Pathological Vascular Invasion and Tumor Differentiation Predict Cancer Recurrence in Stage IA Non–Small-Cell Lung Cancer After Complete Surgical Resection

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Introduction: The appropriate therapeutic strategy and postoperative management for patients with stage IA non–small-cell lung cancer (NSCLC) still remain a matter of debate because of the prognostic heterogeneity of this population, including the risk of cancer recurrence. The objective of the current study was to identify the clinicopathological factors that affect overall prognosis and cancer recurrence of stage IA NSCLC.

Methods: We reviewed the data of 532 patients in whom complete resection of stage IA NSCLC had been performed. Overall survival and recurrence-free proportion (RFP) were estimated using the Kaplan–Meier method. RFP was estimated from the date of the primary tumor resection to the date of the first recurrence or last follow-up. We performed univariate and multivariate analyses to determine the independent prognostic factors.

Results: On multivariate analyses, three variables were shown to be independently significant recurrence risk factors: histological differentiation (hazard ratio [HR] = 1.925), blood-vessel invasion (HR = 1.712), and lymph-vessel invasion (HR = 1.751). On subgroup analyses combining these risk factors, the 5-year RFP was 91.3% for patients with no risk factors, 79.5% for those with either poorly differentiated carcinoma or vascular invasion, ($p < 0.001$ for both), and 62.9% for those with both poorly differentiated carcinoma and vascular invasion ($p = 0.068$).

Conclusion: These results indicated that vascular invasion and tumor differentiation have a significant impact on the prediction of cancer recurrence in patients with stage IA NSCLC. Patients with these predictive factors of recurrence may be good candidates for adjuvant chemotherapy.

Key Words: Prognostic factor, Non–small-cell lung cancer, Recurrence, Stage IA, Vascular invasion, Tumor differentiation.

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The tumor, node, metastasis (TNM) staging system for non–small-cell lung cancer (NSCLC) is currently the best confirmed predictor of survival and guide for treatment. NSCLC patients with pathologic stage IA disease have the best chance of survival, and resection is standard in such cases. However, even after curative resection, the 5-year survival rate is between 80% and 87% in pathologic stage IA patients as shown in large-scale Japanese lung cancer studies,[1–3] and recent data from the lung cancer staging project of the International Association for the Study of Lung Cancer revealed a 5-year survival rate of 73% for pathological stage IA patients.[4] Therefore, up to 10% of patients with stage IA NSCLC have recurrence after surgery, even in cases with early-stage disease.

Many studies of resected specimens have been performed to determine various clinicopathological prognostic factors other than the pathologic stage for these patients, such as sex, age,[5] smoking history,[6] serum level of carcinoembryonic antigen (CEA),[7] extent of operation,[5] tumor size, vascular invasion,[7–18] and the grade of differentiation of the tumor.[14,17,19] Patients, including those with stage IA NSCLC, who have such factors may be good candidates for receiving systemic therapy such as adjuvant chemotherapy. The objective of the present study was to identify the clinicopathological factors that affect overall prognosis and cancer recurrence of stage IA NSCLC in a single institution.

PATIENTS AND METHODS

Patients

From January 1990 to December 2007, a total of 1973 patients underwent complete pulmonary resection for NSCLC at our hospital. Complete resection was defined as cancer-free surgical margins both grossly and histologically. All the patients underwent radical surgical resection and systematic mediastinal lymph node dissection. Of these, 674 patients with consecutive pathologic stage IA NSCLC were identified in our departmental database. The number of resected lymph nodes ranged from one to 49, with a mean of 15. We excluded 142 patients who had undergone preoperative chemotherapy

or radiotherapy (n = 17), postoperative treatment including chemotherapy or chemoradiotherapy (n = 105), and those who had low-grade malignant tumors including carcinoids, mucoepidermoid carcinomas, or adenoid cystic carcinomas (n = 20). The remaining 532 patients comprised the subjects of this study.

Preoperative evaluation included physical examination, chest radiography, computed tomography (CT) of the chest and abdomen, bone scintigraphy, blood examination, and since the early 2000s, positron-emission tomography (PET) scan (recently performed as integrated PET-CT scan). Most patients were postoperatively evaluated by physical examination, chest radiography, and CT of the chest and abdomen to confirm relapse. In some patients, we used PET-CT, magnetic resonance imaging or bone scintigraphy to detect recurrence. The disease stage was determined in accordance with the 7th edition of the TNM classification for lung and pleural tumors.[20]

Histopathology

The available pathology slides from all 532 surgical specimens were reviewed in this study. After fixing the specimens with either 10% formalin and embedding them in paraffin, serial 4-μm sections were stained with hematoxylin and eosin and by elastica van Gieson (EvG) to visualize elastic fibers. Histologic subtypes of lung cancer were determined according to World Health Organization classification.[21] The histological tumor grade was categorized as well-differentiated, moderately differentiated, or poorly differentiated carcinoma according to the degree of structural and cytologic atypia.

Blood vessels were identified by the presence of erythrocytes in the lumen and/or an endothelial cell lining and/or the presence of elastic tissue around larger vessels. Sections stained by EvG were examined for the presence of blood-vessel invasion. The presence of blood-vessel invasion was determined by identifying conspicuous clusters of intravascular cancer surrounded by an elastic layer.

Lymph-vessel invasion was determined to be present when tumor cells floating in lymphatic vessels with no supporting smooth muscles or elastic fibers were identified. We confirmed that lumens within the bronchovascular bundle, subpleural, and intralobular pleural space were lymphatic vessels by immunostaining with anti-D2-40 antibody.

Data Collection

Clinical characteristics were retrieved from available clinical records. The following clinicopathological factors were assessed in the retrospective prognostic analysis: age (dichotomized at the median age of 64 years), sex, smoking status, preoperative serum CEA level (cutoff at the normal upper limit of 5 ng/ml), tumor size, tumor differentiation (well or moderate versus poor), blood-vessel invasion (absence versus presence), lymph-vessel invasion (absence versus presence), histology (adenocarcinoma versus other), tumor laterality, and extent of resection (single-lobe lobectomy versus more extensive resection; bilobectomy or pneumonectomy).

Statistical Analysis

Overall survival (OS) was measured from the date of surgery to the date of death from any cause or the date on which the patient was last known to be alive. The length of the recurrence-free period was calculated in months from the date of resection to the date of the first recurrence or last follow-up showing no recurrence. To calculate the recurrence-free proportion (RFP), patients who died without recurrence or who were known to have no recurrence at the date of last contact were censored. OS and RFP curves were plotted using the Kaplan–Meier method, and differences in variables were determined using the log-rank test. Categorical comparison was performed using the Pearson

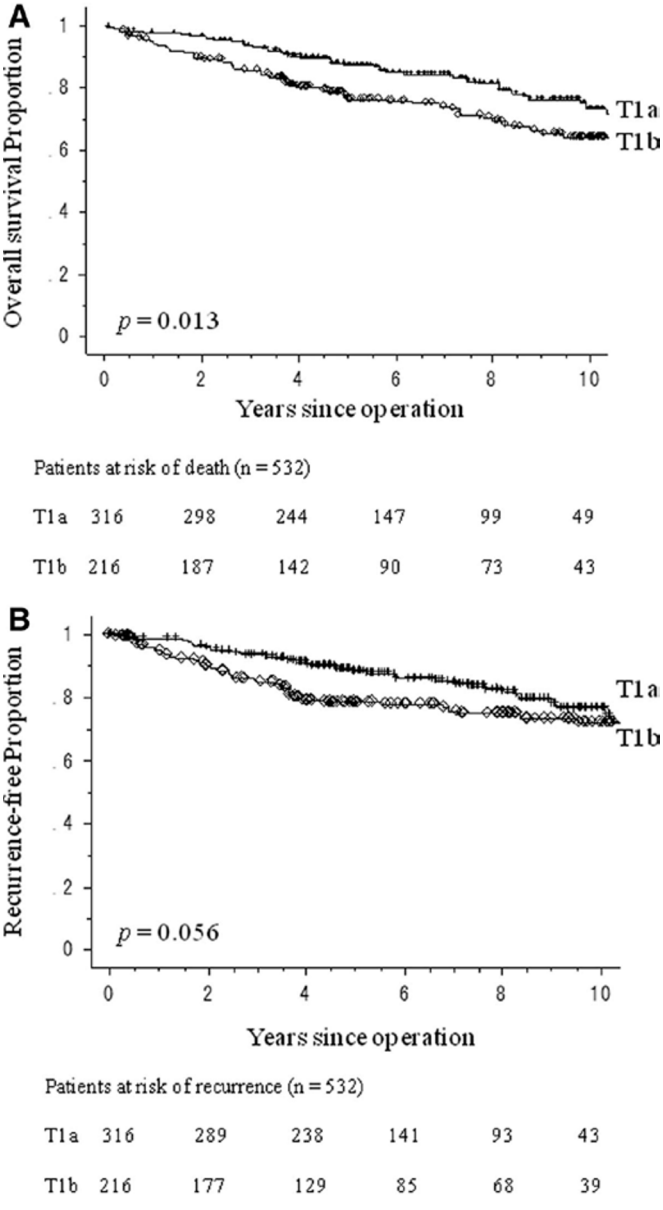

FIGURE 1. *A*, Overall survival curves of patients with T1a or T1b disease. *B*, Recurrence-free proportion curves of patients with T1a or T1b disease.

χ^2 test. Multivariate analyses were performed using the Cox proportional hazards regression model. All tests were two-sided, and p values of less than 0.05 were considered to indicate a statistically significant difference. Statview 5.0 software (SAS Institute Inc., Cary, NC) 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 of our institution.

RESULTS

The median follow-up for survivors was 5.1 years. Figure 1*A* and *B* show the OS and RFP curves of 316 patients with T1aN0M0 NSCLC and 216 patients with T1bN0M0 NSCLC. For those patients with T1aN0M0 NSCLC and those with T1bN0M0 NSCLC, the 5-year OS rates were 87.1% and 77.2% ($p = 0.013$), respectively, whereas the 5-year RFPs were 88.6% and 78.6% ($p = 0.056$), respectively.

Table 1 shows the 5-year OS proportions and RFPs according to the clinicopathological characteristics of the stage IA NSCLC patients. On univariate analysis, nine variables were found to be significantly associated ($p < 0.05$) with poorer OS: older age, male sex, smoking history, T1b, poorly differentiated carcinoma, blood-vessel invasion, lymph-vessel invasion, nonadenocarcinoma, and type of surgery (bilobectomy or pneumonectomy). For RFP, five variables (male sex, poorly differentiated carcinoma, blood-vessel invasion, lymph-vessel invasion, and nonadenocarcinoma) were identified as statistically significant factors on univariate analysis.

A multivariate Cox proportional hazards model demonstrated that older age (hazard ratio [HR] = 1.936; $p < 0.001$), male sex (HR = 2.096; $p = 0.005$), tumor size (HR = 1.501; $p = 0.045$), poorly differentiated carcinoma (HR = 1.632; $p = 0.028$), lymph-vessel invasion (HR = 1.579; $p = 0.042$), and nonadenocarcinoma (HR = 1.704; $p = 0.016$) were statistically significant predictors of OS (Table 2). Poorly differentiated carcinoma (HR = 1.925; $p = 0.006$), blood-vessel invasion (HR = 1.712; $p = 0.020$), and lymph-vessel invasion (HR = 1.751; $p = 0.017$) were identified as statistically significant predictors of cancer recurrence (Table 3). Figures 2*A*, *B*, and *C* show the RFP curves of patients with stage IA NSCLC according to tumor differentiation, blood-vessel invasion, and lymph-vessel invasion, respectively. Table 4 shows the results of 5-year RFP of patients in each T subclassification (T1a and T1b) according to these significant predictors of cancer recurrence.

Subgroup analysis with a combination of these recurrence predictive factors in the patients with stage IA NSCLC revealed 5-year RFPs of 91.3%, 79.5%, and 62.9% for patients with no risk factor, poorly differentiated carcinoma or vascular invasion (blood-vessel invasion or lymph-vessel

TABLE 1. Patient Characteristics and Univariate Analysis of Survival and Recurrence

Variable	No. of Patients	5-Yr OSP (%)	*p* Value	5-Yr RFP (%)	*p* Value
Age (yrs: median 64)					
< 64	279	88.9		84.2	
≥ 64	253	76.6	< 0.001	85.3	0.946
Sex					
Male	290	77.7		81.4	
Female	242	89.6	< 0.001	88.4	0.009
Smoking status					
Ever smoker	279	81.5		82.6	
Never smoker	253	84.9	0.039	86.8	0.102
CEA (ng/ml: NUL of 5)					
< 5	447	83.7		85.2	
≥ 5	59	75.9	0.108	77.2	0.212
Tumor size					
T1a (≤ 2.0 cm)	316	87.1		88.6	
T1b (≥ 2.1 cm)	216	77.2	0.013	78.6	0.056
Differentiation					
Well or moderate	425	86.4		87.7	
Poor	96	71.4	< 0.001	71.8	< 0.001
Blood-vessel invasion					
Absent	402	86.2		88.1	
Present	116	72.1	0.002	71.3	< 0.001
Lymph-vessel invasion					
Absent	392	85.4		87.1	
Present	122	76.4	0.003	76.1	0.001
Histology					
Adenocarcinoma	439	86.6		86.6	
Nonadenocarcinoma	93	66.3	< 0.001	74.3	< 0.001
Tumor laterality					
Right	357	82.9		84.3	
Left	175	83.6	0.685	85.4	0.732
Type of surgery					
Single-lobe lobectomy	510	84.0		84.5	
More extensive resection (more than bilobectomy)	22	66.7	0.046	88.7	0.946

OSP, overall survival proportion; RFP, recurrence-free proportion; NUL, normal upper limit; CEA, preoperative serum carcinoembryonic antigen level.

TABLE 2. Multivariate Cox Proportional Hazards Regression Analysis of Overall Survival

Variable	Risk Factors	Hazard Ratio	95% Confidence Interval	*p* Value
Age	≥ 64	1.936	1.314–2.852	< 0.001
Sex	Male	2.096	1.251–3.510	0.005
Smoking status	Ever smoker	1.219	0.781–1.901	0.383
Tumor size	T1b (≥ 2.1 cm)	1.501	1.009–2.233	0.045
Differentiation	Poor	1.632	1.054–2.527	0.028
Blood-vessel invasion	Present	1.169	0.749–1.827	0.492
Lymph-vessel invasion	Present	1.579	1.017–2.449	0.042
Histology	Nonadenocarcinoma	1.704	1.103–2.632	0.016
Type of surgery	More extensive resection (more than bilobectomy)	1.981	0.984–3.984	0.055

TABLE 3. Multivariate Cox Proportional Hazards Regression Analysis of Cancer Recurrence

Variable	Risk Factors	Hazard Ratio	95% Confidence Interval	*p* Value
Sex	Male	1.171	0.747–1.834	0.492
Differentiation	Poor	1.925	1.210–3.063	0.006
Blood-vessel invasion	Present	1.712	1.088–2.694	0.020
Lymph-vessel invasion	Present	1.751	1.103–2.779	0.017
Histology	Nonadenocarcinoma	1.615	0.994–2.623	0.053

invasion), and both poorly differentiated carcinoma and vascular invasion, respectively (Fig. 3*A*). The differences in RFP were statistically significant between patients without any risk factors (A group) and those with poorly differentiated carcinoma or vessel invasion (B group) ($p < 0.001$). The 5-year RFP of patients with both poorly differentiated carcinoma and vascular invasion (C group) tended to be unfavorable compared with that of patients in the B group, but the difference was not statistically significant ($p = 0.068$). In patients with T1a, the 5-year RFP of patients without any risk factors (A group) was statistically different from that of patients with poorly differentiated carcinoma or vessel invasion (B group) (92.0% versus 83.7% in A and B, respectively; $p = 0.002$), whereas

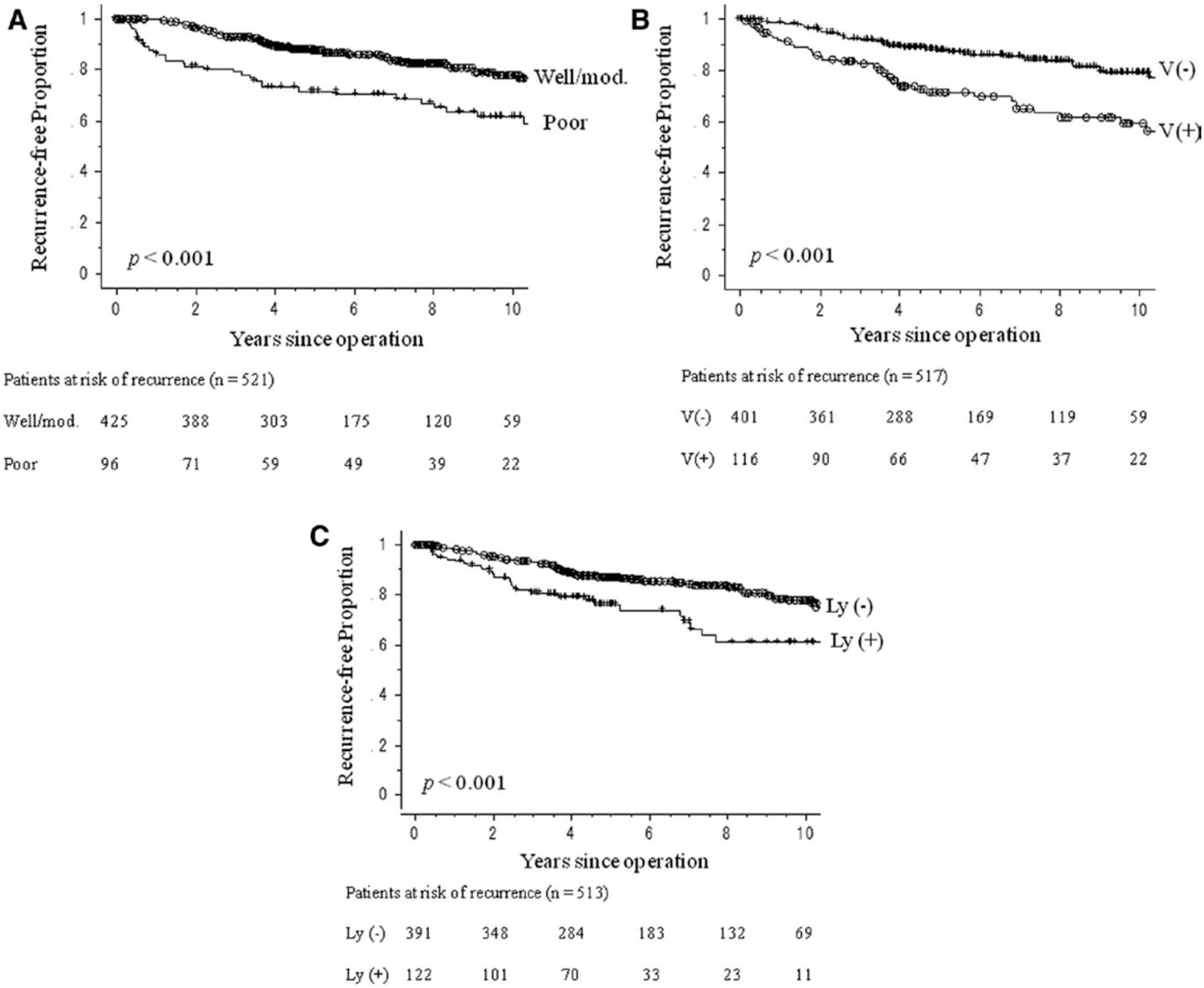

FIGURE 2. *A*, Recurrence-free proportion curves according to tumor differentiation. *B*, Recurrence-free proportion curves according to blood-vessel invasion. *C*, Recurrence-free proportion curves according to lymph-vessel invasion.

TABLE 4. 5-Year Recurrence-Free Proportion for Each T Subclassification According to Histological Grade and Vascular-Invasion Status

T-Factor category	No. of Patients	5-Yr RFP (%)	*p* Value
T1a (≤ 2.0 cm)			
Well/mod.	249	90.3	
Poor	60	83.8	0.126
T1b (≥ 2.1 cm)			
Well/mod.	176	83.7	
Poor	36	51.3	< 0.001
T1a (≤ 2.0 cm)			
BVI (−)	265	90.2	
BVI (+)	44	77.5	0.005
T1b (≥ 2.1 cm)			
BVI (−)	137	83.8	
BVI (+)	72	67.0	0.011
T1a (≤ 2.0 cm)			
LVI (−)	252	90.2	
LVI (+)	54	79.4	0.003
T1b (≥ 2.1 cm)			
LVI(−)	140	81.4	
LVI (+)	68	73.2	0.181

RFP, recurrence-free proportion; Well/mod., well- or moderately differentiated carcinoma; Poor, poorly differentiated carcinoma; BVI, blood-vessel invasion; LVI, lymph-vessel invasion.

no significant difference was shown between patients in the B group and those with both poorly differentiated carcinoma and vascular invasion (C group; 79.4% at 5-year RFP for C group; $p = 0.812$) (Fig. 3*B*). The RFP curves for T1b patients of the A, B, and C groups were shown in Fig. 3*C*. The differences in recurrence were statistically significant between A and B (89.6% versus 75.1% at 5-year RFP in A and B, respectively; $p = 0.006$), B and C (43.3% at 5-year RFP for the C group; $p = 0.002$).

We tested for a correlation between histological grade or vascular-invasion status and clinicopathological variables in stage IA patients. A comparison of variables between well- or moderately differentiated carcinoma and poorly differentiated carcinoma groups showed that a statistically significant difference in the prevalence of poorly differentiated carcinoma was seen in patients of male sex ($p < 0.001$), those who were smokers ($p < 0.001$) those in whom vascular invasion was present ($p < 0.001$), and those who had nonadenocarcinoma histology ($p < 0.001$). Vascular invasion was significantly associated with male sex ($p = 0.035$), smoking ($p = 0.001$), T1b ($p < 0.001$), and poorly differentiated carcinoma ($p < 0.001$) (data not shown).

Table 5 shows the number of patients with recurrence and their initial recurrence pattern according to histological grade and vascular-invasion status. The proportion of patients who developed distant metastases was higher in these recurrence predictive factor positive populations than in the negative populations (histological grade; $p = 0.048$, vascular invasion; $p = 0.024$).

DISCUSSION

We set out to identify the clinicopathological factors that affect overall prognosis and cancer recurrence of stage IA NSCLC. Curative surgical resection is the most effective therapy for patients with stage IA NSCLC. However, a considerable number of patients develop recurrence, which results in cancer death. Previous studies have reported the following factors to be associated with a poor prognosis in patients with stage IA NSCLC: tumor size,[5] preoperative serum CEA level,[7] lymph-vessel invasion,[18] blood-vessel invasion,[7,13–15,17] and histological grade.[14,17,19] In addition, according to the Surveillance, Epidemiology, and End Result Program database, age, sex, and extent of resection are also important prognostic factors.[22] However, prognostic factors such as age and sex do not accurately predict or explain recurrence in patients with stage IA NSCLC. Therefore, we focused on the risk factors for recurrence and unfavorable OS in the present study. When describing the survival experience of a group of patients, the OS parameter is typically used. However, OS is affected by death resulting from causes other than lung cancer itself, including complications and comorbidities, and is considered to be affected by treatment after relapse. For example, epidermal growth factor receptor tyrosine kinase inhibitors are highly effective against mutated epidermal growth factor receptor recurrent NSCLC patients, suggesting potential improvements in postoperative survival regardless of surgery effect. Therefore, in evaluating pure surgical impact on the natural history of early-stage NSCLC, we consider that RFP may be a better prognostic indicator than OS. On multivariate analyses, we identified five independently significant predictors for poor prognosis: older age (HR = 1.936), male sex (HR = 2.096), tumor size (HR = 1.501), poorly differentiated carcinoma (HR = 1.632), lymph-vessel invasion (HR = 1.579), and nonadenocarcinoma (HR = 1.704); we also identified three predictors of recurrence: poorly differentiated carcinoma (HR = 1.925), blood-vessel invasion (HR = 1.712), and lymph-vessel invasion (HR = 1.751). The present study showed that independent predictive factors of poor survival were slightly different from predictive factors of recurrence.

Several authors reported that patients with poor differentiated carcinomas after resection had a higher risk of recurrence and death.[14,23,24] Although the histological grading system may provide useful information in defining the aggressiveness of tumors and has a significant impact on the survival of patients,[19] the four-tiered system of grading (well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated carcinomas) for lung cancer is assumed to lack objectivity, because no original criteria have been developed for standardizing lung cancer histology. However, the current result indicates that poor differentiation contributes to unfavorable clinical outcome, suggesting that this factor may be a useful indicator of a need for postoperative adjuvant chemotherapy in patients with stage IA NSCLC. Consistent grading criteria need to be established for reproducible assessment.

Blood-vessel invasion is considered to be a fundamental step in hematogenous metastasis. The presence of blood-vessel invasion was previously found to be a strong

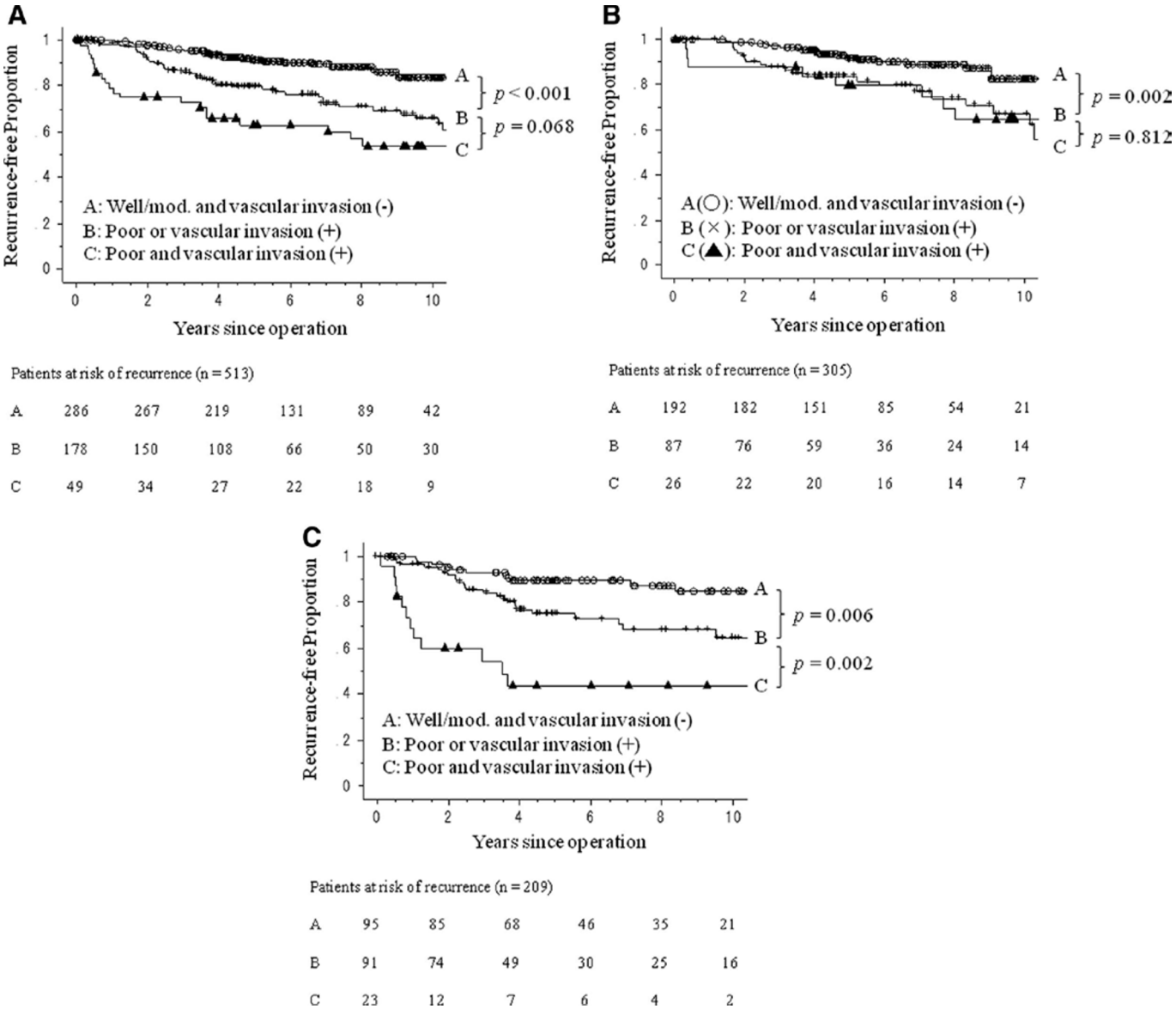

FIGURE 3. *A*, Recurrence-free proportion curves for all stage IA; *B*, T1a; and *C*, T1b patients with well- or moderately differentiated carcinoma and no vascular invasion (curve A), poorly differentiated carcinoma or vascular invasion (curve B), and both poorly differentiated carcinoma and vascular-invasion (curve C).

independent unfavorable prognostic factor, and vascular invasion should be considered for inclusion in the staging criteria and indications for adjuvant chemotherapy.[10,11,13] Fujisawa et al.[25] demonstrated that blood-vessel invasion is a very important prognostic factor in resected NSCLCs with intrapulmonary metastasis, and may correlate with the anatomical aspect of pulmonary metastasis. The current study also suggests that the presence of blood-vessel invasion is a significant risk factor for recurrence in stage IA NSCLC patients.

To identify blood-vessel invasion more accurately, we used hematoxylin and eosin and EvG stains to visualize elastic fibers in all cases. We recommend the routine use of elastic stains in the pathological evaluation of lung cancer, not only for the determination of visceral pleural invasion but also for the determination of blood-vessel invasion, particularly in patients with stage IA NSCLC.

Lymph-vessel invasion has been reported to be an independent indicator of cancer invasiveness and poor prognosis in most studies that included this factor in their analyses.[9,18,26,27] The present study shows that as it is for histological grade, lymph-vessel invasion was a significant predictor of both poor prognosis and cancer recurrence, surpassing tumor size in pathologic stage IA NSCLC.

Recent randomized controlled trials have demonstrated the usefulness of postoperative adjuvant chemotherapy in stage IB to IIIA NSCLC patients who have undergone complete resections.[28–30] Although surgery alone remains the

TABLE 5. Initial Observed Cancer Recurrence Patterns of Patients According to Histological Grade and Vascular-Invasion Status

Initial Recurrence Pattern	Tumor Differentiation			Vascular Invasion		
	Well/ mod.	Poor	*p* Value	Absent	Present	*p* Value
Overall (%)	425 (82)	96 (18)		340 (65)	180 (35)	
Patients with recurrence (%)	64 (15)	35 (36)		46 (14)	53 (29)	
Local recurrence only	24 (38)	9 (25)	0.048	19 (41)	14 (26)	0.025
Distant recurrence	39 (62)	27 (75)		27 (59)	39 (74)	

Well/mod., well- or moderately differentiated carcinoma; Poor, poorly differentiated carcinoma.

standard treatment for patients with stage IA NSCLC, larger studies on resected cases comparing uracil-tegafur adjuvant chemotherapy versus observation showed that uracil-tegafurimproved survival for patients with stage I adenocarcinoma, and also showed a clear survival benefit in the T1-disease subgroup of patients with a tumor of diameter more than 2 cm.[31,32] However, tumor size might not be the only factor found to have a benefit on adjuvant chemotherapy after complete resection of stage IA NSCLC. In the present study, when we divided the study population into A (patients without any risk factors), B (those with either poorly differentiated carcinoma or vascular invasion), and C (those with both poorly differentiated carcinoma and vascular invasion) groups, the 5-year RFP of all stage IA patients were 91.3%, 79.5%, and 62.9%, respectively. In particular, the subgroup analysis of patients with stage IA disease stratified by tumor size showed a 5-year RFP of 43.3% for the T1b C group. These results indicated high-risk small-tumor N0 patients, identified by factors other than tumor size, such as tumor differentiation and vascular invasion, may be good candidates for adjuvant chemotherapy.

This study has limitations and biases that should be mentioned. As a retrospective single-institute study, patient-selection bias and time-trend bias regarding the diagnosis for cancer recurrence might be inevitable compared with multi-institutional prospective study. Moreover, the definition of an ipsilateral lung metastasis as a local recurrence also generated inherent bias while allowing the differentiation of a new primary lung cancer from a recurrent NSCLC.

The anatomical extent of disease, as described by the TNM for lung and pleural tumors, remains the most powerful prognostic instrument in NSCLC. A challenge for the future will be to integrate the TNM with specific pathological factors, such as vascular-invasion status or tumor differentiation, to create a composite prognostic index for NSCLC.

CONCLUSION

Even though most patients comprised an early-staging subset, those with stage IA NSCLC comprised a heterogeneous group with different prognoses and risk of cancer recurrence. The current study demonstrates that vascular-invasion status and tumor differentiation were far more powerful recurrence predictive factors than tumor size, and this information can be useful for the selection of the appropriate therapeutic strategy, including adjuvant chemotherapy, which can be tailored to the individual patient's risk of developing recurrence.

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