Prognostic evaluation based on a new TNM staging system proposed by the International Association for the Study of Lung Cancer for resected non-small cell lung cancers

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Objective: The TNM classification has been widely used as a guide for estimating prognosis and is the basis for treatment decisions on various solid tumors. The International Association for the Study of Lung Cancer Staging Committee has proposed a new staging system for the next revision scheduled in 2009. However, its validity has not been established fully. Here we assessed its utilities and drawbacks.

Methods: We reviewed 1556 consecutive patients with non-small cell lung cancers who underwent pulmonary resection in our institution and reviewed their survival characteristics based on the 2009 system compared with the current (1997) system.

Results: The numbers of patients with stage IIA disease increased remarkably when using the 2009 system because of the reclassification of stages IB and IIB. Although the 5-year survival rates of the patients with stage IB and IIA disease in the 1997 system showed no difference with the 2009 system, the survival rates of patients with stage IB disease was 68.0%, which is better than that of patients with stage IIA disease (57.6%). The patient survival curves showed stepwise deterioration as the numbers increased, except for patient with stage IV disease.

Conclusions: Our study supported the proposal for this new staging system. Compared with the 1997 system, the 2009 system appears to be superior in separating stage IB and IIA disease and provides an even distribution among the stage groupings, although it is slightly complicated. The survival characteristics of 1556 resected cases in this single Japanese institution validated the proposed 2009 system.

The TNM classification of cancers proposed by the Union Internationale Contre le Cancer has been widely accepted as a guide for estimating patient prognosis and is the basis for treatment decisions in practice. In lung cancer the first edition of the TNM classification was published in 1968, and it has been revised 5 times: in 1974 (second edition), 1978 (third edition), 1987 (fourth edition), 1997 (fifth edition), and 2002 (sixth edition). The 1997 revision has undergone an extensive correction for many deficiencies in the old staging system.¹ The sixth and current edition from 2002 is a minor revision of the fifth edition, and the next revision is scheduled in 2009.

Thus the staging system has been revised many times to make it better. However, there are still some controversies and proposals for revision in the current edition. In a large-scale retrospective study of non-small cell lung cancer (NSCLC) performed by the Japanese Joint Committee of Lung Cancer Registry, no difference in prognosis between stage IB and IIA disease was seen in either clinical or pathologic settings.² Many investigators reported similar discordant results concerning stage IB and IIA disease.³⁻⁶ In addition, although a satellite tumor nodule in the primary lobe is defined as T4 in the current system, some suggested that it might behave more favorably than in patients with another subgroup of T4.⁷ As a result, distinguishing the prognoses of

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Abbreviations and Acronyms

BAC = bronchioloalveolar carcinoma

IASLC = International Association for the Study of Lung Cancer

patients with stage IIIA and IIIB disease is sometimes unclear.^{5,8,9} To correct these controversies, the International Association for the Study of Lung Cancer (IASLC) Staging Committee proposed a new staging system for the next revision (summarized in Table 1 and Figure 1).¹⁰⁻¹³

The purpose of this retrospective study was to review the survival characteristics of patients based on the new staging system proposed by the IASLC. We studied 1556 consecutive patients who underwent pulmonary resection in a single institution, Aichi Cancer Center Hospital. We also discuss the utilities and drawbacks of the new staging system.

Materials and Methods**Patient Cohort**

Approval for this study was obtained from and the need for individual patient consent was waived by the institutional review board. During a 21-year period from 1982 through 2002, 1556 patients with primary NSCLCs were enrolled in this study. The patients with pathologic stage IA to IV disease, including clinical patients with N2 disease, underwent surgical intervention. All patients underwent surgical resection with nodal dissection at the Aichi Cancer Center Hospital and were followed up for at least 5 years or until death. Data extracted from each patient's medical record included age, sex, smoking history, tumor histology and location, adjuvant and induction therapies, date of last follow-up, and death from any cause. The median follow-up period was 104 months. The patients comprised 1021 (66%) men and 535 (34%) women, ranging in age from 24 to 89 years (mean $\pm$ standard deviation, 62 ± 9.8 years). There were 977 (63%) adenocarcinomas, 429 (28%) squamous cell carcinomas, 87 (5%) large cell carcinomas, and 63 (4%) other types of cancers. Evaluation of pN classification was determined from pathologic examination of resected specimens, including determination of the location and number of lymph nodes examined and the number found to be positive.

Preoperative therapy was performed in 52 (3%) patients. They comprised 16 patients with clinical stage IIB, 25 with stage IIIA, 8 with stage IIIB, and 2 with stage IV disease. Among them, 27 and 8 patients underwent chemotherapy or radiotherapy, and 16 patients underwent chemoradiotherapy. Postoperative adjuvant chemotherapy was administered to only 10 (0.6%) patients with stage IB or higher disease in this cohort.

New Staging System

Changes in the new TNM staging system for lung cancer proposed by the IASLC are listed in Table 1. Concerning the T descriptor, the IASLC proposed a subclassification of the current T2 tumors according to tumor size: those larger than 3 cm to 5 cm or less or classified as T2a, those larger than 5 cm to 7 cm or less are defined as T2b, and

TABLE 1. Summary of the proposal for changes to the sixth edition of the TNM classification¹⁰**Tumor size**

- Reclassify T2 tumors >7 cm as T3
- Subclassify:
 - T1 as
 - T1a (≤ 2 cm) or
 - T1b (>2 cm to ≤ 3 cm); and
 - T2 as
 - T2a (>3 to ≤ 5 cm or T2 by other factor and ≤ 5 cm) or
 - T2b (>5 to ≤ 7 cm)

Separate tumor nodule

- Reclassify T4 tumors with additional nodules in the lung (primary lobe) as T3
- Reclassify M1 with additional nodules in the ipsilateral lung (different lobe) as T4
- Subclassify M1 with additional nodules in the contralateral lung as M1a

M factor

- Reclassify pleural dissemination (malignant pleural or pericardial effusions, pleural nodules) from T4 to M1a
- Subclassify M1 with distant metastases (outside the lungs or pleura) as M1b

Stage grouping

- Reclassify T2a N1 tumors (≤ 5 cm) as stage IIA (from IIB)
- Reclassify T2b N0 tumors (>5–7 cm) as stage IIA (from IB)
- Reclassify T4 N0 and T4 N1 tumors as stage IIIA (from IIIB)

those larger than 7 cm are defined as T3. An additional tumor nodule in the same lobe is classified as T3 and in the ipsilateral different lobe as T4 but as M1a if it is in the contralateral lung. In addition, pleural dissemination is classified as M1a. Concerning the N classification, the IASLC supported the continued use of the current N0, N1, N2, and N3 stage descriptors.¹² In the stage grouping the IASLC proposed to reclassify T2a N1 (current IIB) and T2b N0 (current IB) collectively as stage IIA disease and T4 N0 and T4 N1 (current IIIB) as stage IIIA disease.

Survival Analyses

The Kaplan–Meier method was used to plot the survival curves, and the log-rank test was used to evaluate differences between subgroups. To evaluate the significance of the new classification as an independent prognostic factor, we performed multivariate analysis by using the Cox proportional hazards model with 2 different

	T1a, T1b	T2a	T2b	T3	T4
N0	IA	IB	IIA	IIB	IIIA
N1	IIA	IIA	IIB	IIIA	IIIA
N2	IIIA	IIIA	IIIA	IIIA	IIIB
N3	IIIB	IIIB	IIIB	IIIB	IIIB

Figure 1. The stage grouping according to the proposed system by the IASLC.¹⁰

models: one that included the current staging system (the 1997 system) and the other being the proposed one (the 2009 system). Trend *P* values were assessed by using score tests. Statistical calculations were performed with a statistical package (StatView version 5.0; SAS Institute, Inc, Cary, NC).

Results

Distribution of Pathologic Stage

According to the 1997 system, patients were distributed as follows: stage IA, *n* = 448 (28.8%); stage IB, *n* = 368 (23.7%); stage IIA, *n* = 44 (2.8%); stage IIB, *n* = 194 (12.5%); stage IIIA, *n* = 317 (20.4%); stage IIIB, *n* = 122 (7.8%); and stage IV, *n* = 63 (4.0%). When applied to the 2009 system, they were distributed as follows: stage IA, *n* = 448 (28.8%); stage IB, *n* = 278 (17.9%); stage IIA, *n* = 175 (11.2%); stage IIB, *n* = 155 (10.0%); stage IIIA, *n* = 378 (24.3%); stage IIIB, *n* = 41 (2.6%); and stage IV, *n* = 81 (5.2%; Figure 2). Comparing the 2 distributions, the proportion of patients with stage IIA disease was increased remarkably by the reclassification of patients with stage IB and IIB disease. Sixty patients with current stage IB disease were redefined as having new stage T2b N0 M0 disease, and 71 patients with current stage IIB disease were redefined as having new stage T2a N1 M0 disease and shifted to a new stage, IIA. One hundred thirty-seven patients were shifted to a higher stage with the 2009 system, mostly from IB to IIA (*n* = 60). On the other hand, 139 patients were shifted to a lower stage, and most of these were from stages IIB to IIA (Table 2).

Survival Analysis

Survival curves and the 5-year survival rates according to the 1997 and 2009 staging systems are shown in Figure 3. The

Figure 2. Distribution of the patients according to the current and proposed new stage groupings. The proportion of patients with stage IIA disease increased remarkably because they were reclassified from current stages IB and IIB.

TABLE 2. Comparison between current and proposed pathologic stages

1997 system	2009 system							Total
	IA	IB	IIA	IIB	IIIA	IIIB	IV	
IA	448	0	0	0	0	0	0	448
IB	0	278	60	30	0	0	0	368
IIA	0	0	44	0	0	0	0	44
IIB	0	0	71	114	10	0	0	195
IIIA	0	0	0	0	316	0	0	316
IIIB	0	0	0	11	38	36	37	122
IV	0	0	0	0	14	5	44	63
Total	448	278	175	155	378	41	81	1556

5-year survival rates of the patients with current stage IB and IIA disease were 64.9% and 65.9%, respectively, in this cohort, being almost identical (*P* = .54). With respect to the 2009 system, the survival curves showed stepwise deterioration as the stage increased, except for patients classed as having stage IV disease. The 5-year survival rate of patients classed as having stage IB disease was 68.0%, which was better than that of those with stage IIA disease (57.6%; *P* = .09; Figure 3, B). We analyzed the patient survival

Figure 3. Survival curves for patient subgroups stratified according to stage groupings. The 5-year survival rate and the number of patients in each subgroup are indicated. A, With regard to the current staging system, no survival difference was observed between patients with stage IB and IIA disease (*P* = .54). B, With regard to the proposed system, the survival curves showed significant stepwise deterioration as the numbers increased, except for patients with stage IV tumors. There was a difference in the prognoses of patients with stage IB and IIA disease, although this was not statistically significant (*P* = .09).

Figure 4. Survival curves for patient subgroups stratified according to T descriptors. The 5-year survival rate and the number of patients in each subgroup are indicated. **A**, With regard to the current staging system, the survival curves showed significant stepwise deterioration as the numbers increased. **B**, For the proposed system, there was no significant prognostic difference between the new T1a and T1b stages ($P = .35$).

characteristics for the T descriptors and found no prognostic difference between T1a and T1b tumors ($P = .35$, Figure 4). Concerning satellite tumor nodules, 22 patients who were classified as having T4 tumors only because of their satellite tumor nodules showed significantly better survival than that of other patients with T4 tumors. The 5-year survival rate of these 22 patients was 36%, whereas it was 17% in the other T4 group ($P = .038$).

Multivariate analysis with the Cox proportional hazard model was performed to evaluate the significance of the stage groupings, including the following variables: age, sex, histology, and 1997 and 2009 stage grouping. Each stage grouping was tested independently in the same combination with other variables. The result is summarized in Table 3. Hazard ratios for stage IB and IIA disease in the 1997 system referred to as stage IA disease were 1.83 and 1.80, respectively, versus 1.72 and 2.17 in the 2009 system. Among the clinicopathologic variables analyzed, each stage grouping was an independent prognostic factor.

Discussion

The staging system for cancer according to TNM classification is an accepted principle used by oncologists. It serves many objectives: to give some indication of prognosis, to plan treatments, to evaluate the results of treatments, to

TABLE 3. Comparison of hazard ratios by means of 2 multivariate analyses with the Cox hazard model

	1997 staging system		2009 staging system	
	Hazard ratio	95% CI	Hazard ratio	95% CI
IA	1.00		1.00	
IB	1.83	1.46–2.30	1.72	1.35–2.20
IIA	1.80	1.13–2.85	2.17	1.67–2.83
IIB	3.11	2.42–3.99	3.16	2.43–4.11
IIIA	4.68	3.77–5.81	4.96	4.02–6.12
IIIB	7.34	5.64–9.55	10.60	7.35–15.4
IV	6.50	4.66–9.07	7.35	5.46–9.89
Trend $P < .0001$			Trend $P < .0001$	

Each stage grouping was tested independently in the same combination with other variables. Other variables are as follows: age ($<62/\geq 62$ years), sex (male/female), and histology (squamous/nonsquamous). CI, Confidence interval.

facilitate the exchange of information among institutions, and to contribute to the continuing investigation of human cancer.^{14,15} Therefore the system should be revised according to the prognosis of patients with relatively homogeneous backgrounds. For lung cancers, the American Joint Committee on Cancer and Union Internationale Contre le Cancer adopted several revisions to the 1986 stage classification, changes that were later published by Mountain¹ in 1997 as the fifth edition. For the next revision scheduled in 2009, the IASLC Staging Committee has proposed a new staging system based on a well-organized, large international database covering more than 80,000 patients with lung cancers.¹⁰⁻¹³ In the present study we attempted to assess the validity of the proposed revision.

One of the most important aims for the next revision is to correct the similar survival rates of patients with stage IB and IIA disease, which is partly caused by the relatively few patients with stage IIA disease, as reported by many investigators: 1.4% in Mountain's series,¹ 3.5% in the Japanese series,² 3.7% in the series by Naruke and colleagues,⁶ and 4.4% in the series by Inoue and associates.³ Mountain had already reported the similar prognoses for patients with stage IB and IIA disease: 57% and 55%, respectively.¹ In our cohort no survival difference was observed between patients with stage IB or IIA disease (64.9% and 65.9%, respectively), and patients with stage IIA disease accounted for only 2.8% of the whole. According to this proposal, the number of patients categorized as having stage IIA disease increased to 175 (11%) from 44 (2.8%) in our cohort. The survival analysis showed differences between the prognoses of patients with stage IB and IIA disease, although the difference was not statistically significant ($P = .09$).

Other overlapping prognoses of patients with neighboring stages were seen between stages IIIB and IV in this study. In the 2009 system an additional tumor nodule in the same lobe is classified as T3 and pleural dissemination

as M1. Therefore the patients with stage IIIB disease decreased from 122 (7.8%) to 41 (2.6%). The worse 5-year survival rates than seen with current stage IIIB disease (12.2% and 19.6%) seem to be because of the shifting of patients who behaved more favorably than other subgroups of patients with T4 tumors to the earlier stages. Because this retrospective study only included resected cases and most patients with advanced stages are generally not candidates for surgical intervention, the patients with stage III and IV disease in this study did not represent the whole population of these stage groups.

In the 1997 TNM classification, a satellite tumor nodule in the primary lobe is defined as T4. However, some investigators suggested that patients with a satellite tumor nodule in the primary lobe might behave more favorably than patients with other subgroups of T4 tumors.^{7,16} Because 22 patients with satellite tumor nodules in the same lobe showed significantly better survival than the other patients with T4 tumors in this study, the 2009 system seems to be appropriate. Usually, any satellite tumor nodule in a different lobe is regarded as metastatic, but it remains arguable whether the nodule is really a metastatic lesion or a synchronous lung neoplasm. However, it is very difficult to distinguish them by means of preoperative evaluations with imaging studies in clinical practice.

Many investigators have reported the effects of tumor size on stage, curability, and patient survival.^{9,17-19} In the 2009 system current T1 tumors should be divided into T1a (tumors ≤ 2 cm in greatest dimension) and T1b (tumors >2 cm but ≤ 3 cm) tumors, although the subclassification would not be reflected in stage grouping.^{10,11} In this study we analyzed the survival characteristics according to the T descriptors and found no prognostic difference between the new T1a and T1b classifications (Figure 3). One possible reason might be the limited value of the evaluation of invasiveness by tumor size alone. Recent clinical use of high-resolution computed tomographic analysis has greatly advanced the diagnosis of small lesions of the peripheral lung. Bronchioloalveolar carcinoma (BAC), which is detected as such a small lesion, is the noninvasive form of an adenocarcinoma and often included in the smaller T category. In the revised World Health Organization histologic classification, a BAC is classified as a noninvasive carcinoma with no evidence of stromal, vascular, or pleural invasion. The excellent prognosis for patients after surgical resection of BACs is already well recognized.²⁰ In the present study the histologic category as an adenocarcinoma might have included a BAC, and its prognostic significance was not demonstrated independently. Asamura and coworkers²¹ suggested that these noninvasive BACs should be newly termed as T_i and excluded from the T1 category. On the other hand, hilar or mediastinal nodal metastases have been found even in patients with adenocarcinomas of 1.0 cm or less.^{22,23} Moreover, in our cohort lymph node involvement had been found in 3 patients among 18

adenocarcinomas measuring 1 cm or less in diameter (detailed data not shown). Thus tumor size alone cannot be an indicator of the invasive nature of the small lung adenocarcinomas.²⁴

On the other hand, subclassification by tumor size might have an effect on postoperative adjuvant therapy. The standard of care for resected stage II to IIIA NSCLC now includes adjuvant chemotherapy based on the results of 3 phase III studies using cisplatin-based regimens.²⁵⁻²⁷ However, the role of adjuvant chemotherapy for stage I disease remains controversial. Updated results from the Cancer and Leukemia Group B 9633 trial, the only trial to focus exclusively on patients with stage IB disease, no longer shows a statistically significant survival benefit from adjuvant chemotherapy in this population.²⁸ The patient who would take a survival benefit might be found by the subclassification of current T1 and T2 tumors in the 2009 system.

Concerning the N classification, the survival rates decreased as the N number progressed, whereas prognostic significance was found between N classes in our cohort (Figure 5). We reported previously that the number of positive lymph nodes was a strong independent prognostic factor in patients with resected NSCLCs and could stratify the patients with N2 disease into a homogenous subgroup.²⁹ We hope that consideration will be given to its inclusion in pathologic staging in the future. Regarding the lymph node map showing the sites of nodes, the Japan Lung Cancer Society has produced the Naruke map,³⁰ which is based on bronchial trees, thoracotomy findings, and resected specimens, and there is also a map based on the Mountain–Dresler modification of the map from the American Thoracic Society,³¹ which is based on mediastinal pleura and mediastinoscopic identification. The 2 maps have different views on the definition between levels 7 and 10, which causes confusion in the definitions of N1 and N2. Although the proposal by the IASLC included the “zone” concept, which groups lymph nodes from several nodal stations, and suggested that this concept also reconciled the slight differences in nomenclature between the 2 maps,¹² discussion on the issue is still underway.

Figure 5. Survival curves for patient subgroups stratified according to N descriptors. The survival curves showed significant stepwise deterioration as the numbers increased.

Our study supports the proposals for the new TNM staging system of lung cancer as reported by the IASLC Staging Committee. Our survival characteristics of 1556 patients with resected NSCLCs in a single Japanese institution validated this proposed staging system, which is based on a large international database, particularly among patients with pathologic stage IA to IIIA disease. In this study patients with stage IIIB disease showed a worse survival rate than those with stage IV disease. Because this retrospective study only included resected cases, the patients with stages III and IV disease did not represent the whole population of these stage groups. In any case we should always prepare for future modifications of the TNM staging system as we gain more knowledge about the biology of lung cancer. Last, we hope to make the revised staging system easier to remember and less cumbersome for clinicians involved in the management of lung cancer.

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