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Clinical significance of lymphatic vessel invasion in stage I non-small cell lung cancer patients

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ABSTRACT. The aim of this retrospective study was to evaluate the prognostic influence of lymphatic vessel invasion (LVI) in stage I non-small cell lung cancer (NSCLC) patients. From January 2004 to December 2007, LVI was detected in 57 patients with T1N0M0 NSCLC; therefore, 114 patients with the same pathology, T stage, and surgery method, but without LVI, were selected as the control group to compare survival. The overall survival and relapse-free survival rates were estimated using the Kaplan-Meier method, log-rank test, and Cox proportional hazards analysis. The average follow-up length was 59.94 ± 23.1 months. The 5-year overall survival rates of the LVI-negative and the LVI-positive groups were 90.54 and 70.1%, respectively (P = 0.002). A multivariate analysis revealed LVI to be an independent predictive factor (hazard ratio = 4.562; P = 0.004). The 5-year overall survival rates for patients who received postoperative adjunctive therapy and those who did not in the LVI-positive group were 88.2 and 61.5%, respectively, with a P value less than 0.05 in both univariate and multivariate analyses. LVI is a poor prognostic factor in stage I NSCLC patients; postoperative adjunctive therapy is needed to improve the

prognosis of NSCLC patients with LVI.

Key words: Lymphatic vessel invasion (LVI); Prognosis; Postoperative adjunctive therapy; Stage I non-small cell lung cancer (NSCLC)

INTRODUCTION

Non-small cell lung cancer (NSCLC) constitutes approximately 80% of primary lung cancers, which is the most common malignancy worldwide (Jemal et al., 2011). Surgical resection remains the most effective therapy for NSCLC, especially early stage disease. However, the 5-year survival rate of patients with stage I NSCLC is only 79.4%. Dozens of factors lead to disease recurrence and death for early stage NSCLC patients, and according to recent reports, angiogenesis and lymphangiogenesis are involved in tumor metastasis (Folkman, 1990; Padera et al., 2002). To investigate the clinical significance of lymphangiogenesis in NSCLC, we evaluated lymphatic vessel invasion (LVI). In the tumor-node-metastasis (TNM) staging system, LVI is not considered an independent prognostic factor. Thus, in accordance with lung cancer treatment guidelines, postoperative adjuvant therapy is not routinely recommended for stage I NSCLC, regardless of the presence of LVI (Scott et al., 2007).

We retrospectively reviewed the medical records of 57 NSCLC patients with LVI and 114 patients without LVI to investigate the relationship between LVI and prognosis and to determine whether postoperative adjuvant therapy should be administered to early stage NSCLC patients with LVI.

MATERIAL AND METHODS

Patient selection

We retrospectively reviewed the records of 171 patients with stage I NSCLC, admitted to our hospital from January 2004 to June 2007, who underwent surgery. This included 57 patients with LVI and 114 with the same pathology, T stage, and surgery method, but without LVI. All cases were classified into 2 subgroups according to the presence or absence of LVI (LVI+ or LVI-, respectively). Clinical data were obtained from medical records, and follow-up was conducted by direct patient contact; overall survival (OS), relapse-free survival (RFS), and metastasis location were recorded. The follow-up period ranged from 49 to 90 months, with an average follow-up of 59.94 months. Tumors were pathologically staged according to the seventh edition of the TNM classification for lung and pleural tumors of the International Union Against Cancer (Sobin et al., 2009). Histopathological studies were done based on World Health Organization criteria. Sections were stained with hematoxylin and eosin, and the Elastica van Gieson method was used to identify the existence of LVI. Patients' clinicopathologic characteristics are shown in Table 1.

Statistical analyses

OS and RFS were calculated using the Kaplan-Meier method, and differences in survival were tested by the log-rank method and Breslow method in univariate analyses. OS was

from the date of pulmonary resection to the date of death from any cause. The last follow-up observation was censored when the patient was alive or lost to follow-up. To determine independent prognostic factors, multivariate analysis was conducted using the Cox proportional hazards model (Wald stepwise backward elimination method). P values less than 0.05 were considered to be statistically significant. All statistical analyses were performed with the PASW statistics software package version 13 (SPSS, Inc., Chicago, IL, USA).

Table 1. Patient characteristics in the LVI+ and LVI- groups based on various clinicopathologic factors.

	LVI+	LVI-	P value
Cases (N)	57	114	
Age [years (mean)]	57.29	53.08	0.841
Gender (N)			0.669
Male	43	89	
Female	14	25	
Surgical procedure (N)			S
Lobectomy	48	96	
Limited resection	9	18	
Tumor stage (N)			S
T1a	32	64	
T1b	25	50	
Histological type (N)			S
Adenocarcinoma	33	66	
Squamous cell carcinoma	14	28	
Others	10	20	
Postoperative treatment (N)			0.205
Yes	17	24	
No	40	90	

P values were analyzed using the chi-square test, and values <0.05 were considered to be significant. LVI+ = lymphatic vessel invasion-positive; LVI- = lymphatic vessel invasion-negative; S = same proportion of each variable.

RESULTS

At the time of the last follow-up, 15 patients died in the LVI+ group, and 11 died in the LVI- group. The 5-year OS rates of the LVI+ and LVI- groups were 70.10 and 90.54%, respectively. The survival rate curve is depicted in Figure 1. The difference in survival was statically significant (P = 0.002). Patients' OS and RFS rate are shown in Table 2.

Metastasis and recurrence occurred in 19 patients in the LVI+ group and 16 patients in the LVI- group. The 5-year RFS rate in the LVI- group was 88.75%, significantly higher than that in the LVI+ group (69.68%; P = 0.001). The survival rate curve is shown in Figure 2.

Patients' OS rates and RFS rates are shown in Table 2. A univariate analysis determined LVI (yes *vs* no 70.1 *vs* 90.54%; P = 0.002) and postoperative adjuvant treatment (yes *vs* no 94.9 *vs* 79.7%; P = 0.024) were significant poor prognostic factors. The remaining prognostic factors, such as T stage (T1a *vs* T1b: 85.71 *vs* 81.53%; P = 0.475), surgical procedure (lobectomy *vs* limited resection: 84.72 *vs* 73.94%; P = 0.249), and pathology (adenocarcinoma *vs* squamous carcinoma *vs* others: 87.08 *vs* 81.57 *vs* 77.12%; P = 0.398), were not significant predictive factors for survival (Table 3).

To determine whether these indicators were independently prognostic of OS, we also performed a multivariate analysis with a Cox proportional hazards model. The multivariate analysis revealed the independent prognostic influence of LVI and postoperative adjuvant therapy on OS, with hazard ratios of 4.562 (95% confidence interval: 1.430-6.986; P = 0.004) and 3.161 (95% confidence interval: 1.062-19.589; P = 0.041), respectively (Table 4).

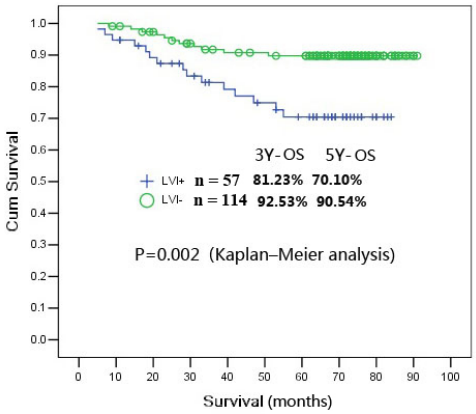

Figure 1. Overall survival of the LVI+ and LVI- groups (Kaplan-Meier method). The 5-year overall survival (OS) rates of the lymphatic vessel invasion (LVI)-positive group and the LVI-negative group were 70.10 and 90.54%, respectively, as determined by the Kaplan-Meier method and tested with the log-rank test. It was obvious that the prognosis of patients in the LVI-negative group was inferior to that of patients in the LVI-positive group.

Table 2. Overall survival and relapse-free survival rates in the LVI+ and LVI- groups.

	OS (%)		P value	RFS (%)		P value
	LVI+	LVI-		LVI+	LVI-	
6 months	98.25	100	P = 0.002	98.25	100	P = 0.001
1 year	94.67	99.12		92.94	99.12	
2 years	87.25	95.50		82.01	97.31	
3 years	81.23	92.53		74.11	91.69	
5 years	70.10	90.54		69.68	88.75	

P values were analyzed using the Kaplan-Meier method and tested using the log-rank test. P values < 0.05 were considered to be significant. The survival differences for both OS and RFS were significant, with P value less than 0.05. This indicates that LVI is a poor prognostic factor in stage I NSCLC patients. LVI+ = lymphatic vessel invasion-positive; LVI- = lymphatic vessel invasion-negative; OS = overall survival; RFS = relapse-free survival; NSCLC = non-small cell lung cancer.

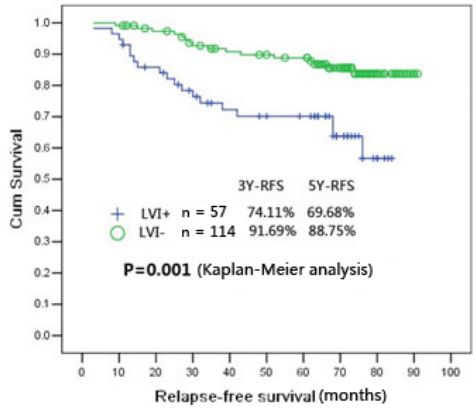

Figure 2. Relapse-free survival (RFS) of the LVI+ and LVI- groups (Kaplan-Meier method). The 5-year RFS rates of the lymphatic vessel invasion (LVI)-positive group and the LVI-negative group were 69.68 and 88.75%, respectively. The survival difference was significant (P = 0.001) by analysis using the Kaplan-Meier method and tested with the log-rank rest.

Table 3. Relationship between categorical variables and patient survival by univariate prognostic analysis (Kaplan-Meier method).

	Cases (N)	5-year survival (%)	P value
Pathology	171		0.398
Adenocarcinoma	99	87.08	
Squamous carcinoma	42	81.57	
Other	30	77.12	
T stage	171		
T1a	96	85.71	0.475
T1b	75	81.53	
Postoperativetreatment	171		
No	130	79.70	0.024
Yes	41	94.90	
Surgery method	171		
Lobectomy	144	84.72	0.249
Limited resection	27	73.94	
LVI	171		
Yes	57	70.10	0.002
No	114	90.54	

P values were analyzed using the Kaplan-Meier method and tested using the log-rank test. P values < 0.05 were considered to be significant. Postoperative treatment, postoperative adjuvant chemotherapy and radiotherapy; T stage, T1a and T1b according to the TNM classification system of the International Union Against Cancer (7th edition); LVI = lymphatic vessel invasion.

Table 4. Multivariate analysis of risk factors for overall survival in stage I NSCLC patients using the Cox proportional hazards model.

	P value (Wald)	95%CI for EXP B		
		EXP (B)	Min	Max
Pathology	0.257	1.356	0.800	2.298
LVI	0.004	4.562	1.430	6.986
T stage	0.476	0.746	0.333	1.671
Postoperative treatment	0.041	3.161	1.062	19.589
Surgery method	0.658	1.264	0.449	3.556

P values < 0.05 were considered to be statistically significant. CI = confidence interval; Pathology = adenocarcinoma, squamous carcinoma, and other NSCLC types; LVI = lymphatic vessel invasion; T stage = T1a and T1b according to the TNM classification system of the International Union Against Cancer (7th edition); Postoperative treatment = postoperative adjuvant chemotherapy and radiotherapy; Surgery method = lobectomy and limited resection.

There were 17 patients who received postoperative adjuvant therapy in the LVI+ group, and the 5-year survival rate was 88.2%, significantly higher than that of remaining patients (61.5%; P = 0.047; Figure 3). Metastasis locations are shown in Figure 4.

DISCUSSION

The TNM staging system is the most effective instrument for assessing NSCLC, and lymph node metastasis is a well-known poor prognosis factor. For stage I NSCLC patients, the 5-year survival rate is 79%, which means that up to 20% of patients will experience distant or local recurrence (Sawabata et al., 2010). This indicates that there are unknown poor prognostic factors in early stage NSCLC that result in unfortunate outcomes for patients. In recent years, more and more authors have emphasized the influence of LVI on the poor prognosis of NSCLC

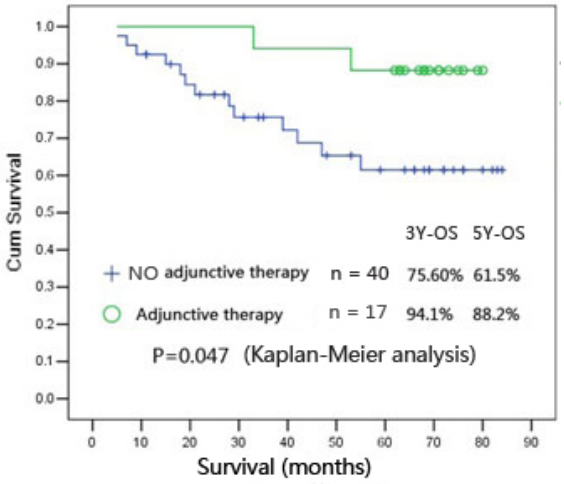

Figure 3. Overall survival (OS) of patients in the LVI+ group by receipt of postoperative adjunctive therapy (Kaplan-Meier method). In the lymphatic vessel invasion (LVI)-positive group, there were 17 patients who received adjunctive therapy, including chemotherapy and radiation therapy. The 5-year OS rate of the 17 patients was 88.2%, significantly better than that of the remaining 40 patients who did not receive adjunctive therapy (5-year survival 61.5%; P = 0.047).

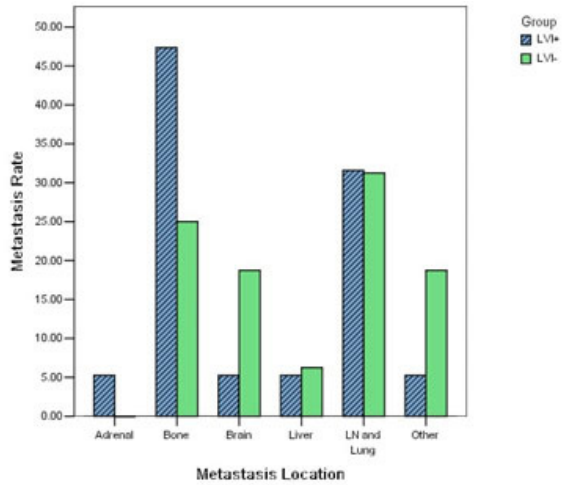

Figure 4. Metastasis location of two groups. Metastasis and disease recurrence occurred in 19 patients in the lymphatic vessel invasion (LVI)-positive group and 16 patients in the LVI-negative group. In the LVI-positive group, bone metastasis occurred in 9 patients, lymph node (LN) and lung metastasis occurred in 7 patients, and liver, brain, and adrenal metastasis each occurred in 1 patient. However, in the LVI-negative group, LN and lung metastasis occurred in 6 patients, bone metastasis occurred in 4 patients, brain metastasis occurred in 3 patients, liver metastasis occurred in 1 patient, and there was no case of adrenal metastasis.

patients, including stage I patients, who have undergone radical resection (Ichinose et al., 1994; Kessler et al., 1996; Duarte et al., 1998; Port et al., 2003; Gabor et al., 2004; Sakao et al., 2004); the frequency of radical resection generally ranges from 15 to 36% in the literature (Rigau et

al., 2002; Funai et al., 2011). In our research, we retrospectively studied the follow-up records of stage I NSCLC patients to analyze the relationship between LVI and prognosis.

The OS and RFS rates in the LVI+ group were both inferior to those in the LVI- group by univariate analysis, and these differences were statistically significant. This demonstrates that LVI is a poor prognostic factor for OS and tumor metastasis. Tumor metastasis and progression are complicated and multistep processes that begin with local invasion of tumor cells into the host stroma within or surrounding the primary tumor. Tumor cells can detach and arrest in the microvasculature and then penetrate the peripheral lymphatic system (Hanahan and Weinberg, 2011). LVI indicates that the tumors are in a metastatic phase and also predicts a poor postoperative prognosis. Tumor microvessel formation is also a key factor of lung cancer metastasis and indicates poor prognosis from the molecular level (Angeletti et al., 1996; Pastorino et al., 1997; Offersen et al., 2001). Tumor cells may secrete and release a variety of active factors, such as vascular endothelial growth factor, to induce tumor angiogenesis (Mattern et al., 1996; Fontanini et al., 1997; O'Byrne et al., 2000), thus contributing to vascular invasion, including LVI and blood vascular invasion. Goldstein et al. (1999), who reported that LVI is the worst prognostic factor in stage I NSCLC, and Shoji et al. (2010), who reported that blood vascular invasion is the worst prognostic factor in stage I NSCLC, hold opposite views. The argument will not cease because survival results between patients with blood vessel invasion (BVI) and LVI have not been compared, because no patients with BVI have been recruited to survival studies. Cote et al. (1995) concluded that LVI plays a very important role in bone metastasis in NSCLC patients. In our research, there were 19 patients (33.33%; 19/57) who had distant metastasis or recurrence; 47.37% (9/19) of patients in the LVI+ group had bone metastasis as the most likely metastasis location, and only 16 (14.04%, 16/114) patients in the LVI- group had metastasis, with 4 (25.0%, 4/16) cases occurring in the bone. However, the difference in metastasis locations between the 2 groups was not statically significant, with a P value greater than 0.05. LVI is also highly correlated with intrapulmonary metastasis in non-small cell cancer of the lung, and in some reports, it plays an important role in the metastasis and spread of lung satellite lesions (Fujisawa et al., 1995).

The survival of stage III NSCLC patients could clearly be prolonged through postoperative adjunctive therapy (Ettinger et al., 2010); it is unclear whether postoperative adjunctive therapy will also benefit stage I NSCLC patients with LVI. In studies by Kelsey et al. (2009) and Saynak et al. (2011), adjuvant chemotherapy and radiotherapy were ineffective for patients with LVI; however, Kato et al. (2004) and Tsuchiya et al. (2007) demonstrated the usefulness of oral uracil-tegafur chemotherapy after resection for stage I NSCLC. Our univariate analysis provides strong evidence that postoperative adjunctive therapy is a prognostic factor for survival in patients with NSCLC. In addition, in the multivariate analysis with the Cox regression model, postoperative treatment ($P = 0.041$) was also identified as a significant independent predictor of OS and RFS. A total of 15 patients received postoperative adjunctive therapy in the LVI+ group, and among these patients, the 5-year survival rate was 88.2%, better than patients who did not receive postoperative adjunctive therapy, with a 5-year survival rate of only 61.5%. This suggests that adjuvant therapy should be a common treatment option for patients.

Most lung cancer treatment failures occur within the first 2 years after surgery (Poleri et al., 2003), and once metastasis occurs, the survival rate is generally less than 3 years (Kato et al., 2012). A total of 10 (52.63%; 10/19) patients suffered from tumor metastasis in the first 2 years after their operation in the LVI+ group, and in the LVI- group, tumor metastasis only occurred in 3 (18.75%; 3/16) patients; this difference was statically significant, with a P value

less than 0.05. Some authors believe that LVI is also a predictor of early mortality (Fujisawa et al., 1995; Pechet et al., 2004); 46.67% (7/15) and 45.45% (5/11) of the deaths in this study occurred in the first 2 years for the LVI+ group and LVI- group, respectively. However, this difference was not statistically significant ($P > 0.05$).

Recently, D2-40, a new, selective, monoclonal immunohistochemical marker, has been demonstrated to be useful in the diagnosis of NSCLC LVI, and there have been few reports about the correlation of D2-40-positive LVI and prognosis (Kadota et al., 2010; Schuchert et al., 2011). The use of D2-40 for the detection of LVI has also been reported for cancers of the breast, stomach, colon, prostate, cervix, endometrium, and skin (melanoma, squamous cell carcinoma) (Kahn and Marks, 2002; Dumoff et al., 2005; Shida et al., 2005; Van der Auwera et al., 2005). It also offers a useful approach to identify aggressive lung squamous cell carcinoma, while others have argued the opposite (Faoro et al., 2008; Iwakiri et al., 2009).

In conclusion, the prognostic value of LVI is underestimated in stage I NSCLC, and a multicenter, randomized, prospective study is needed to confirm the findings. Our data demonstrated that postoperative adjuvant treatment in patients with LVI can improve prognosis. However, a prospective, randomized, controlled trial that evaluates the impact of adjuvant chemotherapy on survival in patients with stage I NSCLC and LVI is also needed.

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