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Prognosis of 6644 resected non-small cell lung cancers in Japan: A Japanese lung cancer registry study

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Summary For the scheduled future revision of the TNM staging system for lung cancer, it is important that the present 1997 version be evaluated in a large population. In 2001, the Japanese Joint Committee of Lung Cancer Registry sent a questionnaire to 320 Japanese institutions regarding the prognosis and clinicopathological profiles of patients who underwent the resection for primary lung neoplasms in 1994. We compiled the data for 7408 patients from 303 institutions (94.7%). Among these, 6644 patients with non-small cell histology were studied in terms of prognosis. The 5-year survival rate of the entire group was 52.6%. The 5-year survival rates by clinical (c-) stage were as follows: 72.1% for IA ($n=2423$), 49.9% for IB ($n=1542$), 48.7% for IIA ($n=150$), 40.6% for IIB ($n=746$), 35.8% for IIIA ($n=1270$), 28.0% for IIIB ($n=366$) and

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20.8% for IV (n=147). The difference in prognosis between neighboring stages was significant except for between IB and IIA and between IIIB and IV. The 5-year survival rates by pathological (p-) stage were as follows: 79.5% for IA (n=2009), 60.1% for IB (n=1418), 59.9% for IIA (n=232), 42.2% for IIB (n=757), 29.8% for IIIA (n=1250), 19.3% for IIIB (n=719) and 20.0% for IV (n=259). The difference in prognosis between neighboring stages was significant except for between IB and IIA and between IIIB and IV. The survival curves of stages IB and IIA were almost superimposed in both c- and p-settings. These findings indicated that the present stages IB and IIA should be merged into the same stage category. Otherwise, the present TNM staging system seemed to well characterize the stage-specific prognosis in non-small cell lung cancer. The future revision should focus on the subdivision of stages I and II.

1. Introduction

The TNM classification published by the Union Internationale Contre le Cancer (UICC) has been available worldwide since 1978 [1]. It has been respected as a useful tool for describing the extent of tumour spread, planning treatment and estimating the prognosis of patients. The present version of the UICC staging system for lung cancer was promulgated in 1997, and appeared in the 5th edition of the TNM classification of malignant tumours. This version divided stages I and II into subcategories A and B, respectively, and T3N0M0 tumours were transferred from stages IIIA to IIB. Furthermore, tumours in T4 category were defined to include those with satellite intrapulmonary metastasis within the same lobe.

The TNM staging system is scheduled to be revised in 2007, or some later year. To ensure this revision is meaningful, issues in the present system need to be addressed based on a database that includes a large number of patients. Therefore, two major Japanese societies dealing with lung cancer, the Japan Lung Cancer Society and the Japanese Association for Chest Surgery, sought to perform a retrospective registry on the prognosis and clinicopathological profiles of resected lung neoplasms.

The purpose of the present study was to clarify the appropriateness and problems of the present TNM-staging system from a prognostic viewpoint based on the results of this retrospective registry.

2. Materials and methods

2.1. Questionnaire

The Japan Lung Cancer Society and the Japanese Association for Chest Surgery established an ad hoc task force, the Japanese Joint Committee of Lung Cancer Registry, to perform a retrospective study on the prognosis and clinicopathological profiles of resected lung neoplasms. Only primary lung neoplasms that had been resected in 1994 at certified teaching hospitals in Japan were considered to ensure a follow-up period of at least 5 years. Tumors which were not resected at the time of thoracotomy (exploratory thoracotomy) were not included. In 2001, the committee sent a questionnaire form to 320 teaching hospitals in Japan. The following 27 items were included in the questionnaire: gender, age, clinical (c-) T, c-N, c-M, c-stage, preoperative treatment, surgical procedure, extent of lymph node dissection, curability, residual tumor, primary site by lobe, tumor diameter, histology, organ invasion, pleural involvement, pleural dissemination, intrapulmonary metastasis, pleural cytology, pathological (p-) T, p-N, p-M, p-stage, location of nodal metastasis, survival time, recurrence and cause of death. Recurrent or multiple lung cancers were not included in this registry. There were replies from 303 institutions (94.7%), and the data forms of 7408 patients were compiled. The histology of the tumor was described according to the World Health Organization classification [2], and low-malignant tumors were also included in this registry. All of the patients were staged according to the 5th edition of the UICC-TNM staging system, which was published in 1997 [1].

2.2. Patients

Fifteen patients (0.2%) were excluded from the study because of an incomplete description of data. The present study focused on patients with only non-small cell histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma and adenosquamous carcinoma). Therefore, among the remaining 7393 cases, excluding 749 patients with a histology of small cell carcinoma or other low-grade malignant tumour, 6644 patients (89.9%) were studied with regard to their prognosis. There were 4601

males (69.6%) and 2010 females (30.4%), and the description regarding the gender was not given in 33 patients. They ranged in age from 19 to 90 years, with an average of 64.5 years. The most common histologic type was adenocarcinoma in 3922 patients (59.0%), followed by squamous cell carcinoma in 2300 (34.6%), large cell carcinoma in 245 (3.7%) and adenosquamous carcinoma in 177 (2.7%).

2.3. Statistical analysis

The survival time was defined from the date of surgery to the last follow-up date. The survival curves were estimated by the Kaplan–Meier method, and the difference in survival was tested by the log-rank test. The influence of variables on the survival was also analyzed by the Cox's proportional hazard model. A P-value of less than 0.05 was considered significant.

3. Results

3.1. Distribution of c-/p-stage

Patients were staged both before (c-) and after (p-) surgery. Patients were distributed according to c-stage as follows: stage IA ($n=2423$, 36.5%), stage IB ($n=1542$, 23.2%), stage IIA ($n=150$, 2.3%), stage IIB ($n=746$, 11.2%), stage IIIA ($n=1270$, 19.1%), stage IIIB ($n=366$, 5.5%) and stage IV ($n=147$, 2.2%). Patients were distributed according to p-stage as follows: stage IA ($n=2009$, 30.2%), stage IB ($n=1418$, 21.3%), stage IIA ($n=232$, 3.5%), stage IIB ($n=757$, 11.4%), stage IIIA ($n=1250$, 18.8%), stage IIIB ($n=719$, 10.8%) and stage IV ($n=259$, 3.9%).

3.2. Survival by c-stage

A survival curve for the entire 6644 patients is shown in Fig. 1. The 5-year survival rate was 52.6%. Survival curves according to the c-stage are shown in Fig. 2. The 5-year survival rates according to c-stage were as follows: 72.1% for IA ($n=2423$), 49.9% for IB ($n=1542$), 48.7% for IIA ($n=150$), 40.6% for IIB ($n=746$), 35.8% for IIIA ($n=1270$), 28.0% for IIIB ($n=366$) and 20.8% for IV ($n=147$). The difference in survival was tested between neighboring stages. There was a significant difference in survival between stages IA and IB ($P=0.0000$), between IIA and IIB ($P=0.0458$), between IIB and IIIA ($P=0.0439$) and between IIIA and IIIB ($P=0.0000$). However, there was no difference between IB and IIA ($P=0.4969$) or between IIIB and IV ($P=0.1577$). The survival curves of stages IB and IIA were almost superimposed. Survival was further compared in stages IA, IB, IIA and IIB.

The differences between stages IA and IIA ($P=0.0000$) and between IB and IIB ($P=0.0000$) were significant.

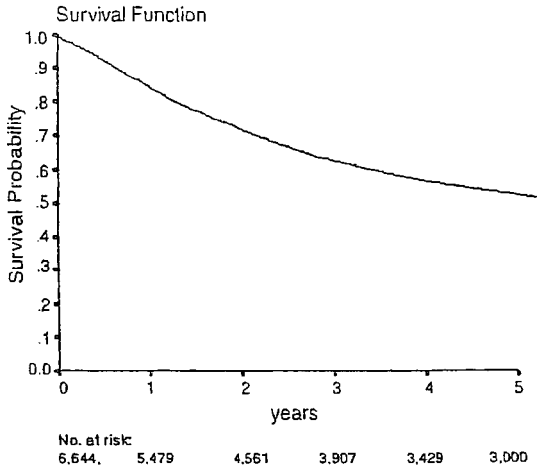

Fig. 1 A survival curve for all of the patients ($n=6644$). The 5-year survival rate for the entire group is 52.6%.

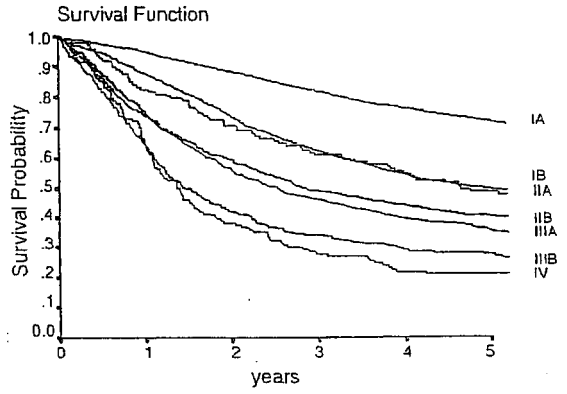

Fig. 2 Survival curves according to c-stage. The 5-year survival rates according to c-stage were as follows: 72.1% for IA ($n=2423$), 49.9% for IB ($n=1542$), 487% for IIA ($n=150$), 40.6% for IIB ($n=746$), 35.8% for IIIA ($n=1270$), 28.0% for IIIB ($n=366$) and 20.8% for IV ($n=147$). There is a significant difference in survival between stages IA and IB ($P=0.0000$), between IIA and IIB ($P=0.0458$), between IIB and IIIA ($P=0.0439$) and between IIIA and IIIB ($P=0.0000$). There is no difference between IB and IIA ($P=0.4969$) or between IIIB and IV ($P=0.1577$).

3.3. Survival by p-stage

Survival curves according to the p-stage are shown in Fig. 3. The 5-year survival rates by pathological p-stage were as follows: 79.5% for IA ($n=2009$), 60.1% for IB ($n=1418$), 59.9% for IIA ($n=232$), 42.2%

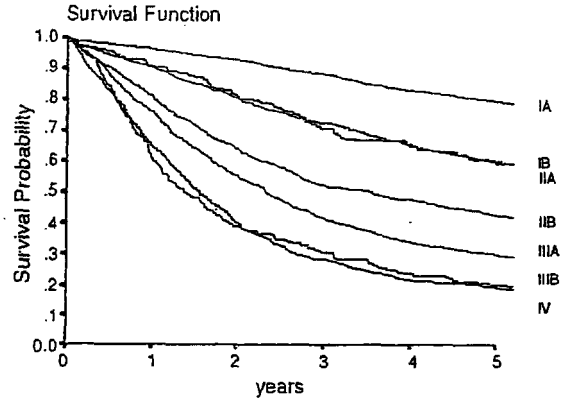

Fig. 3 Survival curves according to p-stage. The 5-year survival rates by pathological p-stage were as follows: 79.5% for IA ($n=2009$), 60.1% for IB ($n=1418$), 59.9% for IIA ($n=232$), 42.2% for IIB ($n=757$), 29.8% for IIIA ($n=1250$), 19.3% for IIIB ($n=719$) and 20.0% for IV ($n=259$). There is a significant difference in survival between stages IA and IB ($P=0.0000$), between IIA and IIB ($P=0.0000$), between IIB and IIIA ($P=0.0000$) and between IIIA and IIIB ($P=0.0000$). However, there is no difference between IB and IIA ($P=0.9832$) or between IIIB and IV ($P=0.8833$).

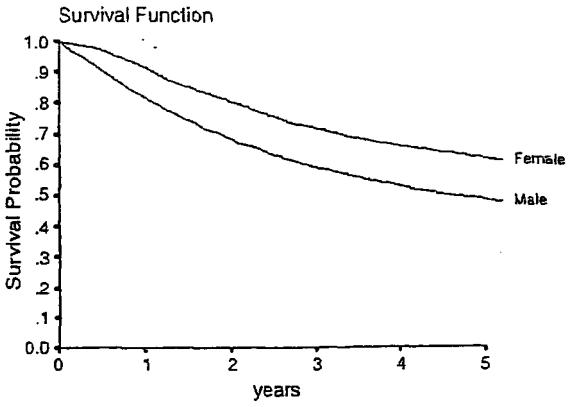

Fig. 4 Survival curves according to gender. The 5-year survival rates of men ($n=4601$) and women ($n=2010$) are 48.6% and 61.8%, respectively. The difference is significant ($P=0.0000$).

for IIB ($n=757$), 29.8% for IIIA ($n=1250$), 19.3% for IIIB ($n=719$) and 20.0% for IV ($n=259$). The difference in survival was tested between neighboring stages. There was a significant difference in survival between stages IA and IB ($P=0.0000$), between IIA and IIB ($P=0.0000$), between IIB and IIIA ($P=0.0000$) and between IIIA and IIIB ($P=0.0000$). However, there was no difference between IB and IIA ($P=0.9832$) or between IIIB and IV ($P=0.8833$). The survival curves of stages IB and IIA were almost superimposed. Survival was further compared in stages IA, IB, IIA and IIB. The differences between stages IA and IIA ($P=0.0000$) and between IB and IIB ($P=0.0000$) were significant.

3.4. Survival by gender, age and histology

Survival was also studied with regard to gender, age and histology. The survival curves according to gender are shown in Fig. 4. The 5-year survival rates for men ($n=4601$) and women ($n=2010$) were 48.6% and 61.8%, respectively. This difference was statistically significant ($P=0.0000$). The survival curves according to three age groups are shown in Fig. 5: less than 50 years ($n=548$), equal to or more than 50 years and less than 70 years ($n=3908$) and equal to or more than 70 years ($n=2185$). Their 5-year survival rates were 56.6%, 55.7% and 45.7%, respectively. The patients of equal to or more than 70 years of age had significantly worse prognosis than patients of other age groups ($P=0.0000$, 0.0000). The survival curves according to histologic type are shown in Fig. 6. The 5-year survival rates by histologic type were as follows: 56.0% for adenocarcinoma ($n=3922$), 48.6% for squamous cell carcinoma ($n=2300$), 46.7% for large cell carcinoma ($n=245$) and 35.6% for adenosquamous carcinoma ($n=177$). Survival worsened in the order of adenocarcinoma, squamous cell carcinoma, large cell carcinoma and adenosquamous carcinoma. Adenocarcinoma had a significantly better prognosis than all of the other histologic types ($P=0.0000$). There were also significant differences in survival between adenocarcinoma and squamous cell carcinoma ($P=0.0000$) and between large cell carcinoma and adenosquamous carcinoma ($P=0.0313$).

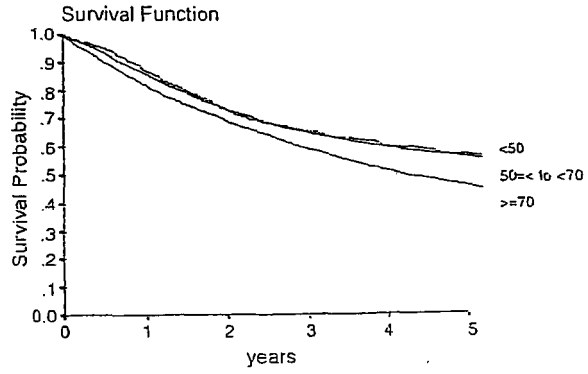

Fig. 5 Survival curves according to three age groups. Groups were defined as those <50 ($n=548$), 50≤ to <70 ($n=3908$), ≥70 ($n=2185$). The 5-year survival rates are 56.6%, 55.7% and 45.7%, respectively. Age of equal to or more than 70 years has a significantly worse prognosis than the other two age groups ($P=0.0000$, 0.000).

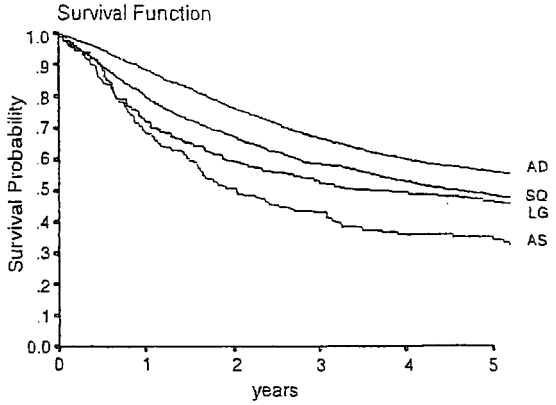

Fig. 6 Survival curves according to histologic type. The 5-year survival rates according to histologic type are as follows: 56.0% for adenocarcinoma ($n=3922$), 48.6% for squamous cell carcinoma ($n=2300$), 46.7% for large cell carcinoma ($n=245$) and 35.6% for adenosquamous carcinoma ($n=177$). Adenocarcinoma has a significantly better prognosis than all of the other histologic types ($P=0.0000$). A significant difference in survival is also seen between adenocarcinoma and squamous cell carcinoma ($P=0.0000$) and between large cell carcinoma and adenosquamous carcinoma ($P=0.0313$). AD, adenocarcinoma; SQ, squamous cell carcinoma; LG, large cell carcinoma; AS, adenosquamous carcinoma.

3.5. Multivariate analysis

To identify the significant factors possibly affecting the survival of the patients with resected lung cancer, the following variables were entered to the multivariate analysis: gender, age, histology, c- and p-stage. Since c- and p-stages obviously correlate each other, theses two viariables were tested independently in the combination with other variables. The results of the multivariate analysis was shown in Table 1 (including p-TNM stage). These factors (gender, age, histology and p-stage) were all significantly prognostic. In a setting including c-TNM stage, they were also demonstrated to be significant prognostic factors.

4. Discussion

The present study had some characteristic features because of the nature of the data obtained by the questionnaire-based retrospective registry. First, the number of patients analyzed was the greatest among all similar published studies. Second, treatments were administered only during 1994. Third, more than 300 Japanese teaching institutions, not just one, participated in this study. Fourth, the registry was limited to surgically resected cases.

In the past literature, there have been four major studies that have dealt with the prognosis of 1000 or more patients with lung cancer who were surgically resected (Tables 2 and 3) [3–6]. These data were all obtained from a single institution and cases were accumulated over a very long period of

Table 1 Factors influencing survival by multivariate analysis (p-stage and other variables)

Variables	Risk ratio	Multivariate Cox analysis	
		95% CI	P-value
Gender			
Male	Reference		
Female	0.722	0.662–0.787	0.000
Age (years)			
<50	Reference		
50≤, <70	1.131	0.987–1.297	0.077
70≤	1.647	1.430–1.897	0.000
Histologic type			
Adenocarcinoma	Reference		
Squamous cell carcinoma	1.032	0.953–1.118	0.432
Large cell carcinoma	1.129	0.945–1.350	0.180
Adenosquamous carcinoma	1.422	1.179–1.715	0.000
Pathological stage			
IA	Reference		
IB	1.958	1.734–2.212	0.000
IIA	2.087	1.676–2.601	0.000
IIB	3.252	2.847–3.714	0.000
IIIA	4.924	4.397–5.515	0.000
IIIB	7.237	6.395–8.190	0.000
IV	7.629	6.455–9.015	0.000

Table 2 Clinical 5-year survival rate (%) reported in the literature with 1000 or more patients according to the 1997 TNM staging system

	Present series (2005)	Mountain [3]	Van Rens et al. [4]	Naruke et al. [5]	Fang et al. [6]
No. of patients	6644	5319	2361	3043	1905
Accumulation period (year)	1	14	23	34	35
Histology	Non-small cell	Non-small cell	Non-small cell	All	All
c-Stage					
IA	72.0	61	–	70.8	–
IB	49.9	38	–	44	–
IIA	48.7	34	–	41.1	–
IIB	40.6	24	–	38.8[a]/32.6[b]	–
IIIA	35.9	13	–	22.3[c]/22.9[d]	–
IIIB	28.0	5	–	11.7[e]/24.3[f]	–
IV	20.8	1	–	–	–

[a] T2N1M0.
[b] T3N0M0.
[c] T1-2N2M0.
[d] T3N1-2M0.
[e] AnyTN3M0.
[f] T4anyNM0.

from 14 to 35 years. In contrast, the present study considered a large number of patients who were all treated within the same year. Therefore, the background of patients in the present study differs from that of previous studies with regard to their heterogeneity. While single institution studies might be able to minimize any institutional differences in surgical care, the long period of case accumulation strongly affects the quality of the evaluation of patients with regard to the extent of local and systemic tumour spread. For example, preoperative assessment should be considered completely different before and after the introduction of CT, which only became available in early 1980s. Other diagnostic modalities have also greatly advanced over such long periods. In this regard, the present study more precisely reflected the contemporary stage-specific prognoses of patients with lung cancer, by limiting the time-dependent factors such as changes in patient evaluation and care.

An important finding in this study is that the stage-specific survival curves were in exactly the same order from stages IA–IV in both the c- and p-settings. These suggest that the present staging system could be used to successfully categorize patients into groups with similar prognostic properties and makes it possible to plan their treatment and predict the prognosis before and even after

Table 3 Pathological (postoperative) 5-year survival rate (%) reported in the literature with 1000 or more patients according to the 1997 TNM staging system

	Present series (2005)	Mountain [3]	Van Rens et al. [4]	Naruke et al. [5]	Fang et al. [6]
No. of patients	6644	5319	2361	3043	1905
Accumulation period (year)	1	14	23	34	35
Histology	Non-small cell	Non-small cell	Non-small cell	All	All
p-Stage					
IA	79.5	67	63	79	72
IB	60.1	57	46	59.7	61
IIA	59.9	55	52	56.9	32.9
IIB	42.2	39	33	45	34.5
IIIA	29.8	23	19	23.6	22.6
IIIB	19.3	–	–	16.5	15.9
IV	20.0	–	–	5.1	7.1

treatment. Therefore, in general, the present TNM staging system should be considered acceptable, except for a few points discussed below.

The survival noted in the present study was compared with that in previous reports as shown in Tables 2 and 3. Even though the same TNM staging system was used, the survival rate of stage IA, especially of pathological stage IA, was better in the present and Naruke's studies than in the others by approximately 10%: about 80% versus 70%. In contrast, for other stage categories, the difference in survival was not so remarkable. This might be attributed to a difference in surgical/pathological evaluations, especially for lymph nodes in the hilum and mediastinum. Hilar/mediastinal lymph node dissection was routinely performed in most teaching hospitals throughout Japan, which made nodal assessment more accurate after surgery. Therefore, the stage IA was more homogeneous, and its survival was estimated to be better. The difference in survival might be mainly explained by the stage migration, and the prognostic impact of nodal dissection is still unclear.

The most remarkable finding in the present study was the overlapping prognoses of patients with neighboring stages. Such overlap was seen between stages IB and IIA as well as between stages IIIB and IV. The former is a much more important, since the patients with resected stage IIIB and IV disease in this study might not represent the whole population of these stages. Despite the different stage categories, the survival curves of stages IB and IIA were almost superimposed, with 5-year survival rates of 49.9% and 48.7% (c-stage) and 60.1% and 59.9% (p-stage), respectively. There was no significant difference in survival for both the c- and p-settings. These findings clearly indicate that there is a need to revise the stage grouping. The current stages IB and IIA should be merged together into the same group as a new stage IB or IIA. In the former case, the current stage IIB is called new stage II without a subcategory. In the latter case, the current stage IA is to be called new stage I without a subcategory. Otherwise, the division of stage IB may generate two categories with two different prognoses. The better IB subcategory is defined as new stage IB, and the worse IB subcategory is defined as a new stage IIA, together with the current IIA. The subcategorization of the current IB according to a tumour diameter of 5 cm might be one idea, as has been described previously [7]. A discussion is underway to make a proposal for the next revision by the Committee.

One more important finding of the present study was the demonstration of several important factors which are closely related the prognosis of the patients with resected lung cancer. In this study, the prognostic significance of the gender, age and histologic type was clearly demonstrated in both univariate and multivariate analyses in these large populations. That is, the female patients of less than 70 years of age with adenocarcinoma histology had a significantly better survival than those without, and these findings corresponded to the former publications [8]. These findings might be important in the future trial involving resectable lung cancer when we stratify the patients by prognostic factors. In the present study, the histologic category as adenocarcinoma might have included bronchioloalveolar carcinoma (BAC). Since the BAC has been defined as the non-invasive, earlier form of adenocarcinoma since 1997, the better survival is being shown. However, we did not include BAC as an independent category in this registry study (all cases were resected before 1997), and its prognostic significance was not demonstrated. The future study should definitively include this category independently.

The limits of the present study must also be addressed. This retrospective registry only included resected cases. Generally, patients with advanced disease such as stages III and IV are not candidates for surgery, and chemoradiotherapy or chemotherapy is selected as standard care in such cases. Therefore, the patients in stages III and IV in this study did not represent the whole population of these stage groups. To clarify their "true" prognoses, it would be important to include unresected cases, which were excluded from this retrospective, questionnaire-based study. Another prospective registry is underway by the Japanese Joint Committee of Lung Cancer Registry, and the results should be available soon.

For the future scheduled revision of the TNM staging system in 2007 or some later date, the accumulation of a large volume of solid survival data and rational discussion are indispensable in the international community. The revision should also consider the case of use and the wide applicability of the system. Thus, the next few years should be an important time for future revisions in this area worldwide.

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