mo)	5-Year Survival (%)	*p**	*n*	Median Survival (mo)	5-Year Survival (%)	*p**	*n*	Median Survival (mo)	5-Year Survival (%)	*p**
pT3	619	36	41		711	32	38		1224	24	31	
pT4 by same-lobe nodules	144	48	45	0.6488	160	46	45	0.3685	363	21	28	0.2838
pT4 by other T4 factor	72	25	35	0.1679	114	23	30	0.0050	340	15	22	0.0029
pT4 by pleural dissemination	22	33	31	0.7365	87	42	24	0.6870	245	18	11	0.2904
pM1 by same-side nodules†	39	59	48	0.1090*	54	24	42	0.0250*	180	18	22	0.4115*
Total	896				1126				2352			

*Significance value from log-rank test of equality of survival hazard functions, relative to preceding row, except †pM1 by same-side nodules compared with pT4 by other T4 factor.

TABLE 8. Comparisons of Overall Survival between Patients Staged cT4 because of Pleural Dissemination vs. Other cT4 Factors (Excluding Same-Lobe Nodule), Using UICC6 Classification

	cN0				Any cN			
	n	Median Survival (mo)	5-Year Survival %	*p**	*n*	Median Survival (mo)	5-Year Survival %	*p**
cT4 by other T4 factor	144	21	25		418	13	14	
cT4 by pleural dissemination	146	8	2	<0.0001	471	8	2	<0.0001
Total	290				889			

*Significance value from log-rank test of equality of survival hazard functions.

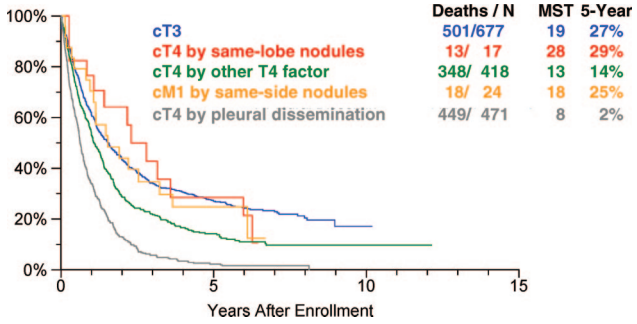

FIGURE 6. Overall survival for patients with cT3 tumors versus same-lobe nodules versus pleural dissemination by clinical finding versus other cT4 factor versus cM1 by same-side nodule, using UICC6 classification.

ings that could be used to refine the present definitions of the T component of the TNM classification. In addition to the two size criteria, that were based on the 3-cm landmark, three more cutpoints were identified, and the five resulting size groups showed distinct survival differences. The results show that T1 tumors can be divided into two subgroups on the basis of the best cutpoints identified by the running log-rank analysis. Therefore, without altering the 3-cm landmark between T1 and T2 tumors, T1 tumors can be subdivided into two prognostic groups: those 2 cm or smaller (T1a) and those larger than 2 cm but no larger than 3 cm (T1b). This finding was validated by geographical region and database type, and by the SEER registry data. Results from other series support this division. Padilla et al.,[9] in a study on 158 patients with pT1- or pT2 NSCLC 3 cm or smaller in diameter, found that those 2 cm or smaller had better survival, and that size was a better indicator of prognosis than endobronchial invasion and visceral pleura involvement. Mulligan et al.[10] also found that tumors 2 cm or smaller in diameter had a different prognosis from that of larger tumors; they have suggested that these tumors alone should constitute T1, and that those larger than 2 cm but no larger than 4 cm, or T1 with pleural invasion, should constitute T2. In a large Japanese multicenter series of patients with T1 NSCLC, the same subgroups as those found in the analysis of the IASLC database were formed according to tumor size. Five-year survival rates for those clinically staged as T1a (1204 patients) and T1b (993 patients) were 77.5 and 69.3%, respectively ($p < 0.001$). For those pathologically staged as T1a (1065 patients) and T1b (886 patients), 5-year survival rates were 83.7 and 76%, respectively ($p < 0.001$).[11]

This study also shows that T2 tumors can be divided into three subgroups of different prognosis; these could be called T2a (larger than 3 cm but no larger than 5 cm), T2b (larger than 5 cm but no larger than 7 cm), and T2c (larger than 7 cm). These cutpoints were consistent across databases and geographical regions and were supported by the SEER external validation. Other authors, on the basis of results from institutional series, have reported on the prognostic significance of the 5-cm landmark and have suggested that T2 tumors larger than 5 cm should be upgraded.[12,13] A multicenter study on clinical and pathologic size found that the prognostic landmarks were 2, 4, and 7 cm, and suggested that T2 tumors larger than 7 cm should be upgraded to T3.[14,15] This is in agreement with the findings of this study: T2 tumors larger than 7 cm and T3 tumors have similar prognosis. This finding has been validated in all geographic areas and databases of the IASLC for clinical or pathologic size and in the SEER registry for both.

The results of this study also have shown that T4 tumors classified by the presence of additional nodules in the lobe of the primary tumor have better prognosis than other T4 tumors and similar prognosis to T3 tumors. This finding has been validated by the SEER registry and by all geographic areas and databases with sufficient numbers of patients. This is a very controversial point in the TNM classification, and large and small series have contradictory results. In a series of 1534 patients with completely resected NSCLC, the 5-year survival rate for 54 patients with T4 tumors without additional nodules was similar to that of 105 patients with T4 tumors by additional nodules: 34% in both cases.[16] Nevertheless, it has been reported from smaller series that survival of patients with T4 tumors by additional nodules can be better than that of those with stage IIIB tumors[17] or similar to that of patients with stage IV tumors.[18] These discrepancies may be attributable to the few patients with T4 tumors by additional nodules or to the difficulty in determining whether an additional nodule of the same histological type as the primary tumor is a second primary or a metastasis. Their different biologic behaviors may be responsible for the prognostic differences found in the quoted series.

Tumors associated with malignant pleural effusion are now classified as T4 for mere taxonomic reasons: all situations within the hemithorax of the primary tumor should belong to the T component, except for nodules in another

ipsilateral lobe. Nevertheless, their prognosis is much worse than that of other T4 tumors; this will be shown in a forthcoming article in the context of M1 disease. Further, they are usually treated in the same manner as patients with M1 disease. In the present study, the 5-year survival rate for patients with clinical malignant pleural effusion was 2%, and the 5-year survival rate for patients with other cT4 tumors was around 30%. Survival was better for patients with pathologic malignant pleural effusion, with 5-year survival rates of around 20%, but there were few patients in this situation, and the extent of their disease must have been very reduced and amenable to complete resection, which is not the rule with malignant pleural effusion. The poor prognosis of this situation was validated in Europe and North America and in the clinical and pathologic series of the SEER registry.

The main limitation of this study is that most databases that have contributed to the IASLC international database were not designed to study the TNM classification. So, although more than 81,000 patients fulfilled the inclusion criteria, not all their records included information on the T descriptors that defined a certain T. Table 1 shows a summary of the number of patients with cT and pT tumors. For example, the population of surgical patients with cN0 tumors was 15,347, but only 3554 (23%) had sufficient information on T descriptors. This drop in patient numbers increased with higher T factors, and it is only 19% (110 of 582) in patients with cT4 tumors. This loss of information is even more evident in patients who did not undergo surgical treatment (Table 1). Lack of T descriptors is the reason most T2- and T3 descriptors, and all T4 descriptors (except for the additional nodule(s) in the same lobe as the primary tumor), could not be validated with the analysis of the IASLC international database. This limitation could be overcome with a prospective database with the objective of studying the TNM classification. In this database, the specific T descriptors for each tumor should be registered.

From the analysis of the T component of the TNM classification in the IASLC international database, we can conclude that there is sufficient validated information to consider the following recommendations for changes in the seventh edition of the TNM classification of lung cancer: 1) to subclassify T1 as T1a ($\leq$2 cm) or T1b ($>$2 cm to $\leq$3 cm); 2) to subclassify T2 as T2a ($>$3 cm to $\leq$5 cm or T2 by other factor and $\leq$5 cm) or T2b ($>$5 cm to $\leq$7 cm); 3) to reclassify T2 tumors $>$7 cm as T3; 4) to reclassify T4 tumors by additional nodule(s) in the lung (primary lobe) as T3; 5) to reclassify M1 by additional nodule(s) in the ipsilateral lung (different lobe) as T4; and 6) to reclassify pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) as M1.

The recommendations drawn from this study are solidly based. The database used is the largest ever collected for the purpose of evaluating lung cancer classification and staging. Data were collected from worldwide sources representing four distinct geographical areas. Information was collected both from highly audited datasets, such as clinical trials, and from registries, which generally are less strictly audited. Finally, the findings of this study hold when comparing different geographic regions, histologic types, and data sources, thus making the findings generalizable.

This is one of several papers from the IASLC International Staging Committee that has the purpose of presenting our current considerations on the basis of analysis of the large dataset submitted for this project. With this publication, we hope to generate feedback from the community of physicians working in the lung cancer field to engage any positive suggestions that might allow for improvements in the present TNM classification of lung cancer.

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