average of the recurrence-negative group, and having Mann-Whitney U-test P-values of <0.05 between the recurrence-negative group and the recurrence-positive A subgroup. A total of 721 probe sets were selected as DEG for A. Similarly, we obtained 274 probe sets as DEGs for B, which showed a >2-fold change and P-values of< 0.05 by the Mann-Whitney U-test, as compared with the recurrence-negative group.

Biological analysis of the DEG lists

We searched 171 and 33 enriched GO terms for DEGs determined for the A and B group, respectively, with the annotation analysis plug-in of the Subio platform (data not shown). We further analyzed these lists with the DAVID functional annotation web tool (http://david.abcc.ncifcrf.gov) and obtained the lists of enriched KEGG pathways (Tables I and II).

Table I

Patient information regarding the 24 adenocarcinoma samples.

Table II

Enriched pathways in group A.

Ethical considerations

Written informed consent was obtained from the patients for tissue procurement prior to surgery and their medical records were maintained according to protocols approved by the Institutional Review Board of Tokyo Medical University (no. 965).

Results

Patient information

As shown in Table I, there were 14 male and 10 female patients enrolled in this study. The mean age was 65.3 years (range, 42–76). The histological classifications were all adenocarcinoma; 14 were well/moderately differentiated and 10 were poorly differentiated. The distribution of clinical staging demonstrated that most of the patients were early-stage IAB cases. Histological differentiation was significantly correlated with early recurrence (P=0.026), whereas no significant correlations were found among pathological stages IA, IB and IIA (P=0.061).

Correlation of patient outcome with putative adenocarcinoma classes

We aimed to ascertain whether lung cancer patient outcome correlates with the subclasses of lung adenocarcinomas defined herein. Based on the results of PCA of this series, two adenocarcinoma subgroups were identified within the early-relapse group of early-stage adenocarcinoma cases, which differentially expressed a broad range of gene patterns (Fig. 1).

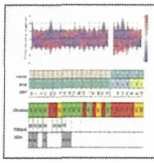

Figure 1

Principal component analysis correlated with differentiation and histological subtype. W, well differentiated; M, moderately differentiated; P, poorly differentiated; BAC, bronchio-alveolar carcinoma; pap, papillary carcinoma.

Statistical analysis of the microarray data, when compared with the non-early-relapse group C, revealed 723 genes with significant differences in expression in the samples of group A, whereas 274 genes showed significant differences in expression in samples of group B. We searched 171 and 33 altered GO terms for DEGs in the A and B lists, respectively, with the annotation analysis plug-in of the Subio platform (data not shown).

The histological classification of all samples of group A was poorly differentiated, whereas only one out of three cases in group B was classified as poorly differentiated. In this series of early-stage IA-IIA adenocarcinomas, no papillary or bronchio-alveolar carcinoma subtypes were associated with recurrence within 2 years after complete resection.

Biological function analysis

Tables II and III document the 16 and 17 enriched pathways in groups A and B, respectively. Clusters of genes related to oncological or immunological functional signaling were found enriched in group A as were pathways such as cell adhesion molecules (CAMs), cell cycle, and antigen processing and presentation. In group B, the pathways included CAMs, T cell receptor signaling, cytokine-cytokine receptor interaction, toll-like receptor signaling, chemokine signaling pathway, primary immunodeficiency and natural killer cell mediated cytotoxicity. The CAM pathway was found to be enriched in both groups A and B.

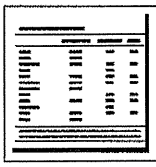

Table III

Enriched pathways in group B.

Discussion

The development of microarray technologies has made it possible to quantitate the expression of many thousands of genes simultaneously in a given sample (3,4). Comprehensive analysis of gene expression patterns in individual tumors should, therefore, provide detailed molecular portraits that can facilitate tumor classification. Several expression profiling studies concluded that expression profiles are distinctive and recapitulate known histological subtypes (5-7).

Genomic methods offer promise for the classification of human lung carcinomas. In one previous study, it is important to note that the performance of the adenocarcinoma classifier showed a better predictive accuracy than the squamous cell lung carcinoma (SCC) classifier (adenocarcinoma AUC = 0.83, SCC AUC = 0.68). This could have been due to the heterogeneity of the SCC samples as indicated by the two distinct subgroups showing differing clinical outcomes in this tumor type (9). Multiple independent studies of mRNA expression profiles in lung adenocarcinoma have proven highly reproducible. Analyses of the relationship between expression profiles and tumor development and differentiation, the presence or absence of specific pathogenic mutations, patient prognosis and survival after surgical treatment, and specific histopathology all appear to be promising (13).

Adenocarcinoma is currently the predominant histological subtype of NSCLC. NSCLC composes the majority of bronchogenic carcinoma cases with a lesser fraction being small-cell lung carcinomas. The three main subtypes of NSCLC are adenocarcinoma (60%), SCC (25%) and large-cell cancer (5%). Adenocarcinoma has replaced SCC as the most frequent histological subtype over the last 25 years (1,2,14). Therefore, we focused on adenocarcinoma of the lung, and particularly whether we could identify a novel prognostic signature of early recurrence in early-stage lung adenocarcinoma using cDNA microarray techniques.

The data indicated that patterns of gene expression obtained from cDNA microarray studies of crudely dissected lung tumors can be used to detect tumor subtypes that correlate with biological and clinical phenotypes. Specifically, patterns of gene expression were found that corresponded to the major morphological classes of lung tumors. In addition, we were able to define two subgroups of early recurrence in the adenocarcinoma cases that differed not only in gene expression patterns, but also in clinical and pathological properties, including histological differentiation and subtype. In the statistical analysis of microarray data, when compared with the non-early-recurrence group C, we revealed 723 genes with significant differences in expression in the samples of group A, whereas 274 genes showed significant differences in expression in group B. The differentially expressed genes were classified according to biological processes. We searched 171 and 33 enriched GO terms for DEGs for the A and B lists, respectively, with the annotation analysis plug-in of the Subio platform (data not shown).

Gene annotation enrichment analysis is a functional analysis technique that has gained widespread attention and for which many tools have been developed. The differentially expressed genes were classified according to biological processes and molecular functions using the functional annotation clustering tool of the DAVID bioinformatics resources. The DAVID functional clustering analysis revealed 16 significantly altered biological pathways in group A that included 3 distinct functionally related metastatic categories, specifically CAMs, cell cycle, and antigen processing and presentation. In group B, there were 17 significantly altered biological pathways, including 7 distinct functionally related metastatic categories. Notably, the CAM pathway was the most interrelated in both groups. In addition, the T cell receptor signaling pathway, cytokine-

cytokine receptor interaction, toll-like receptor signaling pathway, chemokine signaling pathway, primary immunodeficiency and natural killer cell mediated cytotoxicity were also altered (Tables II and III). These results suggest that the possibility of metastasis of early-stage lung adenocarcinoma was closely related to the CAM pathway. Interestingly, considering the relationship between group A or group B and histological differentiation as poor or well/moderate, respectively, the metastatic possibility of poorly differentiated early adenocarcinoma appeared to be correlated with tumor development factors, such as the cell cycle, whereas that of well/moderately differentiated early-stage adenocarcinoma appeared to be correlated with host immunological factors, such as the T cell receptor signaling pathway, cytokine-cytokine receptor interaction, the toll-like receptor signaling pathway, the chemokine signaling pathway, primary immunodeficiency and natural killer cell mediated cytotoxicity.

Our results suggest that the particular genes that define the clusters and molecular pathways, or that are associated with early recurrence, likely reflect the characteristics of the particular tumors included in the analysis. Current therapy for patients with early-stage disease usually consists of surgical resection without adjuvant treatment. Clearly, the identification of a high-risk group among early-stage patients would lead to consideration of additional therapeutic interventions, possibly leading to improved survival of these patients.

To our knowledge, this is the first study utilizing cDNA microarray techniques, followed by molecular functional pathway analysis, concerning the early recurrence of early-stage adenocarcinoma of the lung. However, there were some limitations to this study. Firstly, this was a small data set analysis at a single institute. A large cohort sample of patients from multiple institutions is needed. Secondly, the potential interactions of the many specific individual genes and their clusters in lung tumor biology and clinical outcome exist. This may be due to the different platforms used (different genes analyzed) and the different algorithms for selecting functional categories. Thirdly, hierarchical clustering methods and functional analysis offer a powerful approach to class discovery, but provide no means of determining validity for the classes discovered. This is still a putative functional analysis. It is important to state that several *in vitro* and *in vivo* studies are still needed to demonstrate whether these mechanisms are effective in reality.

In conclusion, in the present study, we present a comprehensive gene expression analysis and functional pathway analysis of early-stage lung adenocarcinomas, wherein we identified a distinct molecular pathway category, the CAMs, which correlated with the early relapse of early-stage lung adenocarcinoma subclasses. Further *in vitro* and *in vivo* studies, which can demonstrate these mechanisms, are warranted.

Acknowledgements

We are indebted to Dr Clifford A. Kolba, to Associate Professor Edward F. Barroga and to Professor J. Patrick Barron, Chairman of the Department of International Medical Communications of Tokyo Medical University, for their editorial review of the English manuscript. This study was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology (grant no. 21791332).

References

1 Sawabata N, Asamura H, Goya T, et al: Japanese Lung Cancer Registry Study: first prospective enrollment of a large number of surgical and nonsurgical cases in 2002. J Thorac Oncol. 5:1369–1375. 2010.

2 Asamura H, Goya T, Koshiishi Y, et al: A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J Thorac Oncol. 3:46–52. 2008.

3 Schena M, Shalon D, Davis RW and Brown PO: Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science. 270:467–470. 1995.

4 Chee M, Yang R, Hubbell E, et al: Accessing genetic information with high-density DNA arrays. Science. 274:610–614. 1996.

5 Beer DG, Kardia SL, Huang CC, et al: Gene-expression profiles predict survival of patients with lung adenocarcinoma. Nat Med. 8:816–824. 2002.

6

Bhattacharjee A, Richards WG, Staunton J, et al: Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. Proc Natl Acad Sci USA. 98:13790–13795. 2001.

7 Garber ME, Troyanskaya OG, Schluens K, et al: Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci USA. 98:13784–13789. 2001.

8 Wigle DA, Jurisica I, Radulovich N, et al: Molecular profiling of non-small cell lung cancer and correlation with disease-free survival. Cancer Res. 62:3005 –3008. 2002.

9 Raponi M, Zhang Y, Yu J, et al: Gene expression signatures for predicting prognosis of squamous cell and adenocarcinomas of the lung. Cancer Res. 66:7466–7472. 2006.

10 Lu Y, Yao R, Yan Y, et al: A gene expression signature that can predict green tea exposure and chemopreventive efficacy of lung cancer in mice. Cancer Res. 66:1956–1963. 2006.

11 Potti A, Mukherjee S, Petersen R, et al: A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med. 355:570–580. 2006.

12 Nakamura H, Saji H, Ogata A, et al: cDNA microarray analysis of gene expression in pathologic stage IA nonsmall cell lung carcinomas. Cancer. 97:2798–2805. 2003.

13 Meyerson M and Carbone D: Genomic and proteomic profiling of lung cancers: lung cancer classification in the age of targeted therapy. J Clin Oncol. 23:3219 –3226. 2005.

14 Sawabata N, Miyaoka E, Asamura H, et al: Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol. 6:1229–1235. 2011.

CHEST

Original Research

LUNG CANCER

Prognostic Factors and the Significance of Treatment After Recurrence in Completely Resected Stage I Non-small Cell Lung Cancer

Yoshihisa Shimada, MD, PhD; Hisashi Saji, MD, PhD; Koichi Yoshida, MD, PhD; Masatoshi Kakihana, MD, PhD; Hidetoshi Honda, MD, PhD; Masaharu Nomura, MD, PhD; Jitsuo Usuda, MD, PhD; Naohiro Kajiwara, MD, PhD; Tatsuo Ohira, MD, PhD; and Norihiko Ikeda, MD, PhD

Objective: **The objective of this study was to identify the clinicopathologic factors influencing postrecurrence survival (PRS) in and the effect of postrecurrence therapy (PRT) on patients with completely resected stage I non-small cell lung cancer (NSCLC).**

Methods: **We reviewed the data of 919 patients in whom complete resection of stage I NSCLC had been performed.**

Results: **Of the 919 patients, 170 (18.5%) had recurrent disease. Initial PRT was performed in 118 patients (69.1%) (surgery in eight, chemotherapy in 79, radiotherapy in 10, and chemoradiotherapy in 21). On multivariate analyses, PRT (hazard ratio [HR], 0.542; 95% CI, 0.344-0.853; $P = .008$), female sex (HR, 0.487; 95% CI, 0.297-0.801; $P = .005$), and differentiation (HR, 1.810; 95% CI, 1.194-2.743; $P = .005$) demonstrated a statistically significant association with favorable PRS. Bone metastasis (HR, 3.288; 95% CI, 1.783-6.062; $P < .001$), liver metastasis (HR, 4.518; 95% CI, 1.793-11.379; $P = .001$), chemotherapy (HR, 0.478; 95% CI, 0.236-0.975; $P = .040$), epidermal growth factor receptor-tyrosine kinase inhibitors treatment (EGFR-TKIs) (HR, 0.460; 95% CI, 0.245-0.862; $P = .015$), and nonadenocarcinoma (HR, 2.136; 95% CI, 1.273-3.585; $P = .004$) were independently and significantly associated with PRS in the 118 patients who underwent any PRT. Subgroup analysis with a combination of these five PRS factors in the patients who underwent any PRT revealed median PRS times of 42.4 months for 20 patients lacking all five risk factors and 18.8 months for 98 patients with at least one of these risk factors ($P = .001$).**

Conclusions: **PRT, sex, and differentiation were independently associated with PRS. In the patients who underwent any PRT, PRS was related to EGFR-TKIs, chemotherapy, histology, and initial recurrence sites. One challenge for the future will be to create systematic treatment strategies for recurrent NSCLC according to the risk factor status of individual patients.**

CHEST 2013; 143(6):1626–1634

Abbreviations: EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; HR = hazard ratio; NSCLC = non-small cell lung cancer; PRS = postrecurrence survival; PRT = postrecurrence therapy; PS = performance status; RFP = recurrence-free proportion

Surgical resection with a curative intent is considered the standard of care for early stage non-small cell lung cancer (NSCLC), but > 20% of patients had recurrence, even in pathologic stage I cases.[1-6] Recurrence after complete resection for stages I to III of NSCLC ranges from 30% to 75%, and has been reported to depend on pathologic staging and follow-up period.[1,6-8] The majority of recurrences occur within the first 2 years,[1,6] although there are several studies showing late recurrences ≥ 5 years after resection.[9-11] Long-term, continuous follow-up is required to establish accurate recurrence rates and patterns.

Although several studies focusing on postrecurrence survival (PRS) of patients in stage I or stage I-III NSCLC have been reported,[2-4,8,12-14] no standard treatment strategy for recurrent disease based on prospective studies has been established. However, a standard treatment strategy is necessary because much longer

follow-up periods and robust protocols are required to evaluate PRS objectively. It is difficult to generalize about multifactorial patient backgrounds, which depend on disease, treatment, and performance status (PS) at recurrence. The prognostic factors predicting PRS or the appropriate treatment are still controversial.

Encouraging new treatments (including epidermal growth factor receptor-tyrosine kinase inhibitors [EGFR-TKIs], anaplastic lymphoma kinase inhibitors, pemetrexed, and bevacizumab) have afforded benefits to certain patients with advanced or recurrent NSCLC.[15-21] Advances in postrecurrence therapy (PRT) may provide improvement in overall survival among the patients who undergo surgery. The objective of the present study was to identify the clinicopathologic factors influencing PRS and their effect of PRT on stage I NSCLC.

Materials and Methods

From January 1990 through December 2007, 1,214 patients underwent complete resection for pathologic stage I NSCLC at our hospital. Complete resection was defined as demonstrating cancer-free surgical margins, both grossly and histologically. All patients underwent radical, anatomic, lobar resection and systematic, mediastinal lymph node dissection. The following exclusion criteria were applied: preoperative chemotherapy, radiation therapy, or both (n = 38); low-grade malignant tumors, including carcinoids, mucoepidermoid carcinomas, or adenoid cystic carcinomas (n = 20); and death within 30 days of operation (n = 9). Of the remaining 1,147 patients, complete follow-up was available for 919 patients, who composed the subjects of this study.

Preoperative evaluation included physical examination, chest radiography, CT scan of the chest and abdomen, bone scintigraphy, blood examination, and, since the early 2000s, PET scan (recently integrated PET-CT scan). Histologic subtypes of lung cancer were determined according to the World Health Organization classification,[22] and disease stage was determined in accordance with the *TNM Classification for Lung and Pleural Tumours*, 7th ed.[23]

The follow-up schedule consisted of a clinic visit every 3 months in the first year after resection, every 6 months from the second to the fifth year, and annually thereafter on an outpatient basis, and aimed at continuing follow-up for 10 years after resection. Follow-up procedures included physical examination, chest radiography, and blood examination (including serum tumor markers). CT scans of the chest and abdomen was performed every 6 months in the first 2 years, and annually from the third to the fifth year. Whenever any symptoms or signs of recurrence were detected, MRI of the brain and bone scintigraphy were performed.

Recurrences were diagnosed by physical examination and diagnostic imaging. Histologic or cytologic confirmation of the recurrence was made when clinically feasible. Local recurrence was defined as disease recurrence at the surgical margin, ipsilateral hemithorax, or mediastinum. Radiographic lymph node recurrence was defined as enlarged lymph nodes measuring > 1 cm on the short axis by CT scan and/or hypermetabolic lymph nodes on PET-CT scans. Pathologic confirmation of recurrence was made by endobronchial ultrasound-guided transbronchial needle aspiration of enlarged lymph nodes during follow-up. Distant metastasis was defined as disease recurrence in the contralateral lung or outside the hemithorax and mediastinum. A second primary tumor was recorded when a patient presented with a new histologic type, and with clinical features consistent with a new primary tumor. Data collected from our department database of patients, telephone interviews, and correspondence from outside sources during the follow-up periods were included.

Clinical characteristics were retrieved from available clinical records. The following clinicopathologic factors were assessed in the PRS analysis: age, sex, smoking status, primary tumor status (T1 vs T2), tumor size (0-30 mm vs > 30 mm), tumor differentiation (well/moderate vs poor), pathologic vascular invasion, pleural invasion, histology (adenocarcinoma vs others), and extent of resection (single lobe lobectomy vs more extensive resection, namely bilobectomy/pneumonectomy).

Length of the recurrence-free period was calculated in months from date of resection to date of initial recurrence or last follow-up showing no recurrence. To calculate the recurrence-free proportion (RFP), patients who died without recognized recurrence or who were known to have no recurrence at the date of last contact were censored. Length of PRS was measured from date of initial recurrence to date of death from any cause or date on which the patient was last known to be alive. PRS and RFP curves were plotted using the Kaplan-Meier method, and differences in variables were determined using the log-rank test or the Breslow tests. Categorical comparison was performed using the χ^2 test for discrete data and Student *t* test for continuous data. Multivariate analyses were performed using the Cox proportional hazards regression model. A backward stepwise selection procedure was implemented. All tests were two-sided, and *P* values < 0.05 were considered to indicate a statistically significant difference. Statview 5.0 software (SAS Institute Inc) was used for statistical analyses.

Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived, by the institutional review board at Tokyo Medical University (No. 2133).

Results

Median follow-up time for survivors was 62.0 months (range: 1.4-247.6 months). The RFP was 82.2% at 5 years after operation. Of the 919 patients, 170 (18.5%) had recurrent disease, with a median age of 66 years at the time of initial recurrence. Median PRS time for these patients was 17.6 months (range: 0.4-103.0 months). The 1- and 2-year PRS proportions were 73.5% and 51.4%, respectively (Fig 1).

Table 1 shows 5-year RFPs and univariate/multivariate analyses of recurrence according to clinicopathologic characteristics of patients with stage I NSCLC. Univariate analysis identified five significant risk factors:

Manuscript received July 10, 2012; revision accepted November 26, 2012.

Affiliations: From the Department of Surgery I, Tokyo Medical University Hospital, Tokyo, Japan.

Funding/Support: This study was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology [24592104] and the Ministry of Health, Labor and Welfare [22101601].

Correspondence to: Yoshihisa Shimada, MD, PhD, Department of Surgery I, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan; e-mail: zenkyu@za3.so-net.ne.jp

DOI: 10.1378/chest.12-1717

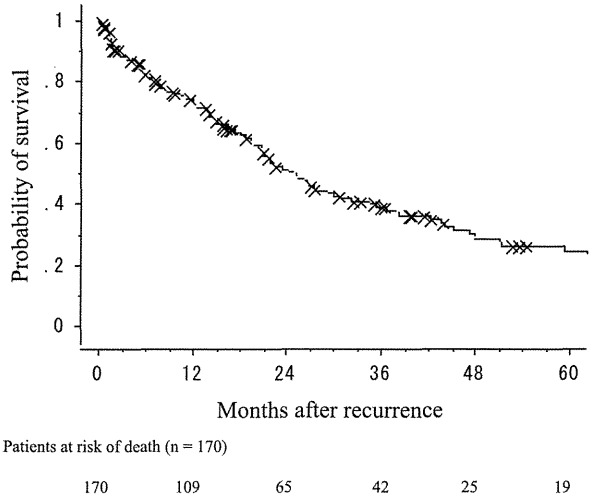

FIGURE 1. Postrecurrence survival curve of patients with non-small cell lung cancer recurrence.

male sex, pathologic vascular invasion, pleural invasion, poorly differentiated carcinoma, and nonadenocarcinoma. Multivariate analysis demonstrated that pathologic vascular invasion (hazard ratio [HR], 2.306; 95% CI, 1.621-3.280; $P < .001$), pleural invasion (HR, 1.489; 95% CI, 1.048-2.115; $P = .026$), and poorly differentiated carcinoma (HR, 1.842; 95% CI, 1.328-2.555; $P < .001$) were statistically significant predictors of recurrence.

Initial recurrence sites and PRT are shown in Table 2. Type of recurrence included only local recurrence in 43 patients (25.3%), distant in 113 (66.5%), and both in 14 (8.2%). Most commonly involved organs were the lung (the site of recurrence in 66 patients: ipsilateral in 23, contralateral/bilateral in 43), followed by regional lymph nodes in 37, brain in 30, bone in 21, and liver in 16. Initial PRT was performed in 118 patients (69.4%), and included surgery for 8, chemotherapy for 79, radiotherapy for 10, and chemoradiotherapy for 21. Surgical resections (n = 8) were performed in three patients with solitary pulmonary metastasis, three with solitary brain metastasis, one with adrenal gland metastasis, and one with chest wall and axillary lymph node involvement. Forty-one patients (24.1%) had no treatment for recurrent disease. Of the 118 patients who underwent any PRT, 66 (55.9%) underwent second-line or subsequent therapy, including

Table 1—*Patient Characteristics and Univariate and Multivariate Analyses of Recurrence*

	Univariate Analysis			Multivariate Analysis		
Factors	Patients, No.	5-y RFP, %	*P* Value	HR	95% CI	*P* Value
Age,[a] y						
< 65	439	84.1	...	...	...	...
≥ 65	480	80.4	.129	...	...	...
Sex						
Male	542	78.0	...	...	...	...
Female	377	87.8	< .001	...	...	...
Smoking status						
Never smoker	347	85.2	.134	...	...	...
Ever smoker	572	80.2	...	...	...	...
T category						
T1	512	84.7	...	...	...	...
T2	407	78.9	.100	...	...	...
Tumor size						
0-30 mm	663	84.0	...	...	...	...
> 30 mm	256	81.5	.112	...	...	...
Pathologic vascular invasion						
Absent	481	91.0	...	1	...	...
Present	421	72.1	< .001	2.306	1.621-3.280	< .001
Pleural invasion						
Absent	719	84.9	...	1	...	...
Present	191	71.8	< .001	1.489	1.048-2.115	.026
Histology						
Adenocarcinoma	706	83.8	...	...	...	...
Nonadenocarcinoma	213	76.3	.039	...	...	...
Differentiation						
Well or moderate	656	86.7	...	1	...	...
Poor	216	67.7	< .001	1.842	1.328-2.555	< .001
Type of surgery						
Single lobectomy	873	81.9	...	...	...	...
Bilobectomy or pneumonectomy	46	87.2	.942	...	...	...

HR = hazard ratio; RFP = recurrence-free proportion.
[a]Median age = 65 y.

Table 2—*Initial Recurrence Site and Postrecurrence Therapy*

Data of Recurrence Sites and Postrecurrence Therapies	Patients, No.
Overall	170
Type of recurrence	
Distant	113
Local	43
Both	14
Initial recurrence site	
Ipsilateral lung	23
Contralateral/bilateral lung	43
Regional lymph nodes	37
Malignant effusion/dissemination	13
Stump	9
Brain	30
Bone	21
Liver	16
Adrenal gland	10
Others	14
Postrecurrence therapy	
Initial therapy	
Surgery	8 (lung, 3; brain, 3; adrenal gland, 1; lymph nodes, 1)
Surgery alone	6
Surgery + chemotherapy	3
Chemotherapy	79
Radiation therapy	10
Chemoradiotherapy	21
None	41
Unknown	11
Second-line or the subsequent therapy	66
Chemotherapy	58
EGFR-TKIs	27 (gefitinib, 22; erlotinib, 3; both, 2)
EGFR mutation status/histology	Positive 12 (Ad, 11; Sq, 1) Wild 4 (Ad, 3; LCC, 1) Unknown 11 (Ad, 10; LCC, 1)
Others	7

Ad = adenocarcinoma; EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; LCC = large cell carcinoma; Sq = squamous cell carcinoma.

chemotherapy for 58, and EGFR-TKIs for 27 (gefitinib, 22 patients; erlotinib, three patients; and both, two patients). Among the latter 27 patients, *EGFR* mutations were detected in 12; four had wild-type *EGFR*.

Table 3 shows univariate/multivariate analyses of PRS. Univariate analysis identified six significant risk factors for PRS: male sex, smoking, poorly differentiated carcinoma, nonadenocarcinoma, no PRT, and shorter recurrence-free interval (≤ 24 months; median recurrence-free period was 24 months). Multivariate analysis demonstrated that PRT (HR, 0.542; 95% CI, 0.344-0.853; $P = .008$), female sex (HR, 0.487; 95% CI, 0.297-0.801; $P = .005$), and differentiation (HR, 1.810; 95% CI 1.194-2.743; $P = .005$) had a statistically significant association with favorable PRS.

The results of multivariate analysis of PRS determined that PRT had a strong impact on PRS. Therefore, we further examined PRS in the 118 patients who underwent any PRT (Table 4). Univariate analysis identified nine significant risk factors for PRS: male sex, smoking, poorly differentiated carcinoma, bone metastasis, liver metastasis, no chemotherapy or EGFR-TKI, no second-line therapy, and multiple organ metastases. Multivariate analysis demonstrated that bone metastasis (HR, 3.288; 95% CI, 1.783-6.062; $P < .001$), liver metastasis (HR, 4.518; 95% CI, 1.793-11.379; $P = .001$), chemotherapy (HR, 0.478; 95% CI, 0.236-0.975; $P = .040$), EGFR-TKI therapy (HR, 0.460; 95% CI, 0.245-0.862; $P = .015$), and nonadenocarcinoma (HR, 2.136; 95% CI, 1.273-3.585; $P = .004$) had a statistically significant association with PRS.

Subgroup analysis with a combination of these five PRS factors (no EGFR-TKI and chemotherapy, presence of liver or bone metastasis, nonadenocarcinoma) in patients with recurrence who underwent any PRT revealed median PRS times of 42.4 months for 20 patients lacking all five unfavorable factors and 18.8 months for 98 patients with one of these risk factors, respectively (Fig 2). The difference in PRS was statistically significant between the two groups ($P = .001$).

Discussion

We set out to identify clinicopathologic factors influencing PRS of patients with stage I NSCLC. Although curative surgical resection is the most effective therapy for stage I NSCLC, a considerable number of patients will develop recurrence. In the current study, overall incidence of recurrence was 18.5%, and median PRS time was 17.6 months. Initial location of recurrence was at a distant site in 74.7%, and the proportions of recurrences within 2 or 3 years after surgery were 48.2% and 66.5%, respectively (unpublished data). Previous studies have reported that the incidence of recurrence in patients with stage I NSCLC was 14% to 36%, with the 1-year survival rate ranging from 30% to 68% (Table 5).[1-6,8,24]

We examined risk factors for recurrence in stage I NSCLC, and identified three: pathologic vascular invasion, pleural invasion, and poorly differentiated carcinoma. These standard pathologic factors have also been reported to be good predictors of overall survival for patients with stage I NSCLC.[25-36] In our study, univariate analysis for PRS identified six significant risk factors (male sex, smoking, poorly differentiated carcinoma, nonadenocarcinoma, no PRT, and shorter recurrence-free interval [≤ 24 months]), while multivariate analysis revealed that sex, PRT, and differentiation were independent prognostic factors. Only differentiation was a significant predictor of recurrence and poor PRS, and pathologic vascular invasion and pleural invasion had no significant impact on PRS. PRS may be associated

Table 3—*PRS Analyses*

Factors	Univariate Analysis			Multivariate Analysis		
	Patients, No.	Median PRS, mo	*P* Value	HR	95% CI	*P* Value
Age at recurrence,[a] y						
< 66	76	18.9	...	...	...	...
≥ 66	94	15.8	.242	...	...	...
Sex						
Male	118	15.5	...	1	...	...
Female	52	25.6	< .001	0.487	0.297-0.801	.005
Smoking status						
Never smoker	59	25.0	...	...	...	...
Ever smoker	111	14.1	.006	...	...	...
T category						
T1	87	15.8	...	...	...	...
T2	83	19.6	.476	...	...	...
Tumor size						
0-30 mm	132	16.9	...	...	...	...
> 30 mm	38	20.9	.632	...	...	...
Pathologic vascular invasion						
Absent	53	15.8	...	...	...	...
Present	113	17.0	.088	...	...	...
Pleural invasion						
Absent	115	15.8	...	...	...	...
Present	53	18.8	.393	...	...	...
Histology						
Adenocarcinoma	124	20.9	...	...	...	...
Nonadenocarcinoma	46	12.4	< .001	...	...	...
Differentiation						
Well or moderate	97	20.8	...	1	...	...
Poor	65	14.1	.002	1.810	1.194-2.743	.005
Type of surgery						
Single lobectomy	162	17.3	.152	...	...	...
Bilobectomy or pneumonectomy	8	19.5	...	...	...	...
Adjuvant therapy						
Without	134	15.9	.547	...	...	...
With	36	21.0	...	...	...	...
Postrecurrence therapy						
Without	41	7.2	...	1	...	...
With	118	21.4	.021	0.542	0.344-0.853	.008
Recurrence free interval						
≤ 24 mo	82	16.2	...	...	...	...
> 24 mo	88	18.4	.021	...	...	...
Type of recurrence						
Distant	127	15.8	...	...	...	...
Local only	43	18.8	.087	...	...	...
Number of recurrent sites						
Single	132	16.8	...	...	...	...
Multiple	38	18.6	.305	...	...	...

PRS = postrecurrence survival. See Table 1 legend for expansion of other abbreviations.
[a]Median age at recurrence = 66 y.

with recurrent disease characteristics, including the recurrence site, PRT, recurrence-free interval, or PS at time of recurrence, rather than with the biologically aggressive characteristics of lung cancer.

Previous studies have demonstrated the survival benefit of PRT in patients with stage I NSCLC. Nakagawa et al[4] and Hung et al[2,3] demonstrated that patients with stage I NSCLC treated either surgically or nonsurgically had a significantly better PRS than those with supportive care alone. In our study, PRT provided a more favorable PRS than that of no treatment, similarly to previous reports. However, the results of PRS in the patients who underwent any PRT showed that surgical resection was not related to a favorable outcome. This may have been because the number of patients who received surgery for recurrent disease was too small to provide any supportive data in terms of survival benefit. However, in cases of surgical resection for recurrent lung metastasis, objective evidence supporting the role of surgery is limited because it

Table 4—*PRS Analyses in 118 Patients Who Underwent Postrecurrence Therapy*

Factors	Univariate Analysis			Multivariate Analysis		
	Patients, No.	Median PRS, mo	*P* Value	HR	95% CI	*P* Value
Age at recurrence, y						
< 66	63	22.4	...	...	...	...
≥ 66	55	19.5	.151	...	...	...
Sex						
Male	79	20.0	...	...	...	...
Female	39	27.2	.002	...	...	...
Smoking status						
Never smoker	43	27.6	...	...	...	...
Ever smoker	75	17.6	.035	...	...	...
Histology						
Adenocarcinoma	84	24.4	...	1	...	...
Nonadenocarcinoma	34	13.9	< .001	2.136	1.273-3.585	.004
Differentiation						
Well or moderate	66	23.1	...	...	...	...
Poor	46	18.8	.019	...	...	...
Lung metastasis						
Absent	68	19.8	...	...	...	...
Present	49	21.4	.053	...	...	...
Brain metastasis						
Absent	96	19.6	...	...	...	...
Present	21	22.6	.584	...	...	...
Bone metastasis						
Absent	100	21.9	...	1	...	...
Present	17	15.8	.001	3.288	1.783-6.062	< .001
Liver metastasis						
Absent	110	21.9	...	1	...	...
Present	7	10.5	.001	4.518	1.793-11.379	.001
Chemotherapy						
Without	15	9.6	...	1	...	...
With	103	22.7	.009	0.478	0.236-0.975	.040
Surgical resection						
Without	110	20.8	...	...	...	...
With	8	33.7	.209	...	...	...
EGFR-TKI therapy						
Without	91	17.0	...	1	...	...
With	27	41.4	.002	0.460	0.245-0.862	.015
Second line therapy						
Without	52	14.0	...	...	...	...
With	66	27.2	.004	...	...	...
Recurrence free interval						
≤ 24 mo	59	17.0	...	...	...	...
> 24 mo	59	22.4	.394	...	...	...
Type of recurrence						
Distant	85	20.8	...	...	...	...
Local only	33	21.8	.086	...	...	...
Number of recurrent sites						
Single	89	21.0	...	...	...	...
Multiple	29	20.8	.049	...	...	...

See Table 1 and 3 legends for expansion of abbreviations.

may be difficult to distinguish second primary tumors from recurrent pulmonary metastasis. Advances in genomic analysis, molecular biologic tools, or diagnostic imaging may enable more accurate diagnosis of a solitary pulmonary lesion.

Among the cohort of 118 patients with any PRT, we identified five independent favorable prognostic factors of PRS by multivariate analysis: the absence of bone or liver metastasis, chemotherapy, EGFR-TKI therapy, and nonadenocarcinoma. Moreover, the result of the study showed an important aspect of a prognostic-factor based risk stratification. Median PRS times were 42.4 months for the patients lacking all five factors and 18.8 months for the patients with one of these risk factors ($P = .001$).

Some authors have found that the site of initial recurrence was a prognostic factor for PRS, which agrees with the current study. Yoshino et al[8] demonstrated

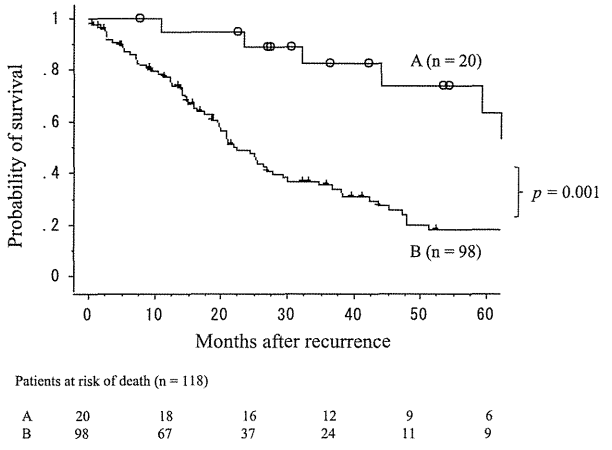

FIGURE 2. Postrecurrence survival curves of the patients lacking (A) all five unfavorable factors (not receiving epidermal growth factor receptor-tyrosine kinase inhibitor therapy and chemotherapy, liver or bone metastasis positive, nonadenocarcinoma), and (B) the patients with one of the five risk factors.

that bone metastasis was a marginally prognostic factor for PRS in patients with stage I-III NSCLC at the first resection. Assessment of bone metastatic type, osteoblastic or osteolytic, may be important as a part of postrecurrence therapeutic strategy because it has been noted that osteoblastic tumors lead to both a better prognosis and activating *EGFR* mutation presence.[37]

Major advances in NSCLC management have resulted from the understanding of molecular biology, development of molecule-targeting agents, and identification of biomarkers for targeted treatment. Since 2002, gefitinib has been used in Japan for the treatment of inoperable or recurrent NSCLC, and we started to administer it around the same period. It is now felt that EGFR-TKIs can improve the survival of some previously treated and untreated patients with advanced NSCLC, with the overall benefit being driven primarily by the subgroup with *EGFR* mutations.[15-17,38,39] EGFR-TKIs have also improved endurance and health-related quality of life compared with platinum-based doublet chemotherapy.[15-17] EGFR-TKIs are, therefore, good candidates for first-line PRT in patients who have had resected adenocarcinoma with distant metastases, but only in those with *EGFR* mutations.

There are several limitations in the present study. This study is retrospective, and bias may exist. First, patient-selection bias regarding PRT was unavoidable. Curative intent therapy or systematic treatment is difficult to perform in patients with poor PS. In the current study, PS or comorbidities at the time of recurrence were not accurately evaluated. Second, distinguishing second primary tumors from recurrent pulmonary metastasis was difficult. Even if a pathologic specimen was obtained, definitive diagnosis could be difficult under the current morphology-based diagnostic criteria. Third, complete follow-up was not available for all eligible patients.

There are presently no clinical guidelines for PRT regarding resected NSCLC based on large-scale prospective studies. Molecularly targeted therapy, chemotherapeutic regimens, and surgical strategies have evolved substantially over the decades. A challenge for the future will be to create systematic treatment strategies for recurrent NSCLC according to the individual patient's recurrent-disease characteristics, including the initial recurrence site, age, sex, PS, or recurrence-free interval, and original tumor characteristics.

CONCLUSION

This study showed that male sex, the absence of PRT, and poorly differentiated carcinoma were independent unfavorable prognostic factors of PRS in patients

Table 5—*PRS of Patients With Stage I Non-small Cell Lung Cancer in Previous Series*

Series/Year	Patients, No.	Incidence of Recurrence, No. (%)	PRS, % (y)	Type of Recurrence	Independent Favorable Factors of PRS
Martini et al[6]/1995	598	159 (26.6)	NR	L/D	NR
al-Kattan et al[1]/1997	123	36 (29.3)	NR	L/D	NR
Nakagawa et al[4]/2008	397	87 (21.9)	67.7 (1)	L/D	Symptom at recurrence, negative
			34.4 (3)		Cervicomediastinum metastases, negative
					Liver metastases, negative
					PRT (surgery/nonsurgery)
Hung et al[2]/2009	933	74 (7.9)	48.7 (1)	L	PRT (surgery, chemotherapy, and/or radiotherapy)
			17.6 (2)		
Hung et al[3]/2010	933	166 (17.8)	30.2 (1)	D	Disease-free interval > 16 mo
			15.1 (2)		PRT
Current series/2013	919	170 (18.5)	73.5 (1)	L/D	PRT
			51.4 (2)		Female sex

D = distant recurrence; L = local recurrence, NR = not reported; PRT = postrecurrence therapy. See Table 3 legend for expansion of other abbreviation.

with resected stage I NSCLC. Moreover, in patients who underwent any PRT, who were receiving EGFR-TKIs and chemotherapy, and with absence of liver or bone metastasis, and with nonadenocarcinoma had a statistically significant association with favorable PRS. Further clinical studies may give more accurate information about the benefits of PRT for survival and lead to the improvement of clinical assessment and therapeutic strategies in recurrent NSCLC.

Acknowledgments

Author contributions: Dr Shimada had full access to all of the data in the study. Dr Saji takes responsibility for the accuracy of the data analysis and Dr Ikeda takes responsibility for the integrity of the data.
Dr Shimada: contributed to the design and coordination of the study, prepared the manuscript, read and approved the final manuscript, and served as principal author.
Dr Saji: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Yoshida: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Kakihana: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Honda: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Nomura: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Usuda: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Kajiwara: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Ohira: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Ikeda: contributed to the design and coordination of the study, revised the article for important intellectual content, and read and approved the final manuscript.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.
Other contributions: The authors thank Clifford A. Kolba, PhD, and J. Patrick Barron, PhD, chairman of the Department of International Medical Communications of Tokyo Medical University, for their editorial review of the English manuscript.

References

1. al-Kattan K, Sepsas E, Fountain SW, Townsend ER. Disease recurrence after resection for stage I lung cancer. *Eur J Cardiothorac Surg*. 1997;12(3):380-384.
2. Hung JJ, Hsu WH, Hsieh CC, et al. Post-recurrence survival in completely resected stage I non-small cell lung cancer with local recurrence. *Thorax*. 2009;64(3):192-196.
3. Hung JJ, Jeng WJ, Hsu WH, et al. Prognostic factors of post-recurrence survival in completely resected stage I non-small cell lung cancer with distant metastasis. *Thorax*. 2010;65(3):241-245.
4. Nakagawa T, Okumura N, Ohata K, Igai H, Matsuoka T, Kameyama K. Postrecurrence survival in patients with stage I non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2008;34(3):499-504.
5. Harpole DH Jr, Herndon JE II, Young WG Jr, Wolfe WG, Sabiston DC Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. *Cancer*. 1995;76(5):787-796.
6. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg*. 1995;109(1):120-129.
7. Martin J, Ginsberg RJ, Venkatraman ES, et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. *J Clin Oncol*. 2002;20(8):1989-1995.
8. Yoshino I, Yohena T, Kitajima M, et al. Survival of non-small cell lung cancer patients with postoperative recurrence at distant organs. *Ann Thorac Cardiovasc Surg*. 2001;7(4):204-209.
9. Maeda R, Yoshida J, Hishida T, et al. Late recurrence of non-small cell lung cancer more than 5 years after complete resection: incidence and clinical implications in patient follow-up. *Chest*. 2010;138(1):145-150.
10. Martini N, Rusch VW, Bains MS, et al. Factors influencing ten-year survival in resected stages I to IIIa non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 1999;117(1):32-36.
11. Okada M, Nishio W, Sakamoto T, Harada H, Uchino K, Tsubota N. Long-term survival and prognostic factors of five-year survivors with complete resection of non-small cell lung carcinoma. *J Thorac Cardiovasc Surg*. 2003;126(2):558-562.
12. Endo C, Sakurada A, Notsuda H, et al. Results of long-term follow-up of patients with completely resected non-small cell lung cancer. *Ann Thorac Surg*. 2012;93(4):1061-1068.
13. Sugimura H, Nichols FC, Yang P, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. *Ann Thorac Surg* 2007;83(2):409-417.
14. Williams BA, Sugimura H, Endo C, et al. Predicting post-recurrence survival among completely resected nonsmall-cell lung cancer patients. *Ann Thorac Surg*. 2006;81(3):1021-1027.
15. Maemondo M, Inoue A, Kobayashi K, et al; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380-2388.
16. Mitsudomi T, Morita S, Yatabe Y, et al; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11(2):121-128.
17. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947-957.
18. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012;13(3):247-255.
19. Reck M, von Pawel J, Zatloukal P, et al; BO17704 Study Group. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol*. 2010;21(9):1804-1809.
20. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355(24):2542-2550.
21. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26(21):3543-3551.
22. Travis WD, Brambilla E, Muller-Hermelink HK, et al. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart*. Lyon, France: IARC Press; 2004.

23. International Union Against Cancer. *TNM Classification of Malignant Tumours*. 7th ed. Oxford, England: Wiley-Blackwell; 2009.
24 Jones DR, Daniel TM, Denlinger CE, et al. Stage IB nonsmall cell lung cancers: are they all the same? *Ann Thorac Surg*. 2006;81(6):1958-1962.
25. Bréchot JM, Chevret S, Charpentier MC, et al. Blood vessel and lymphatic vessel invasion in resected nonsmall cell lung carcinoma. Correlation with TNM stage and disease free and overall survival. *Cancer*. 1996;78(10):2111-2118.
26. Ichinose Y, Yano T, Asoh H, Yokoyama H, Yoshino I, Katsuda Y. Prognostic factors obtained by a pathologic examination in completely resected non-small-cell lung cancer. An analysis in each pathologic stage. *J Thorac Cardiovasc Surg*. 1995; 110(3):601-605.
27. Kobayashi N, Toyooka S, Soh J, et al. Risk factors for recurrence and unfavorable prognosis in patients with stage I non-small cell lung cancer and a tumor diameter of 20 mm or less. *J Thorac Oncol*. 2007;2(9):808-812.
28. Maeda R, Yoshida J, Ishii G, et al. Long-term survival and risk factors for recurrence in stage I non-small cell lung cancer patients with tumors up to 3 cm in maximum dimension. *Chest*. 2010;138(2):357-362.
29. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Prognostic impact of intratumoral vascular invasion in non-small cell lung cancer patients. *Thorax*. 2010;65(12): 1092-1098.
30. Maeda R, Yoshida J, Ishii G, et al. Poor prognostic factors in patients with stage IB non-small cell lung cancer according to the seventh edition TNM classification. *Chest*. 2011; 139(4):855-861
31. Miyoshi K, Moriyama S, Kunitomo T, Nawa S. Prognostic impact of intratumoral vessel invasion in completely resected pathologic stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2009;137(2):429-434.
32. Ruffini E, Asioli S, Filosso PL, et al. Significance of the presence of microscopic vascular invasion after complete resection of Stage I-II pT1-T2N0 non-small cell lung cancer and its relation with T-Size categories: did the 2009 7th edition of the TNM staging system miss something? *J Thorac Oncol* 2011;6(2):319-326.
33. Shimada Y, Ishii G, Hishida T, Yoshida J, Nishimura M, Nagai K. Extratumoral vascular invasion is a significant prognostic indicator and a predicting factor of distant metastasis in non-small cell lung cancer. *J Thorac Oncol*. 2010;5(7):970-975.
34. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2005;130(1):160-165.
35. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion classification in non-small cell lung cancer: a proposal on the basis of outcome assessment. *J Thorac Cardiovasc Surg*. 2004;127(6):1574-1578.
36. Tsuchiya T, Akamine S, Muraoka M, et al. Stage IA non-small cell lung cancer: vessel invasion is a poor prognostic factor and a new target of adjuvant chemotherapy. *Lung Cancer*. 2007;56(3):341-348.
37. Garfield D, Normanno N, Cadranel J. Prognostic factor for non-small cell lung cancer with bone metastases at the time of diagnosis. *Lung Cancer*. 2012;78(2):168.
38. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129-2139.
39. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497-1500.

CHEST Original Research
LUNG CANCER

A Proposal for Combination of Total Number and Anatomical Location of Involved Lymph Nodes for Nodal Classification in Non-small Cell Lung Cancer

Hisashi Saji, MD, PhD; Masahiro Tsuboi, MD, PhD; Yoshihisa Shimada, MD, PhD; Yasufumi Kato, MD, PhD; Koichi Yoshida, MD, PhD; Masaharu Nomura, MD, PhD; Jun Matsubayashi, MD, PhD; Toshitaka Nagao, MD, PhD; Masatoshi Kakihana, MD, PhD; Jitsuo Usuda, MD, PhD; Naohiro Kajiwara, MD, PhD; Tatsuo Ohira, MD, PhD; and Norihiko Ikeda, MD, PhD

Background: **We previously reported the prognostic impact of the number of involved lymph nodes (LNs) on survival in non-small cell lung cancer (NSCLC). However, it remains unknown whether the total number or anatomic location of involved LNs is a superior prognostic factor.**
Methods: **A total of 689 patients with NSCLC who underwent complete resection involving dissection of the hilar and mediastinal LNs with curative intent of ≥ 10 LNs were enrolled. The association between the total number of LNs (nN) involved and survival was assessed by comparison with the anatomic location of LN involvement (pathologic lymph node [pN]), the present nodal category.**
Results: **We classified the patients into five categories according to the combined pN and nN status as follows: pN0-nN0, pN1-nN1-3, pN1-nN4−, pN2-nN1-3, and pN2-nN4. Although there was no statistically significant difference between the pN1-nN4− and pN2-nN1-3 categories, pN2-nN1-3 had better prognoses than pN1-nN4−. On multivariate analysis, the nN category was an independent prognostic factor for overall survival and disease-free survival (vs nN4−; the hazard ratios of nN0 and nN1-3 for overall survival were 0.223 and 0.369, respectively, $P < .0001$ for all), similar to the pN category. We propose a new classification based on a combination of the pN and nN categories: namely, N0 becomes pN0-nN0, the N1 category becomes pN1-nN1-3, the N2a category becomes pN2-nN1-3 + pN1-nN4−, and the N2b category becomes pN2-nN4. Each survival curve was proportional and was well distributed among the curves.**
Conclusions: **A combined anatomically based pN stage classification and numerically based nN stage classification is a more accurate prognostic determinant in patients with NSCLC, especially in the prognostically heterogeneous pN1 and pN2 cases. Further large-scale international cohort validation analyses are warranted.** ***CHEST 2013; 143(6):1618–1625***

Abbreviations: DFS = disease-free survival; LN = lymph node; nN = number of lymph nodes; NSCLC = non-small cell lung cancer; OS = overall survival; pN = pathologic lymph node; pT = pathologic tumor

Various pathologic and molecular markers have been assessed regarding their usefulness in identifying patients at high risk for recurrence. However, the TNM system remains the most important determinant of staging. Because the prognosis of lung cancer is directly proportional to the presence of lymph node (LN) metastasis, accurate LN assessment is crucial in determining treatment. Accurate staging of non-small cell lung cancer (NSCLC) requires assessment of the hilar and mediastinal LNs with pathologic evaluation. However, the present nodal classification still contains some limitations particularly concerning

For editorial comment see page 1527

heterogeneous pN1 and pN2 disease and the lack of a clear biologic definition of the distinguishing of N1 and N2.[1-4]

The seventh edition of the TNM classification for NSCLC[5] has been updated, with some modifications from the sixth edition.[6] However, the LN descriptor in the new classification remains the same as in the previous edition, and depends solely on the anatomic extent of LN involvement, despite the changes in the nodal map. In some other solid tumors, such as breast, gastric, and colorectal tumors, the number of metastatic lymph nodes has been included in the TNM staging system.

In our previous report,[7] we demonstrated that resection of ≥ 10 LNs influenced survival and that the number of involved LNs (four and more) is a strong independent prognostic factor in NSCLC. This may provide new information for determining the N category in the next TNM classification. However, it remains unknown whether the total number or anatomic location of involved LNs is a superior prognostic factor in NSCLC. Therefore, we retrospectively compared or combined the number of metastatic LNs (nN) category and the classic pathologic LNs (pN) category on survival in patients with completely resected NSCLC in whom ≥ 10 LNs had been harvested.

Materials and Methods

Patient Eligibility

A total of 1,311 consecutive patients who underwent surgical resection for primary lung cancer at our institution from 2000 to 2007 were examined retrospectively. The patients with clinical stages IA to IIIA, including patients with stage cN2 with single-station nodal metastasis, underwent surgery. Cases of induction therapy, incomplete resection, and limited resection were excluded from this study. Patients with tumors classified histologically as small-cell lung cancer or low-grade malignancies were also excluded. In addition, those in whom nine or fewer LNs were harvested were also excluded in the present analysis because our previous study suggested that resection of at least 10 LNs was necessary to maintain the optimal quality of surgery and accurate staging.[7] Finally, a total of 689 patients with NSCLC who underwent complete resection involving dissection of ≥ 10 hilar and mediastinal lymph nodes with curative intent, consisting of lobectomy or more extensive resection, were eligible.

Data Collection

The patient charts, including the pathologic diagnosis and operative reports, were reviewed. Staging was determined according to the sixth edition of the TNM staging system.[8] The histologic tumor type was determined according to the World Health Organization classification (third edition).[9] LNs were dissected with the adipose connective tissue of the corresponding anatomic regions, as designated by the surgeon intraoperatively. All dissected LNs were examined pathologically and classified on the basis of anatomic location by the numbering system described in the Naruke map.[10] The number of resected and involved LNs from each defined anatomic location was confirmed on the basis of the pathologic report provided by Drs Nomura, Matsubayashi, and Nagao. We performed two different stratifications of LN status assessment: the absence or presence and anatomic extent of nodal metastases (pN categories), and the number of regional LNs with metastases (nN categories). Based on our previous results, four or more involved LNs is the best benchmark of prognostic variables.[7] Therefore, we classified involved LNs into the three nN categories as follows: nN0, no LN metastasis; nN1-3, metastasis in one to three nodes; and nN4−, metastasis in four or more LNs. The pathologists were blinded to the clinical outcome.

We chose overall survival (OS) and disease-free survival (DFS) as end points and investigated the associations between the nN categories and these endpoints compared with standard pN categories. OS was calculated from the date of surgery to the time of death. Observations were censored at final follow-up if the patient was alive. DFS was defined as the time from surgery to locoregional relapse or distant metastasis of lung cancer, and in cases without relapse, any deaths due to causes other than lung cancer were censored. Patients were examined at intervals of 3 months for the first 2 years and at intervals of 6 months for the next 3 years or thereafter on an outpatient basis. The follow-up evaluation involved the following procedures: physical examination, chest radiography, CT scan of the chest and abdomen, and blood examination, including that of pertinent tumor markers. Further evaluations, including brain MRI or CT scan, bone scintigraphy, and integrated PET scan, were performed on the first appearance of any symptoms or signs of recurrence. The median follow-up time was 3.5 years.

Statistical Analysis

Survival curves were plotted using the Kaplan-Meier method. Differences in survival among the groups were examined using the log-rank test. A two-category comparison was performed using the Student *t* test for quantitative data. Multivariate analysis was performed using the Cox proportional hazards model to examine any possible association between the total number of involved LNs and survival, with adjustment for the effects of other potential prognostic factors, including age, sex, histology, tumor factor, and type of surgery performed. All tests were two-sided, and *P* values of $< .05$ were considered to indicate statistically significant differences. StatView 5.0 software (SAS Institute Inc) was used for statistical analysis.

Ethical Considerations

The approval of the institutional review board of Tokyo Medical University was obtained (project approval no. 965). But, as this was a retrospective study, the need to obtain written informed consent from either the patients or their representatives was waived, in accordance with the American Medical Association.

Manuscript received March 29, 2012; revision accepted October 23, 2012.
Affiliations: From the Division of Thoracic Surgery, Department of Surgery (Drs Saji, Tsuboi, Shimada, Kato, Yoshida, Kakihana, Usuda, Kajiwara, Ohira, and Ikeda), and Department of Anatomic Pathology (Drs Nomura, Matsubayashi, and Nagao), Tokyo Medical University, Tokyo, Japan.
Funding/Support: This study was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology [21791332] and the Ministry of Health, Labour and Welfare [22101601].
Correspondence to: Hisashi Saji, MD, PhD, Division of Thoracic Surgery, Department of Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan; e-mail: saji-q@ya2.so-net.ne.jp

DOI: 10.1378/chest.12-0750

Results

Patient Characteristics

The characteristics of patients were as follows: median age: 64.5 years; sex: 417 men (60.5%) and 272 women (39.5%); histopathologic diagnosis: 497 adenocarcinomas (72.1%), 140 squamous cell carcinomas (20.3%), 42 large cell carcinomas (6.1%), and 10 others (1.5%); pathologic stages: 480 stage I (69.7%), 94 stage II (13.6%), and 115 stage III (14.1%); pN factors: 510 pN0 (74.0%), 93 pN1 (13.5%), and 86 pN2 (12.5%); nN factors: 510 nN0 (74.0%), 101 nN1-3 (14.5%), and 78 nN4− (11.4%). The mean number of resected LNs was 18.1 (right side, 18.5; left side, 17.6). The mean number of involved LNs was 4.5 (range, 1-22) in LN-positive cases (Table 1).

Table 1—*Patient Characteristics (N = 689)*

Variable/Category	No. (%)
Age, y	
Mean	64.5
Range	26-87
Sex	
Male	417 (60.5)
Female	272 (39.5)
Histology	
Adenocarcinoma	497 (72.1)
Squamous cell	140 (20.3)
Large cell	42 (6.1)
Other	10 (1.5)
Tumor location	
Right	452 (65.6)
Upper/middle/lower	274/31/147
Left	237 (34.4)
Upper/lower	134/103
Surgical procedure	
Lobectomy	637 (92.4)
Bilobectomy	37 (5.4)
Pneumonectomy	15 (2.2)
p Stage	
I	480 (69.7)
II	94 (13.6)
III	115 (14.1)
pT factor	
pT1	344 (50.0)
pT2	283 (41.1)
pT3	27 (3.9)
pT4	34 (5.0)
pN factor	
pN0	510 (74.0)
pN1	93 (13.5)
pN2	86 (12.5)
nN factor	
nN0	510 (74.0)
nN1-3	101 (14.6)
nN4−	78 (11.4)
Total No. of resected LNs	
Mean (range)	18.1 (10-49)
10-19	450 (65.3)
20-29	192 (37.9)
≥ 30	47(6.8)
No. involved LNs in positive cases	
Mean (range)	4.5 (1-22)

LN = lymph node, nN = number of lymph nodes; pN = pathologic lymph node; pT = pathologic tumor.

Survival Analysis

First, we classified the patients into three nN categories: nN0, no LN metastasis; nN1-3, metastasis in one to three nodes; and nN4−, metastasis in four or more LNs. We then assessed the OS and DFS in each pN stage classification and nN category (Fig 1). The survival curves showed clear differences in the OS and DFS of each subgroup of both the pN and nN classifications. There was also a significant difference in OS and DFS for each of the nN categories (the 5-year OS rates for nN0, nN1-3, and nN4− were 79.2%, 64.8%, and 39.2%, respectively, $P = .0426$ and $P < .0001$ for nN0 vs nN1-3 and nN1-3 vs nN4−, respectively; the 5-year DFS rates were 83.0%, 71.6%, and 32.9%, respectively, $P = .0024$ and $P = .0002$ for nN0 vs nN1-3 and nN1-3 vs nN4−, respectively).

Second, we performed validation of the nN category in terms of OS for each pathologic tumor (pT) category (Fig 2). Although the differences between each pair of nN categories were not always significant, there was a tendency toward the deterioration of OS from the nN0 to the nN4− subgroup. Similar results were found in terms of DFS (data not shown).

Third, we classified the patients into five categories of combinations of the pN and nN status to compare the prognostic significance of the pN and nN status. The five N categories were as follows: pN0-nN0, pN1-nN1-3, pN1-nN4−, pN2-nN1-3, and pN2-nN4. As shown in Figure 3, patients with pN2-nN1-3 (n = 22) had better prognoses than patients with pN1-nN4− (n = 13). However, there was no statistically significant difference between these two groups due to the small populations. The survival curve of pN2-nN1-3 patients was similar to that of pN1-nN1-3 patients, which is an operable population, while the survival curves of pN1-nN4− patients were similar, but still superior to that of pN2-nN4− patients.

Because of the strong correlation between the pN and nN categories, we performed multivariate analysis for each category to confirm each prognostic impact for OS and DFS.[11] On multivariate analysis, the nN category was an independent prognostic factor for OS and DFS (vs nN4−; the hazard ratios of nN0 and nN1-3 for OS were 0.223 and 0.369, respectively, $P < .0001$ for all categories) as was the case for the pN category (Tables 2, 3). Therefore, both the pN and nN categories were identified as strong prognostic factors for OS and DFS in NSCLC. Moreover, the populations of the pN1-nN1-3 and pN2-nN1-3 categories were small, and the OS of patients within these two groups did not statistically differ. And, there were significant differences between pN1 and pN2

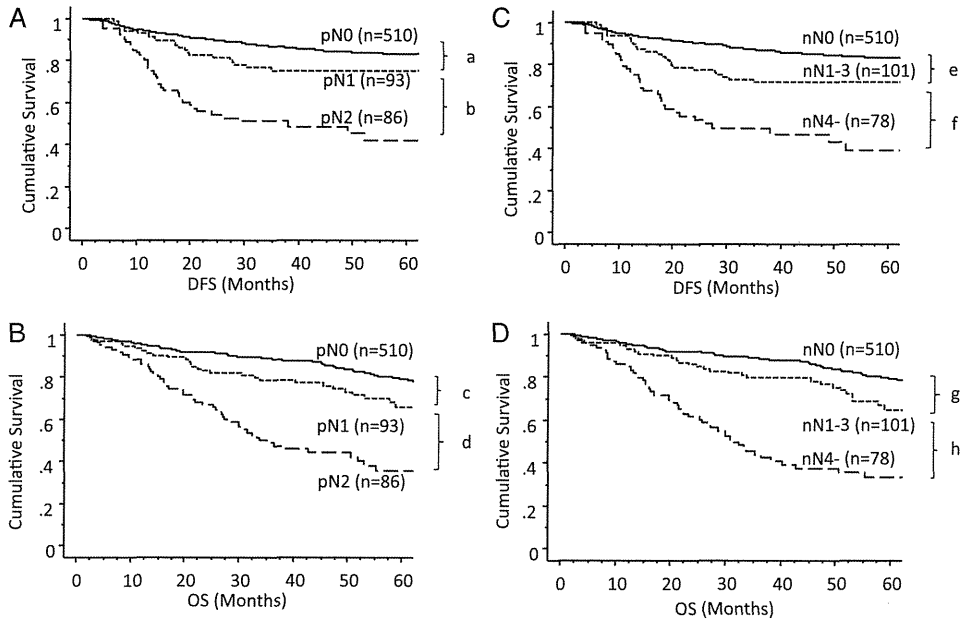

FIGURE 1. DFS and OS according to pN status and nN status. A, DFS curve according to pN status. The 5-year DFS rates for pN0, pN1, and pN2 were 83.0%, 75.3%, and 31.1%, respectively. a, pN0 vs pN1, $P = .0464$; b, pN1 vs pN2, $P < .0001$. B, OS curve according to pN status. The 5-year OS rates for pN0, pN1, and pN2 were 79.2%, 65.9%, and 35.4%, respectively. c, pN0 vs pN1, $P = .0181$; d, pN1 vs pN2, $P < .0001$. C, DFS curve according to nN status. The 5-year DFS rates for nN0, nN1, and nN2-3 were 83.0%, 71.6%, and 39.2%, respectively. e, nN0 vs nN1, $P = .0024$; f, nN1 vs nN2-3, $P = .0002$. D, OS curve according to nN status. The 5-year DFS rates for nN0, nN1, and nN2-3 were 79.2%, 64.8%, and 32.9%, respectively. g, nN0 vs nN1, $P = .0426$; h, nN1 vs nN2-3, $P < .0001$. DFS = disease-free survival; nN = number of lymph nodes; OS = overall survival; pN = pathologic lymph node.

(Figs 1A, 1B) and between nN1-3 and nN4− (Figs 2A, 2B), which mean by a still subcategory exist. We propose a new classification for testing, based on combined pN and nN categories: namely, the new N0 category becomes pN0-nN0, the new N1 category becomes pN1-nN1-3, the new N2a category becomes pN2-nN1-3 + pN1-nN4−, and the new N2b category becomes pN2-nN4. Figure 4 shows the survival curves of the new classifications, which were proportional and well distributed among the curves.

Discussion

The TNM stage classification was developed to provide high specificity for patients with similar prognoses and treatment options. Nodal status is a major determinant of stage and survival of patients with NCSLC after surgery. The seventh TNM staging system included notable changes in the T and M descriptors and in the nodal map, while the N descriptor remained the same as in the previous version and depended solely on the anatomic extent of involved LNs. The anatomically based pN classification has some unsatisfactory aspects. Of these, the heterogeneity of pN1 and pN2 with regard to prognosis is the most notable. Therefore, some subclassifications have been proposed.[1-4,12-17] In addition, differences among surgeons in the labeling of LN stations intraoperatively will occur regardless of the use of a new nodal map. This indicates that it is necessary to refine the currently used pN stage classification and has justified attempts to identify alternative nodal classification methods. In some other solid tumors, such as breast, gastric, and colorectal tumors, the number of metastatic lymph nodes has been included in the TNM staging system. The number of metastatic LNs, when classified into several categories, has been shown to be a prognostic factor for resected NSCLC.[11,15,18] Wei and colleagues[11] evaluated this issue and suggested that the nN category is a better prognostic determinant than the location-based pN stage classification. However, to date, it has remained unknown whether the nN category or the pN stage classification is a better prognostic factor in lung cancer.

It is important to consider how many or to what extent LNs should be harvested for the accurate assessment of nodal status and to maintain the optimal quality of surgery in NSCLC before evaluating the effectiveness of prognostic determinants among the pN and nN categories. The number of resected LNs in early NSCLC has been proven to be a prognostic factor which has influenced survival, similar to that in colorectal, breast, and bladder cancer.[19-24] Some reports have suggested that the optimal number of removed LNs is 11 to 16 in order to accurately assess stage I lung cancer.[24,25] In another study, the removal

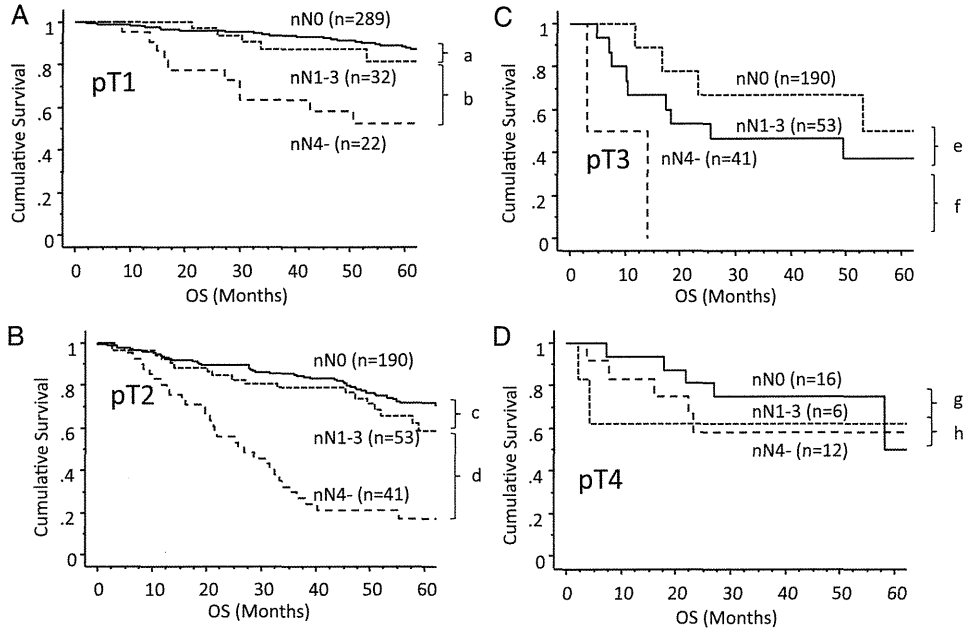

FIGURE 2. OS curves according to nN status across each pT category. A, OS curve according to nN status in pT1 patients. The 5-year OS rates for nN0, nN1, and nN2-3 were 88.5%, 81.4%, and 52.1%, respectively. a, nN0 vs nN1-3, $P = .6757$; b, nN1-3 vs nN4−, $P = .0024$. B, OS curve according to nN status in pT2 patients. The 5-year OS rates for nN0, nN1-3, and nN4− were 71.2%, 58.7%, and 16.7%, respectively. c, nN0 vs nN1-3 $P = .6083$; d, nN1-3 vs nN4− $P < .0001$. C, OS curve according to nN status in pT3 patients. The 5-year OS rates for nN0, nN1-3, and nN4− were 37.3%, 50.0%, and 0%, respectively. e, nN0 vs nN1-3, $P = .2537$; f, nN1-3 vs nN4−, $P = .0046$. D, OS curve according to nN status in pT4 patients. The 5-year OS rates for nN0, nN1-3, and nN4− were 50.0%, 62.5%, and 58.3%, respectively. g, nN0 vs nN1-3 $P = .4305$; h, nN1-3 vs nN4−, $P = .8623$. pT = pathologic tumor. See Figure 1 legend for expansion of other abbreviations.

of 11 LNs was set as a threshold for inclusion.[18] The Staging Manual in Thoracic Oncology of the International Association for the Study of Lung Cancer (IASLC) recommends that at least six LNs/stations be removed or sampled and histologically confirmed to be free of disease in order to define pN0 status.[5] We previously demonstrated that the resection of 10 or more LNs influenced survival while maintaining the quality of surgery.[7] Therefore, in the present analysis, we excluded those for whom < 10 LNs were harvested. In the present series, 617 of 689 cases (89.6%) met this criterion. In the TNM classification for some other tumors, the number of positive LNs has been included in the definition of pN categories.[26] The number of metastatic LNs, when classified into several categories, has been shown to be a prognostic factor for resected NSCLC.[11,15,18] There was a significant difference in OS and DFS among each nN category as well as the pN categories. The OS and DFS survival curves of each nN category are well distributed and proportional (Fig 1). Moreover, as Figure 2 shows, a clear tendency toward the deterioration of OS from nN0 to nN4− in the same pT category was observed when we attempted to validate the results for each pT category. The curves were evenly distributed over pT1, pT2, and pT3. However, the curves were closer in the higher pT stage of pT4, perhaps due to the small population size. Another reason may be that the prognosis of the higher pT category was already poor, regardless of the presence of metastatic LNs. On multivariate analysis, not only the pN status, but also the nN status, was demonstrated to be a major independent prognostic factor for both OS and DFS in the current series, which is consistent with a previous report.[11] These results showed that both pN and nN categories have a powerful discriminative ability concerning the prognosis of NSCLC.

In general, patients with NSCLC with pN1 or pN2 disease are known to exhibit prognostic heterogeneity.[1-4,12-17] The OS and DFS curves of pN1 and pN2 were widely distributed in the current series, indicating that there are some subclassifications required to distinguish the two curves. To evaluate these subgroups and demonstrate which is the most accurate prognostic factor, the anatomic location of involved LNs, or the total number of involved LNs, we classified the patients into five categories combining the pN and nN status as follows: pN0-nN0, pN1-nN1-3, pN1-nN4−, pN2-nN1-3, and pN2-nN4−. Patients with pN2-nN1-3 (n = 22) had better prognoses than patients with pN1-nN4− (n = 13). However, there was no statistically significant difference between the

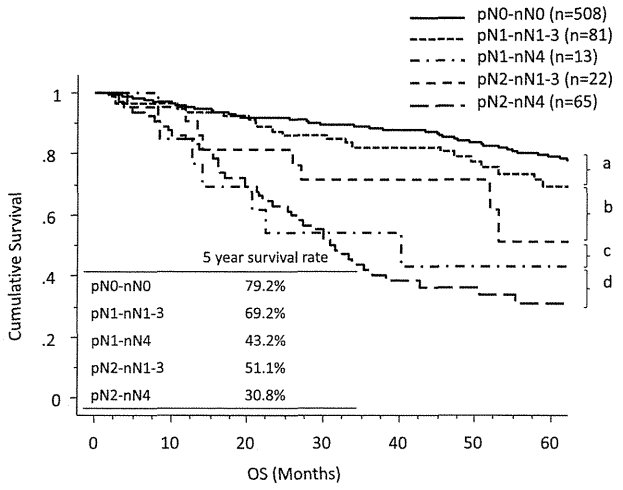

FIGURE 3. OS curves according to combinations between nN status and pN status. Patients with pN2-nN1-3 (n = 22) had better prognoses than patients with pN1-nN4− (n = 13). However, there was no statistically significant difference between the two groups due to the small populations. The survival curve of pN2-nN1-3 was similar to that of pN1-nN1-3, while the survival curves of pN1-nN4− were similar to that of pN2-nN4, a population with worse prognoses. a, pN0-nN0 vs pN1-nN1-3, $P = .2908$; b, pN1-nN1-3 vs pN2-nN1-3, $P = .1102$; c, pN2-nN1-3 vs pN1-nN4, $P = .1292$; d, pN1-nN4− vs pN2-nN4, $P = .7810$. See Figure 1 legend for expansion of abbreviations.

two groups due to the small numbers of patients. This result indicates that the nN category might be used to further subdivide the pN category into two prognostically distinct subgroups. Finally, we propose combining patients with pN2-nN1-3 with those who have a better prognosis into the pN2 category and patients in the pN1-nN4− category with those who have a worse prognosis into a single pN category. Therefore, we reclassified the patients in the current series into four categories as shown in Figure 4. Each OS survival curve of the new classification appears to be proportional with a significant tendency to differ between the new N1 and new N2a and between the new N2a and new N2b categories ($P = .0028$ and $P = .0726$, respectively).

When we subdivided the pN1 and pN2 categories into two subgroups according to the nN category, there was no statistically significant difference between the two groups, but patients with pN2-nN1-3 had better prognoses than patients with pN1-nN4−. This result indicates a possible limitation of the present pN classification for nodal status. The overall disease burden, rather than the anatomic location of LN involvement, has the most relevance in prognosis.[11,27] However, the present pN classification is a major independent prognostic factor in operative NSCLC, as was the nN classification on multivariate analysis in the present series. Therefore, we propose a new nodal classification combination of the pN (anatomic location) and nN (total number) status of LN involvement, which may reflect the survival of operable NSCLC cases more accurately than any single category.

There are some limitations in this study, despite the benefits of the addition of the nN category for predicting survival. First, this was a retrospective and single-institution analysis. Second, it is difficult to accurately estimate the number of LN sites involved both preoperatively and in inoperable patients by CT scan or any other diagnostic imaging methods. The scope of this study involved only the definition of prognosis based on the p stage and not on the c stage, which

Table 2—*Multivariate Analysis of OS and DFS Including pN Classification*

	OS			DFS		
Variable/Category	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, y						
<70	...	...	...	...	...	...
≥70	1.018	0.759-1.366	.9053	0.928	0.650-1.325	.6806
Sex						
Men	...	...	...	...	...	...
Women	0.768	0.548-1.076	.1245	1.025	0.709-1.480	.8965
Histopathology						
Nonadenocarcinoma	...	...	...	...	...	...
Adenocarcinoma	0.560	0.409-0.768	.0003[a]	1.063	0.712-1.588	.7653
pT factor						
T4	...	...	<.0001[a]	...	...	.0002[a]
T1	0.378	0.205-0.696	.0018[a]	0.460	0.227-0.935	.0319[a]
T2	0.863	0.482-1.545	.619	1.074	0.547-2.103	.8366
T3	1.192	0.564-2.522	.212	1.180	0.450-3.093	.7362
pN factor						
pN2	...	...	<.0001[a]	...	...	<.0001[a]
pN0	0.274	0.194-0.386	<.0001[a]	0.257	0.172-0.33	<.0001[a]
pN1	0.297	0.188-0.468	<.0001[a]	0.351	0.206-0.599	.0001[a]

DFS = disease-free survival; HR = hazard ratio; OS = overall survival. See Table 1 for expansion of other abbreviations.
[a]Statistically significant.

Table 3—*Multivariate Analysis of OS and DFS Including nN Classification*

Variable/Category	OS			DFS		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, y						
<70	...	...	...	...	...	...
≥70	1.023	0.764-1.372	1.023	0.919	0.644-1.311	0.6404
Sex						
Men	...	...	...	...	...	...
Women	0.776	0.556-1.082	0.1344	1.016	0.705-1.463	0.9332
Histopathology						
Nonadenocarcinoma	...	...	...	...	...	...
Adenocarcinoma	0.583	0.425-0.799	0.0008[a]	1.157	0.775-1.728	0.4760
pT factor						
T4	...	...	<.0001[a]	...	...	<.0001[a]
T1	0.473	0.256-0.873	0.0167[a]	0.551	0.268-1.131	0.1040
T2	1.120	0.624-2.010	0.7036	1.319	0.665-2.618	0.4284
T3	2.114	0.977-4.573	0.5730	1.654	0.616-4.447	0.3182
nN factor						
nN4−	...	...	<.0001[a]	...	...	<.0001[a]
nN0	0.200	0.141-0.284	<.0001[a]	0.223	0.146-0.339	<.0001[a]
nN1-3	0.197	0.123-0.315	<.0001[a]	0.369	0.219-0.623	0.0002[a]

See Table 1 and 2 legends for expansion of abbreviations.
[a]Statistically significant.

is a limitation of this investigation. Technical improvements in preoperative evaluation to accurately identify all metastatic LN sites are necessary. Although there are various clinical markers to evaluate potential malignant lesions, there is as yet no reliable method or evidence suggesting that PET scans or tumor markers can definitively indicate malignancy. Therefore, this is the reason why we decided to concentrate on the p stage as a step toward establishing preoperative clinical evaluation. Third, the definition of the optimal category in terms of the number of metastatic lymph nodes needs to be further explored; because the definitions, and, therefore, the data, differ according to the institution, it is difficult to determine the optimal category definition. Further multiinstitution studies using identical protocols are needed.

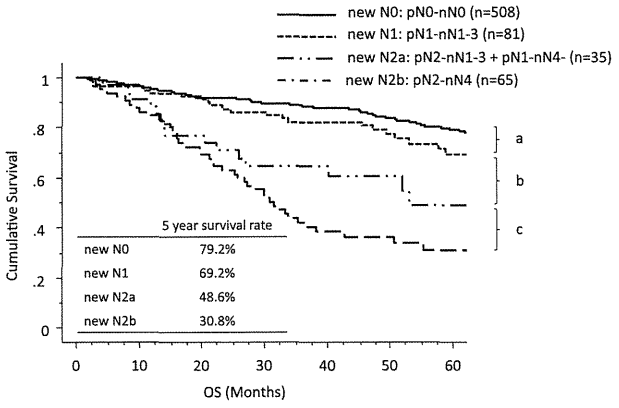

FIGURE 4. OS curves according to combinations of nN status and pN status. We propose a new classification based on combined pN and nN categories: namely, N0 becomes pN0-nN0, N1 becomes pN1-nN1-3, N2a becomes pN2-nN1-3 + pN1-nN4− and N2b becomes pN2-nN4. Each survival curve was proportional and well distributed. a, New N0 vs new N1a, $P = .2908$; b, new N1a vs new N2a, $P = .0028$; c, new N2a vs new N2b, $P = .0726$. See Figure 1 legend for expansion of abbreviations.

Conclusion

The current results demonstrate that combined anatomically based pN and numerically based nN stage classification as proposed in this study is a better prognostic determinant in pN1 and pN2 prognostically heterogeneous patients with NSCLC. Further large-scale cohort studies, including global prospective validation analyses and multiinstitution studies, are warranted to demonstrate the validity of this proposal for the next TNM classification.

Acknowledgments

Author contributions: Dr Saji is guarantor of the article.
Dr Saji: contributed to the design and coordination of the study, statistical analysis, preparing the manuscript, and revising the article for important intellectual content and read and approved the final manuscript.
Dr Tsuboi: contributed to preparing the manuscript and read and approved the final manuscript.
Dr Shimada: contributed to data collection and analysis and read and approved the final manuscript.
Dr Kato: contributed to data collection and analysis and read and approved the final manuscript.
Dr Yoshida: contributed to data collection and analysis and read and approved the final manuscript.
Dr Nomura: contributed to pathologic analysis and read and approved the final manuscript.
Dr Matsubayashi: contributed to pathologic analysis and read and approved the final manuscript.
Dr Nagao: contributed to pathologic analysis and read and approved the final manuscript.