Evaluation of the new TNM staging system proposed by the International Association for the Study of Lung Cancer at a single institution

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Objective: The seventh *TNM Classification of Malignant Tumours* will be published in 2009. The International Association for the Study of Lung Cancer has proposed a revision of the current pathologic staging system. We illustrated the effects of this new system and pointed out potential problems using a retrospective study of surgical cases of non-small cell lung cancer at our institution.

Methods: Subjects were 1532 patients for whom current pathologic staging was possible. These data were migrated into the new staging system. The numbers of patients at various stages determined by using the current and new staging systems were, respectively, as follows: IA (n = 700, n = 700), IB (n = 338, n = 249), IIA (n = 49, n = 164), IIB (n = 129, n = 116), IIIA (n = 204, n = 234), IIIB (n = 77, n = 17), and IV (n = 35, n = 52). Prognoses were compared by using the current and the new systems.

Results: By using the new staging system, 5-year survivals by T classifications were as follows: T1a, 82.6%; T1b, 73.3%; T2a, 63.5%; T2b, 50.1%; T3, 40.6%; and T4, 34.6%. There were significant differences between the new T1a and T1b ($P = .0026$), T1b and T2a ($P = .0027$), and T2a and T2b ($P = .0062$) classifications. In the current system 5-year survivals based on pathologic stages were as follows: IA, 84.8%; IB, 72.9%; IIA, 53.8%; IIB, 53.7%; IIIA, 31.8%; IIIB, 34.0%; and IV, 27.1%. There were significant differences between stages IA and IB ($P < .0001$) and stages IIB and IIIA ($P = .0006$). In the new system these were as follows: IA, 84.8%; IB, 75.2%; IIA, 62.4%; IIB, 52.1%; IIIA, 32.4%; IIIB, 15.2%; and IV, 30.6%. There were significant differences between stages IA and IB ($P = .0004$), IB and IIA ($P = .0195$), IIA and IIB ($P = .0257$), IIB and IIIA ($P = .0040$), and IIIA and IIIB ($P = .0399$).

Conclusion: Although the outcomes for stages IIIB and IV were reversed, the new pathologic staging system was considered valid based on our single-institution evaluation.

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Staging is important for predicting patient prognosis and selecting appropriate treatment for lung cancers. Although the current (sixth edition) *TNM Classification of Malignant Tumours* by the International Union Against Cancer (UICC) is an excellent staging system, various problems have been indicated for many aspects of lung cancer.¹ The next edition of the *TNM Classification of Malignant Tumours*, the seventh, is due to be published in 2009. In preparation for this, the International Association for the Study of Lung Cancer (IASLC) established its Lung Cancer Staging Project in 1998 to formulate recommendations for the seventh edi-

tion.^{2,3} The project has been recognized by the UICC as the primary source for recommendations for revisions to the sixth edition of the *TNM Classification of Malignant Tumours*. Lung cancer treatments are based on staging, and changes in staging greatly affect these treatment strategies. For the evaluation of new treatment strategies, there will be a need for the migration of current data into the new staging system in most institutions. We migrated current data for surgical cases of non-small cell lung cancer at our institution into this new system both to illustrate the effects of this new system and to point out potential problems.

MATERIALS AND METHODS

The subjects were 1532 surgical patients with non-small cell lung cancer at pathologic stages I to IV who were seen at our institution from 1984 to 2007. They underwent resections of tumors with dissection or sampling of lymph nodes, and T, N, and M classifications could be pathologically evaluated. There were 369 patients with squamous cell carcinoma, 1061 with adenocarcinoma, 29 with adenosquamous carcinoma, 35 with large cell carcinoma, and 38 with other types of cancer. The surgical procedures were lobectomy for 1182 patients, bilobectomy for 66 patients, pneumonectomy for 70 patients, completion pneumonectomy for 9 patients, segmentectomy for 130 patients, wedge resection for 74 patients, and 1 other procedure for 1 patient.

The current classification followed the sixth edition of the *TNM Classification of Malignant Tumours*.¹ The new classification followed the revised staging system proposed by the IASLC.³ In the new TNM classifications, tumors that fulfill the definition for T1 and are 2 cm or smaller in the greatest

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Abbreviations and Acronyms
IASLC = International Association for the Study of Lung Cancer
UICC = International Union Against Cancer

dimension should be designated T1a, whereas those that are larger than 2 cm but 3 cm or smaller in the greatest dimension should be designated T1b. Those tumors that fulfill the present definition of T2 and are 5 cm or smaller in the greatest dimension become T2a, whereas those that are larger than 5 cm but 7 cm or smaller in the greatest dimension become T2b. Tumor dimension of larger than 7 cm becomes a T3 descriptor. Additional tumor nodules in the lobe of the primary tumor become T3, nodules in other ipsilateral lobes become T4, and nodules in the contralateral lung remain M1. The presence of malignant pleural effusion, pleural dissemination, or pericardial disease becomes an M classification. The M category is subdivided into the following: M1a, which includes the new classifications added to this category (ie, patients with pleural nodules or malignant pleural or pericardial effusion and additional pulmonary nodules in the contralateral lung) and M1b for those patients with other distant metastases. The existing N classifications were validated, and no changes are proposed. T2a N1 M0 tumors migrate to stage IIA from stage IIB. T2b N0 M0 tumors migrate to stage IIA from stage IB. T4 N0 M0 and T4 N1 M0 tumors migrate to stage IIIA from stage IIIB (Table 1).

Table 2 shows the numbers of patients by T, N, and M classifications in the current and new staging systems. The numbers of patients classified by the current and new staging systems were, respectively, as follows: IA (n = 700, n = 700), IB (n = 338, n = 249), IIA (n = 49, n = 164), IIB (n = 129, n = 116), IIIA (n = 204, n = 234), IIIB (n = 77, n = 17), and IV (n = 35, n = 52). Comparisons of prognoses were performed.

All data were not included in the IASLC database. Computed tomographic analysis of the chest, brain, and upper portion of the abdomen and bone scintigraphic analysis were performed routinely for the preoperative evaluation of the extent of disease. Generally, patients were postoperatively examined at 3-month intervals for 5 years and at 1-year intervals thereafter to check for recurrence and survival. The median follow-up time was 49 months (range, 0–267 months). Since 1997, induction therapy had routinely preceded the cases for which the preoperative evaluation was greater than stage IIIA. Since 1999, video-assisted thoracoscopic surgery was performed for cases for which the preoperative evaluation was clinical stage I. Since 2002, adjuvant therapy was used routinely for cases for which the postoperative evaluation was greater than stage IIB. Patients with recurrent disease received chemotherapy, radiotherapy, or both as often as possible. We obtained informed consent from the patients preoperatively for use of clinical data, and our institutional review board approved this retrospective study.

Survival was determined from the date of surgical intervention until death from any cause. Survival curves were calculated by using the Kaplan–Meier method, and differences in survival were evaluated by using a log-rank test. Statistical calculations were done with Stat View 5.0 (SAS Institute, Inc, Cary, NC).

RESULTS

The 5-year survivals by T classification in the current staging system were as follows: T1, 78.7%; T2, 60.9%; T3, 34.5%; and T4, 36.9 (Table 3). The 5-year survivals by T classifications in the new staging system were as follows: T1, 78.5%; T2, 60.2%; T3, 40.6%; and T4, 34.6% (Table 4). T4 tended to have a worse prognosis than T3 in the new staging system compared with the current system.

TABLE 1. Classifications, proposed T and M categories, and proposed stage groupings

Sixth edition T/M classifications	Proposed T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5–7 cm)	T2b	IIA	IIB	IIIA	IIIB
T2 (>7 cm)	T3	IIB	IIIA	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Entries in bold indicate a change from the sixth edition for a particular TNM category.

The following are the 5-year survivals by subgroups of T classifications, which were newly established in the new staging system: T1a, 82.6%; T1b, 73.3%; T2a, 63.5%; and T2b, 50.1%. There were significant differences between the newly established T1a and T1b ($P = .0026$), T1b and T2a ($P = .0027$) and T2a and T2b ($P = .0062$) classifications (Figure 1).

For the N classifications, the 5-year survivals by the current staging system were as follows: N0, 77.0%; N1, 54.2%; N2, 28.4%; and N3, 0.0%. There were significant differences between N0 and N1 ($P < .0001$), N1 and N2 ($P < .0001$) and N2 and N3 ($P = .0002$, Table 3).

The following are the 5-year survivals by subgroups of M classifications that were newly established in the new staging system: M0, 68.5%; M1a, 30.0%; and M1b, 25.1%.

TABLE 2. Numbers of patients by T, N, and M classifications in the current and new staging systems

	N0	N1	N2	N3	Total
Sixth edition T/M					
T1	707	47	73	3	830
T2	345	76	98	6	525
T3	54	21	23	0	98
T4	42	17	18	2	79
M0	1133	158	198	8	1497
M1	15	3	14	3	35
Total	1148	161	212	11	1532
Proposed T/M					
T1a	440	15	28	3	486
T1b	268	32	45	1	346
T2a	252	54	70	3	379
T2b	80	23	25	2	130
T3	104	31	41	2	178
T4	4	6	3	0	13
M0	1121	151	200	8	1480
M1a	23	7	7	0	37
M1b	4	3	5	3	15
Total	1148	161	212	11	1532

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TABLE 3. Comparisons of overall survival between TNM classifications by using the sixth edition of TNM classifications

Sixth edition TNM	Deaths/no.	Median survival (mo)	5-Year survival (%)	P value
T1	120/830	53	78.7	—
T2	166/525	46	60.9	<.0001
T3	58/98	35	34.5	<.0001
T4	38/79	33	36.9	.8373
N0	192/1148	52	77.0	—
N1	60/161	45	54.2	<.0001
N2	122/212	32	28.4	<.0001
N3	8/11	11	0.0	.0002
M0	360/1497	50	68.2	—
M1	22/35	24	27.1	<.0001
Total	382/1532	49	67.3	—

P value: Significance value from log-rank test of survival hazard functions relative to preceding row.

There were significant differences between M0 and M1a ($P < .0001$) and M1a and M1b ($P = .0434$, Table 4).

For the current staging system, the 5-year survivals by stage were as follows: IA, 84.8%; IB, 72.9%; IIA, 53.8%; IIB, 53.7% ($P = .4951$); IIIA, 31.8%; IIIB, 34.0% ($P = .7812$); and IV, 27.1% (Figure 2, A). There was a significant difference between stages IA and IB ($P < .0001$) and stages IIB and IIIA ($P = .0006$). For the new staging system, the 5-year survivals by stage were as follows: IA, 84.8%; IB, 75.2%; IIA, 62.4%; IIB, 52.1%; IIIA, 32.4%; IIIB, 15.2%; and IV, 30.6%. There were significant differences between stages IA and IB ($P = .0004$), IB and IIA ($P = .0195$), IIA and IIB ($P = .0257$), IIB and IIIA ($P = .0040$), and IIIA and IIIB ($P = .0399$); (Figure 2, B).

DISCUSSION

Although the current (sixth edition) *TNM Classification of Malignant Tumours* by the UICC is an excellent staging system, various problems have been indicated in many aspects for lung cancer.^{1,4,5} The next edition of the *TNM Classification of Malignant Tumours*, the seventh, is due to be published in 2009. In preparation for this, the IASLC estab-

TABLE 4. Comparisons of overall survival between T and M classifications by using the new TNM classifications proposed by the International Association for the Study of Lung Cancer

Proposed TM	Deaths/no.	Median survival (mo)	5-Year survival (%)	P value
T1	122/832	53	78.5	—
T2	162/509	46	60.2	<.0001
T3	90/178	37	40.6	<.0001
T4	8/13	21	34.6	.3343
M0	354/1480	50	68.5	—
M1a	18/37	34	30.0	<.0001
M1b	10/15	10	25.1	.0434
Total	382/1532	49	67.3	—

P value: significance value from log-rank test of survival hazard functions relative to preceding row.

FIGURE 1. Overall survival based on pathologic T classification subgroups proposed by the International Association for the Study of Lung Cancer. There were significant differences between the newly established T1a and T1b ($P = .0026$), T1b and T2a ($P = .0027$), and T2a and T2b ($P = .0062$) classification.

lished its Lung Cancer Staging Project in 1998 to bring together the large databases available worldwide and to formulate recommendations for the seventh edition that would be intensively validated.^{2,3} Analysis of data from 81,015 cases worldwide was performed. The IASLC proposed a revision of the current staging system that was presented at the 12th World Conference on Lung Cancer. In addition, the details were published in the *Journal of Thoracic Oncology*.^{3,6-9} The new staging system was based on an intensive and validated analysis of the largest database available to date. It is highly likely that the next edition of the *TNM Classification of Malignant Tumours* will be based on this new staging system.

In our analyses of prognoses by the T classifications, there were clear differences between T1a and T1b, between T1b and T2a, and between T2a and T2b, which were new subgroups in the new staging system. It has been previously shown that there are clear differences in prognosis based on tumor size.¹⁰⁻¹² In the new staging system optimal cut points for tumor size were determined by using “a running log-rank test.”⁶ Indications for limited operations and the significance of postoperative adjuvant therapy for T1 and T2 cases have been discussed.¹³⁻¹⁶ Furthermore, the detailed studies of subgroupings in the new staging system are more useful. In the new staging system, compared with the current system, T3 tended to show a better prognosis than T4. This resulted as ipsilateral pulmonary nodules in the same lobe were changed from T4 to T3 and ipsilateral pulmonary nodules in another lobe were changed from M1 to T4. The prognoses for these groups were previously considered to be good based on the current classification system, and these changes were considered valid.^{17,18} In the analyses for prognoses by the M classifications, there were differences in prognosis among M1a, M1b, and M0, which were established in the new staging system.⁸ In the analyses for prognoses by stages, there were differences in prognosis between

FIGURE 2. Overall survival based on pathologic stage. Survival based on the sixth edition of the TNM classifications (A) and the new TNM classifications proposed by the International Association for the Study of Lung Cancer (B) is shown. The numbers of patients classified by the current and new staging systems were as follows: IA (n = 700, n = 700), IB (n = 338, n = 249), IIA (n = 49, n = 164), IIB (n = 129, n = 116), IIIA (n = 204, n = 234), IIIB (n = 77, n = 17), and IV (n = 35, n = 52). In the current system there were significant differences between stages IA and IB ($P < .0001$) and between stages IIB and IIIA ($P = .0006$). In the new staging system there were significant differences between IA and IB ($P = .0004$), IB and IIA ($P = .0195$), IIA and IIB ($P = .0257$), IIB and IIIA ($P = .0040$), and IIIA and IIIB ($P = .0399$).

stages IIA and IIB and between stages IIIA and IIIB in the new staging system. These differences were not seen in the current staging system.

A problem with the new staging system is the reversal of outcomes for stages IIIB and IV. These trends were also seen for pathologic staging in the new IASLC staging system.^{3,9} However, the reason for the reversal was not described. For the operative cases, the numbers of pathologic stage IIIB and IV tumors are too small for evaluation. However, the patients with a good prognosis might be included in stage IV, especially M1a. In fact, for our patients, there were significant differences between M1a and M1b. Contralateral pulmonary nodules, which are detected by means of imaging and not proved pathologically, might not be metastatic.¹⁷ Patients with malignant effusion (dissemination) and no distant metastases might be offered a good prognosis with an oper-

ation and adjuvant therapy.¹⁹⁻²² Therefore the M1a classification might have to be reconsidered.

For pathologic staging proposed by the IASLC, the revisions that focused on the T classifications were reflected well by the improvements for stages I to III. Although the outcomes for stages IIIB and IV were reversed, the new pathologic staging system was considered valid based on our single-institution evaluation.

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