Prognostic impact of intratumoral vessel invasion in completely resected pathologic stage I non-small cell lung cancer

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Objective: Intratumoral vessel invasion of non-small cell lung cancer is a readily available tumor-related factor that provides direct evidence of microscopic tumor invasion. We assessed the prognostic influence of intratumoral vessel invasion and its ability to provide a differential prediction of prognosis for completely resected pathologic stage I non-small cell lung cancer.

Methods: We analyzed 258 patients with non-small cell lung cancer who underwent complete resection between January of 1996 and December of 2005 and were diagnosed with pathologic stage I disease. In addition to the conventional staging factors, intratumoral vessel invasion in the primary lesion was histologically evaluated by both hematoxylin-eosin and elastic staining. We examined the significance of intratumoral vessel invasion in prognosis and compared the outcomes between patients with and without this factor with stage IA and IB disease, respectively.

Results: Intratumoral vessel invasion was found in 124 patients (48%). Five-year survival of patients with or without intratumoral vessel invasion was 74% and 93%, respectively. On multivariate analysis, intratumoral vessel invasion and pleural invasion were shown to be independent prognostic factors. Subgroup analyses suggested that patients with pathologic-stage IA with intratumoral vessel invasion and patients with pathologic-stage IB with both intratumoral vessel and pleural invasion had significantly worse prognosis than patients with the same pathologic stage without these factors.

Conclusion: The current study indicated that intratumoral vessel invasion and pleural invasion are independent prognostic factors. Intratumoral vessel invasion status can complement the size-dependent TNM staging system in pathologic stage I non-small cell lung cancer.

Surgical resection still remains the most effective therapy for patients with non-small cell lung cancer (NSCLC) limited to the lung, especially stage I disease. However, reported survival outcome for resected stage I NSCLC may not be enough to be satisfied. According to several large studies, 5-year survivals in resected stage IA and IB disease were 67% to 89% and 57% to 75%, respectively.¹⁻⁶ There is some variation in the survival data in the literature. One of the reasons for this variation is that stage I NSCLC includes populations with a different grade of malignancy. It is important to identify prognostic factors that reflect a risk of mortality more precisely to make a reasonable staging diagnosis and to determine the population who can benefit from adjuvant therapy for stage I NSCLC.

Some prognostic factors have been proposed for patients with NSCLC. We have routinely examined intratumoral vessel invasion (IVI; the evidence of lymphatic vessel invasion [LVI] or blood vessel invasion [BVI]) status in addition to factors for conventional TNM staging. Evaluation of IVI sta-

tus is valuable for 2 reasons: 1) It provides direct microscopic evidence of tumor invasiveness and aggressiveness. 2) It is readily available and can be objectively classified compared with other morphologic classifications, such as grade of differentiation. The purpose of the current study was to examine clinicopathologic factors, including IVI, in 258 patients who were treated in a similar manner and to identify the readily available factors that predict patients with a high risk of mortality with pathologic (p-) stage I NSCLC.

PATIENTS AND METHODS

Between January of 1996 and December of 2005, 452 patients with NSCLC consecutively underwent surgery at Okayama Red Cross General Hospital. Of these patients, 258 were pathologically proven to have single stage I disease. We retrospectively reviewed these 258 cases with regard to patient characteristics, tumor pathologic findings, and follow-up status to examine the prognostic factors of value in patients with p-stage I NSCLC. All patients in this study cohort had a preoperative systemic workup that consisted of enhanced computed tomography of the entire trunk, magnetic resonance imaging of the brain, and bone scintigraphy, which proved that they had no distant metastasis. Patients with multiple lung cancers were excluded. The tumors were resected with no pathologic evidence of residual tumor at the surgical margin. Regional lymph nodes in the hilum and mediastinum were also resected. The majority of patients underwent lobectomy or pneumonectomy for resection of the primary lesion. In cases of lesser pulmonary resection (wedge resection or segmentectomy), segmental or subsegmental nodes were pathologically evaluated by intraoperative frozen-section examination and confirmed as negative. All excised specimens were formalin-fixed and sliced at 10-mm intervals. Histopathologic examination was performed by the same pathologist (T.K.). Pathologic staging was determined according to the International Union Against Cancer

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Abbreviations and Acronyms

BAC	= bronchioloalveolar carcinoma
BVI	= blood vessel invasion
CEA	= carcinoembryonic antigen
IVI	= intratumoral vessel invasion
LVI	= lymphatic vessel invasion
NSCLC	= non-small cell lung cancer
p	= pathologic

TNM classification of malignant tumors.⁷ Histologic subtypes of lung cancer were determined according to World Health Organization classification.⁸ None of the patients received postoperative chemotherapy or radiotherapy. All patients were followed up every 6 months at our outpatient clinic after surgery.

Variables for Prognostic Analyses

We adopted the following factors as variables for this retrospective prognostic analysis: age, gender, tumor diameter, pathologic evidence of pleural invasion and IVI, histologic subtypes, extent of resection, and preoperative serum carcinoembryonic antigen (CEA) levels. Data were abstracted from medical and laboratory records by the authors. Informed consent for use of the clinical data was obtained preoperatively from the patients, and the institutional review board of the Okayama Red Cross General Hospital waived the need for approval of the study. Pleural and vessel invasion in the primary lesion were evaluated by hematoxylin-eosin and elastic staining (Elastica van Gieson stain). The presence of IVI was determined by identifying conspicuous findings of intravascular cancer clusters surrounded by an elastic layer at the maximum section of the primary lesion. Cases that the pathologist considered as equivocal were classified as the absence group. Preoperative serum CEA levels were assessed by enzyme-linked immunosorbent assay kits, with an upper limit of normal of 5.0 ng/mL.

Statistical Analyses

Two-category comparison was performed by Pearson's chi-square test for quantitative data, presupposing a normal distribution. Survival probability was calculated by the Kaplan-Meier method. The prognostic value of the above-mentioned individual variables was tested by the log-rank test in univariate analyses. To determine independent prognostic factors, multivariate analysis was conducted by the Cox proportional hazards model (Wald stepwise backward elimination method). Patient death, regardless of cause, was defined as the terminal event. T1 (p-stage IA) and T2 (IB) cases were respectively classified as 2 subgroups according to the existence of IVI (IVI+ or IVI-), and the difference between the survival curves for each group was analyzed by the log-rank test. Differences were considered as clinically significant at $P < 0.01$. Calculations and statistical tests were performed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Ill).

RESULTS**Clinicopathologic Characteristics**

Patients' clinicopathologic characteristics are shown in Table 1. The study cohort included 166 men and 92 women, with a mean age of 67 years (range: 39–89 years; standard deviation: 9.8). Lobectomy or pneumonectomy was performed in 243 patients (94%), and lesser pulmonary resection was performed in 15 patients (6%). Diagnosis of p-stage IA (T1) disease was made in 176 patients (68%), and diagnosis of p-stage IB (T2) was made in 82 patients

TABLE 1. Clinicopathologic characteristics

Factors	No.(%)
Age	
<70 y	143 (55)
≥70 y	115 (45)
Gender	
Female	92 (36)
Male	166 (64)
p-stage	
IA	176 (68)
IB	82 (32)
Tumor diameter (mm)	
≤30	183 (71)
>30	75 (29)
Pleural invasion	
Absence (p0)	222 (86)
Presence (p1 or p2)	36 (14)
IVI	
Absence	134 (52)
Presence	124 (48)
Histologic types	
Adenocarcinoma	185 (72)
Other	73 (28)
Extent of resection	
Lobectomy or pneumonectomy	243 (94)
Wedge resection or segmentectomy	15 (6)
Preoperative serum CEA level	
Normal	209 (81)
Elevated	49 (19)

IVI, Intratumoral vessel invasion; CEA, carcinoembryonic antigen; p, pathologic.

(32%). Seventy-five patients (29%) had a tumor greater than 30 mm in diameter, and 36 patients (14%) had a tumor with pathologically proven pleural invasion (p1 or p2). There were 185 patients (72%) with adenocarcinoma and 73 patients (28%) with other histologic types. Of 185 patients with adenocarcinoma, 12 had a diagnosis of true bronchioloalveolar carcinoma (BAC). IVI was found in 124 patients (48%). Of these 124 lesions, LVI was found in 114 patients, and BVI was found in 76 patients. The detection rates of LVI and BVI were 44% and 29%, respectively. The preoperative serum CEA level was elevated in 49 patients (19%). Comparison of clinicopathologic features between the absence and the presence of IVI showed that IVI tended to be detected more frequently in those with larger-sized tumors, squamous cell carcinoma, and elevated CEA. A significant difference in the IVI+ rate was seen in tumor diameter and histologic types (Table 2). The median postoperative follow-up time was 56 months (range, 1–136 months). There were 44 deaths during the follow-up period, and 31 of these were cancer related. The overall 5-year survival was 84% (p-stage IA, 89%; p-stage IB, 73%).

Univariate/Multivariate Prognostic Analyses

The results of univariate analysis are shown in Table 3. Clinically significant survival predictors shown by

TABLE 2. Relationship between intratumoral vessel invasion and other clinicopathologic factors

Factors	IVI		Positive rate (%)	P value
	Absence	Presence		
Tumor diameter (mm)				
≤20 (n = 122)	88	34	28	<.001
>20, ≤30 (n = 61)	24	37	61	
>30 (n = 75)	22	53	71	
Histologic type				
Adenocarcinoma (n = 185)	108	77	42	.003
Squamous cell carcinoma (n = 50)	16	34	68	
Other (n = 23)	10	13	57	
Preoperative serum CEA				
Normal (n = 209)	117	92	44	.011
Elevated (n = 49)	17	32	65	

IVI, Intratumoral vessel invasion; CEA, carcinoembryonic antigen.

univariate analysis were age (<70 vs ≥70 years, $P = .004$), tumor diameter (≤30 vs >30 mm, $P = .0007$), pleural invasion (absence vs presence, $P < .0001$), and IVI (absence vs presence, $P < .0001$). Survival curves of the IVI+ and IVI− groups are shown in Figure 1. The 5-year survival of patients with IVI and patients without IVI was 74% and 93%, respectively. The 4 clinicopathologic factors of age, tumor size, pleural invasion, and IVI, which were shown as important predictors in univariate analysis, were included as covariates for multivariate analysis 1. Of these factors, IVI was shown to be a prognostic factor that retained an independent level of significance ($P = .009$), as was pleural invasion ($P = .001$) (Table 4). On multivariate analysis 2, the tumor diameter was stratified into 3 categories (≤20, >20 and ≤30, >30) based on the proposed staging system (dividing T1 ≤ 30 into T1a ≤ 20 and T1b > 20). On this setting, the prognostic influence of IVI decreased but was marginally significant ($P = .032$, hazard ratio 2.3; 95% confidence interval, 1.1–5.0) (Table 5).

Subgroup Survival Analyses

Survival curves of subgroups stratified according to both T factor (T1 or T2) and IVI (IVI+ or IVI−) are shown in Figure 2. The 5-year survival of each stratified group was as follows: T1/IVI− group (n = 114), 95%; T1/IVI+ group (n = 62), 78%; T2/IVI− group (n = 20), 84%; T2/IVI+ group (n = 62), 69%. The difference in survival probability between IVI− and IVI+ was clinically significant in the T1 (stage IA) group ($P = .001$) but not in the T2 (stage IB) group, although the IVI+ group had a tendency toward a worse outcome. Difference in survival probability was not important in the T1/IVI+ versus T2/IVI− ($P = .49$) and T1/IVI+ versus T2/IVI+ ($P = .38$) groups. An additional subgroup analysis focused on the p-stage IB group revealed that patients who had the tumor with both IVI and pleural

TABLE 3. Univariate prognostic analysis

Variable	5-y survival (%)	P value
Age		
<70 y	89	.0042
≥70 y	77	
Gender		
Female	94	.019
Male	79	
Tumor diameter (mm)		
≤30	88	.0007
>30	74	
Pleural invasion		
Absence	89	<.0001
Presence	51	
Histologic types		
Adenocarcinoma	87	.011
Other	76	
IVI		
Absence	93	<.0001
Presence	74	
Extent of resection		
Lobectomy or pneumonectomy	83	.39
Wedge resection or segmentectomy	93	
Preoperative serum CEA level		
Normal	86	.020
Elevated	75	

IVI, Intratumoral vessel invasion; CEA, carcinoembryonic antigen.

invasion (5-year survival, 43%) showed more unfavorable prognosis than other patients with p-stage IB ($P = .007$) (Figure 3).

DISCUSSION

We confirmed IVI (LVI or BVI) and pleural invasion as independent prognostic factors in resected p-stage I NSCLC, and the additional subgroup analyses suggested that patients

FIGURE 1. Kaplan–Meier survival curve for patients with p-stage I NSCLC, stratified according to IVI. OS, Overall survival; IVI, intratumoral vessel invasion.

TABLE 4. Multivariate prognostic analysis 1

Covariates	Hazard ratio (95% CI)	P value (Wald test)
Age		
<70 vs ≥70 y	2.3 (1.2–4.4)	.011
Tumor diameter (mm)		
≤30 vs >30	1.6 (0.9–3.1)	.12
Pleural invasion		
absence vs presence	3.1 (1.6–6.1)	.001
IVI		
Absence vs presence	2.7 (1.3–5.8)	.009

IVI, Intratumoral vessel invasion; CI, confidence interval.

with p-stage IA with IVI and patients with p-stage IB with both IVI and pleural invasion had worse prognosis than those with the same p-stage without these factors. Although the present study was retrospective and relatively small scale, the analyzed patients received a similar quality of treatment with an overall 5-year survival of 84%, which was reasonable for an outcome of p-stage I disease. All operations were performed by the same surgeon, and all specimens were pathologically evaluated by the same single pathologist throughout the study period. Even in patients with IVI (74%), our 5-year survival data show much better results than the data reported by Mountain⁴ for stage IA (67%) and stage IB (57%) disease, on which the current TNM staging system is based. This survival discrepancy may be because more patients with cancer relapse in our series received chemotherapy with the new generation of agents. Our results can be applicable to North American and European patients only if the pathologic staging for each case is sufficiently reliable.

Although the pathologic TNM staging system has been considered to have an impact on survival in NSCLC, problems such as overlapping prognosis for patients with different tumor stages and heterogeneous prognosis for patients with the same tumor stage have been pointed out.^{2,6} These problems need to be resolved to provide reasonable adjuvant treatment or follow-up care for each patient with differing risk of relapse or tumor death. Several retrospective studies have examined the prognostic effect of the clinicopathologic factors to identify patients with a different prognosis at each stage or in some stratified groups. IVI has been shown to be a strong independent predictor for p-stage I disease in most studies that adopted this factor as a variable for analyses,^{9–14}

TABLE 5. Multivariate prognostic analysis 2

Covariates	Hazard ratio (95% CI)	P value
Tumor diameter (mm)		
≤20 vs >20, ≤30	2.3 (1.0–5.6)	.054
≤20 vs >30	3.2 (1.4–7.3)	.005
Pleural invasion		
Absence vs presence	2.7 (1.4–5.2)	.003
IVI		
Absence vs presence	2.3 (1.1–5.0)	.032

IVI, Intratumoral vessel invasion; CI, confidence interval.

FIGURE 2. Kaplan-Meier survival curve for patients with p-stage I NSCLC, stratified according to pathologic T factor and IVI. IVI, Intratumoral vessel invasion.

with few exceptions.^{15,16} Both the current and previous studies suggest that IVI status can provide a differential prediction of prognosis for patients with resected p-stage I disease.

The extent that elastic staining contributes to the detection of IVI is not known. However, the value of elastic staining can be inferred by referring to past literature in which IVI was evaluated. The detection rates of LVI and BVI in p-stage I without the elastic staining method were 0% to 3% and 11% to 16%, respectively.^{10,11} In contrast, the detection rates of LVI and BVI with the elastic staining method were 40% to 52% and 27% to 56%, respectively.^{9,12,17} The reported detection rate of IVI was higher in the studies in which IVI was evaluated by elastic staining. This indicates that elastic staining enables pathologists to more precisely detect IVI. In addition, elastic staining is also helpful to identify visceral pleural invasion. Taube and colleagues¹⁸ reported that elastic staining resulted in the change of tumor stage from IA to IB in 19% of patients

FIGURE 3. Kaplan-Meier survival curve for patients with p-stage IB disease, stratified according to IVI and pleural invasion. OS, Overall survival. IVI, Intratumoral vessel invasion.

with a pathologic negative diagnosis of pleural invasion by means of hematoxylin-eosin staining. This supports the validity of using elastic staining for the histopathologic evaluation of lung cancer specimens.

In most previous studies regarding tumor vessel invasion, BVI and LVI were treated separately. However, we doubt the importance of the separation between LVI and BVI. There is some variation in the reported detection rate of LVI and BVI for p-stage I NSCLC (LVI: 3%–50%; BVI: 11%–44%).^{9,10,12,13,15,16} Pathologists usually differentiate blood vessels from lymphatic vessels according to the evidence of blood cells in endothelium-lined channels, and differentiation between them can be subjective, especially in capillary areas. There is some ambiguity in the differentiation between LVI and BVI. We used hematoxylin-eosin and Elastica van Gieson stain for the evaluation. These staining methods were reliable for the detection of tumor cells in vessels, although the ability to differentiate between LVI and BVI was limited. We think that the IVI factor (grouping together LVI and BVI) is readily available and can be objectively classified (positive or negative).

Among the tumor factors, the tumor diameter in the maximum dimension is a valuable and readily available prognostic factor based on gross anatomic findings. The sixth edition of the *International Union Against Cancer* TNM staging system adopted a diameter of 30 mm for the threshold of stratification between T1 and T2. To improve the ability to provide a differential prognosis, some new thresholds of size stratification (eg, 20 and 50 mm) have been proposed.^{19–21} However, clinicians sometimes encounter patients who have a worse prognosis than they expect, based on tumor size, as well as patients who have a better prognosis. The current study and some previous studies have shown no significance of tumor size for prognosis in resected p-stage I NSCLC by multivariate analysis.^{9,13,22} One of the reasons for the discrepancy between size classification and prognosis is the existence of cases with some discrepancy between tumor size and invasiveness. For adenocarcinoma, an increasing number of tumors with a component of BAC have recently been detected. The BAC component involves neither stroma nor vessels, and patients with a large BAC component have been known to have a good clinical outcome.²³ Differences in the proportion of the BAC component can cause size-independent prognosis in patients with adenocarcinoma. IVI can act as a prognostic factor in patients whose prognosis cannot be precisely predicted on the basis of tumor size. In the next revision, the proposed TNM staging system for lung cancer has created the T1a descriptor for tumors 20 mm or less and the T1b descriptor for tumors more than 20 mm to 30 mm or less. Although the proposed size classification may predict tumor invasiveness and prognosis better than the current system, we think the IVI factor complements the staging system even in the proposed staging setting according to our additional multivari-

ate analysis (Table 5). We think that IVI status directly indicates microscopic tumor progression. Prognostic prediction using IVI is applicable to any tumors regardless of histology and complements the present size-dependent TNM staging system.

In the subgroup analysis of the current study, a survival difference between the IVI+ and IVI– groups was found in patients with stage IA (T1), but not in patients with stage IB (T2). IVI is an especially strong predictor in the stage IA group. Five-year survival of the patients with p-stage IA with IVI was 78%, and no significant survival advantage was found compared with patients with p-stage IB. There was no clinical difference in the p-stage IB group with IVI, perhaps because pleural invasion had an influence on the survival data. Pleural invasion status is well recognized as a strong prognostic factor.^{9,10,15,22,24,25} Our study also confirmed pleural invasion as an independent predictor. Although the stage IB group could not be classified into groups with obviously different prognosis by IVI only, we found a worse prognosis in patients with stage IB with both IVI and pleural invasion than in patients without these factors. The coexistence of IVI and pleural invasion is considered to predict a poor prognosis in patients with stage IB.

Although the survival benefit of adjuvant therapy for resected NSCLC has been expected in some trials,^{26,27} it is, so far, controversial with regard to stage I disease. The latest report of the Cancer and Leukemia Group B protocol 9633 trial revealed no significant overall 5-year survival for adjuvant chemotherapy with carboplatin and paclitaxel in stage IB disease.²⁸ However, there are some problematic points for the Cancer and Leukemia Group B protocol 9633 trial, such as a heterogeneous population of the study cohort.²⁹ Studies on the survival benefit of adjuvant therapy in some subsets of patients should be conducted on the premise that patients are classified using a reasonable staging system. Clinical trials of adjuvant therapy for a well-selected population with stage I disease and poor prognosis are needed. IVI should be considered as one of the tumor-related factors in patient selection for future trials of adjuvant therapy. We diagnosed stage IA in patients with an obviously poor prognosis using stratification by IVI. Even in patients with stage IA, there may be some subsets of patients who benefit from adjuvant chemotherapy, although adjuvant therapy for patients with stage IA is not recommended at present.¹⁴

CONCLUSIONS

IVI status and pleural invasion were found to be independent prognostic factors in resected p-stage I NSCLC. Poor prognosis was observed in patients with p-stage IA with IVI and patients with p-stage IB with both IVI and pleural invasion. Prospective studies that examine the benefit of adjuvant chemotherapy for patients with p-stage I with IVI and pleural invasion are warranted.

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