General Thoracic and Cardiovascular Surgery (2019) 67:861–866
https://doi.org/10.1007/s11748-019-01095-6

ORIGINAL ARTICLE

Lymphatic invasion is a cause of local recurrence after wedge resection of primary lung cancer

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Received: 2 November 2018 / Accepted: 24 February 2019 / Published online: 28 February 2019

Abstract

Objective After securing a sufficient surgical margin at wedge resection and finding no pathologic evidence of residual tumor at the surgical margin, a considerable number of patients develop local recurrence. We investigated the correlation between sub-pleural lymphatic flow and local recurrence.

Methods We retrospectively reviewed the medical records of 144 non-small cell lung cancer patients who underwent wedge resection between January 2006 and December 2014 at our institution.

Results Postoperative recurrence was observed in 36 patients (25%). Of these, local recurrence was observed in 29 patients (80.5%). The proportion of all recurrence and local recurrence were significantly higher among patients with lymphatic vessel invasion (LVI) ($p < 0.0001$). Recurrence-free survival rate was significantly lower in patients with LVI (24.8%) than in patients without LVI (80.2%, $p < 0.0001$). Multivariate logistic regression analysis demonstrated LVI (odds ratio = 6.420, $p = 0.0009$) as a significant predictor of local recurrence.

Conclusions Intratumoral lymphatic invasion represents a major cause of local recurrence. Although we should aim for radical surgery whenever possible, when limited surgery is the only option, postoperative adjuvant treatment may need to be considered for patients showing lymphatic invasion even at an early stage.

Keywords Lung cancer · Wedge resection · Lymphatic invasion

Introduction

For early-stage lung cancer, complete surgical resection is the most curative treatment. In recent years, due to aging and advances in diagnostic techniques, opportunities for surgery are increasing for cases with metachronous lung cancer or multiple complications. In such cases, wedge resection or segmental resection as a reduction surgery is inevitable. However, the locoregional recurrence rate has been reported to be significantly increased among patients undergoing limited resection. Causes of this increased local recurrence are considered to be inadequate resection of the primary tumor or failure to identify and resect intrapulmonary microscopic and lymphatic spread of the tumor [1]. On the other hand, sub-pleural lymph flow has been reported to lead to metastasis [2, 3] and may potentially also relate to local recurrence in limited resection. This study focused on local recurrence in cases who underwent wedge resection. We investigated the relationship between local recurrence and lymphatic invasion in cases where local relapse has occurred despite securing adequate margin.

Subjects and methods

This retrospective study was approved by the Ethics Committee at Kagawa University.

Patients

From January 2006 to December 2014, a total of 1006 patients underwent pulmonary resection for non-small cell lung cancer (NSCLC) at our hospital. Data were obtained

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from the medical records of patients with NSCLC who underwent wedge resection of lesions during the same period. Cases of adenocarcinoma in situ were excluded. All patient data were analyzed retrospectively.

Preoperative evaluation consisted of physical examination, blood tests including tumor markers, chest radiography, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging (MRI) of the brain, and bone scintigraphy or positron emission tomography (PET). Only cases diagnosed as cN0 by these tests were included in the present study. Reasons for wedge resection were metachronous or simultaneous multiple occurrence, poor pulmonary function, and various comorbidities. All tumors in this study were resected with no pathological evidence of residual tumor at the surgical margin. The mean surgical margin was 18.0 mm, and surgical margins exceeding tumor diameter were secured in 94 cases.

Postoperative follow-up was conducted at 3- to 4-month intervals for the first year, and at 6-month intervals thereafter. Follow-up evaluations included physical examination, chest radiography, blood tests including concentrations of tumor markers, CT of the chest and abdomen, MRI of the brain, and PET if necessary. Postoperative recurrence was clinically diagnosed by these tests with or without pathological diagnosis. Local recurrences were defined as those occurring at the staple line, hilar or mediastinal lymph nodes, or pleural cavity.

Histopathologic evaluation

Surgical specimens were fixed in formalin and underwent routine histopathological workup with paraffin embedding. Intratumoral lymphatic invasion was evaluated using hematoxylin and eosin staining and immunohistochemistry using a mouse monoclonal antibody for D2-40. All sections were evaluated by pathologists at our hospital.

Statistical analysis

Categorical variables were compared using the χ^2 test. Survival was estimated using the Kaplan–Meier method and compared between groups using log-rank testing. Multivariate analyses were estimated using logistic regression modeling to identify independent factors. Results were considered significant for values of $p < 0.05$. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Clinical and pathological features

Characteristics and clinicopathological features of all patients are shown in Table 1. Participants comprised 106 men (73.6%) and 38 women (26.4%), with a mean age of 74 years (range 21–90 years). The histopathological type was adenocarcinoma in 98 patients (68.1%), squamous cell carcinoma in 35 patients (26.3%), and other types in 11 patients (5.6%), including large-cell neuroendocrine carcinoma in 7 patients, large-cell carcinoma in 1 patient, pleomorphic carcinoma in 1 patient, adenosquamous carcinoma in 1 patient, and unclassified NSCLC in 1 patient. Mean tumor size was 19.4 mm (range 2–40 mm). Visceral pleural invasion was observed in 32 patients (22.2%). Lymphatic vessel invasion (LVI) and blood vessel invasion (BVI) were

Table 1 Characteristics of the study population

	N	%
Age, years, mean (range)	74 (21–90)	
Sex		
Male	106	73.6
Female	38	26.4
Histopathology		
Adenocarcinoma	98	68.1
Squamous cell carcinoma	35	24.3
LCNEC	7	4.8
Others	4	2.8
Reasons for wedge resection		
Multiple occurrence	65	45.1
Comorbidities	34	23.6
Poor pulmonary function	23	16.0
Age	14	9.7
Others	8	5.6
Tumor size, mm, mean (range)	19.4 (2–40)	
≤ 20	112	77.8
> 20	32	22.2
Surgical margin, mm, mean (range)	18.0 (5–35)	
Exceeding tumor size	97	67.4
Less than tumor size	47	32.6
Visceral pleural invasion		
pl(+)	32	22.2
pl(−)	112	77.8
Lymphatic vessel invasion		
ly(+)	37	25.7
ly(−)	107	74.3
Blood vessel invasion		
v(+)	38	26.4
v(−)	106	73.6

Table 2 Correlation between intratumoral vessel invasion and other clinicopathologic factors

	ly(+), *n*	*p* value	v(+), *n*	*p* value
Age (years)		0.1551		0.2396
>74	26		26	
≤74	11		12	
Sex		0.0034		0.0097
Male	34		34	
Female	3		4	
Histology		0.0033		< 0.0001
Non-adenocarcinoma	19		23	
Adenocarcinoma	18		15	
Tumor size (mm)		0.0004		0.0006
>20	16		16	
≤20	21		22	

Table 3 Postoperative recurrent pattern

Recurrent site	*n*	ly(+), *n*	*p* value	v(+), *n*	*p* value
Recurrence	36	20	< 0.0001	14	0.0494
Mean tumor size (mm)	15.4				
Local	29	17	< 0.0001	11	0.2122
Staple line	18	9		4	
Lymph nodes	9	5		4	
Pleural cavity	5	3		4	
Distant	7	3		3	

observed in 37 patients (25.7%) and 38 patients (26.4%), respectively. Both LVI and BVI were observed in 22 patients (15.2%). Prevalence of LVI was significantly higher in male patients ($p = 0.0034$), patients with non-adenocarcinoma ($p = 0.0033$), and tumor diameter > 20 mm ($p = 0.0004$). Prevalence of BVI was significantly higher in male patients ($p = 0.0097$), patients with non-adenocarcinoma ($p < 0.0001$), and tumor size > 20 mm ($p = 0.0006$) (Table 2).

Patterns of postoperative recurrence

Postoperative recurrence was observed in 36 patients (25%). Mean tumor diameter was 15.4 mm (range 8–40 mm). Of these, local recurrence was observed in 29 patients (80.5%) and distant metastases were seen in 7 patients (19.5%). Proportions of all recurrence and local recurrence were significantly higher among LVI patients ($p < 0.0001$) (Table 3).

Survival analysis

The 5-year overall survival rate (OS) in this study population was 64.8% (Fig. 1a). OS was significantly lower among patients with BVI (42.0%) than among patients without BVI (70.8%, $p = 0.0018$; Fig. 1b). OS was significantly lower in patients with LVI (42.2%) than in patients without LVI (71.6%, $p = 0.0006$; Fig. 1c). Overall recurrence-free survival rate (RFS) at 5 years in this study population was 67.0% (Fig. 2a). RFS was significantly lower

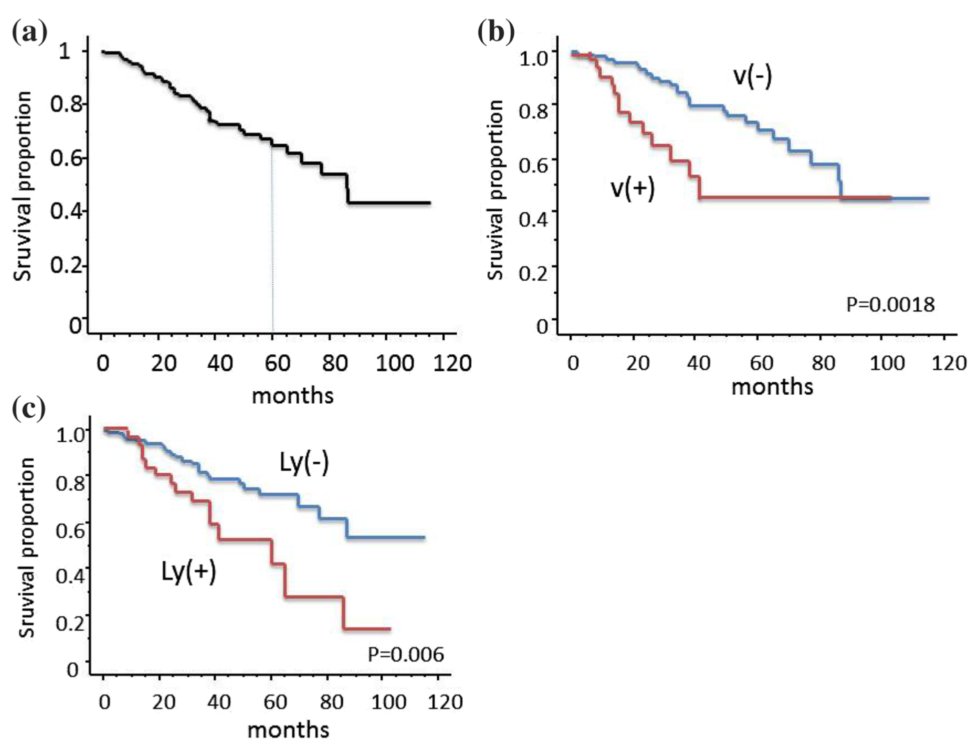

Fig. 1 **a** Overall survival curve. **b** Overall survival curves according to blood vessel invasion. **c** Overall survival curves according to lymphatic vessel invasion

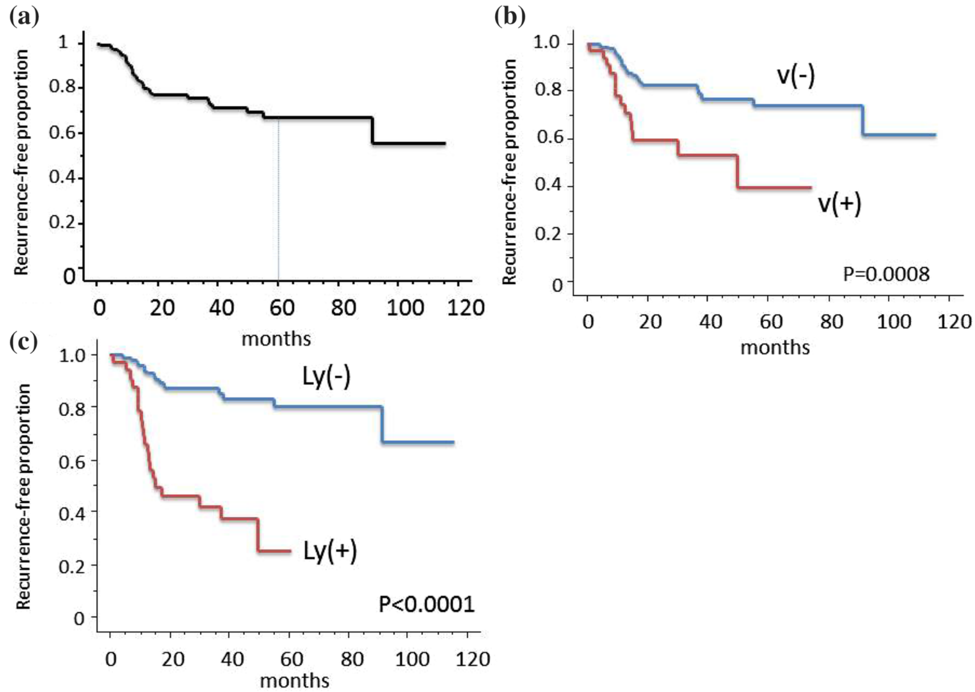

Fig. 2 **a** Recurrence-free survival curve. **b** Recurrence-free survival curves according to blood vessel invasion. **c** Recurrence-free survival curves according to lymphatic vessel invasion

in patients with BVI (35.2%) than in patients without BVI (74.0%, $p = 0.0008$; Fig. 2b). RFS was significantly lower in patients with LVI (24.8%) than in patients without LVI (80.2%, $p < 0.0001$; Fig. 2c).

Uni- and multivariate analyses of local recurrence

On univariate analysis, age (> 74 years), sex (male), LVI, tumor size (> 20 mm), and histology (non-adenocarcinoma) were significantly associated with poorer RFS. Multivariate logistic regression analysis demonstrated that only LVI (odds ratio (OR) = 6.420, $p = 0.0009$) was a significant predictor of local recurrence (Table 4).

Discussion

In this study, local recurrence was significantly more frequent among patients with LVI, and in multivariate analysis, only LVI correlated significantly with local recurrence after wedge resection.

Although the treatment most likely to achieve cure for early-stage lung cancer patients is curative surgical resection [1, 4], many patients cannot undergo such radical surgery due to various reasons. With aging and improvements in treatment technology for other diseases, the opportunities for limited resection are increasing because of reasons such as comorbidities, poor pulmonary reserve, and high age. Evidently the risk of recurrence increases when passive limited resection is performed. The cause of local recurrence at wedge resection is mainly the short length of the stump and the lack of lymphatic dissection. However, even

Table 4 Uni- and multivariate analyses for local recurrence

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age (> 74 years vs ≤ 74 years)	3.513 (1.262–11.384)	0.0103	2.780 (0.907–8.520)	0.0736
Sex (male vs female)	5.794 (1.328–8.910)	0.00857	2.770 (0.486–15.800)	0.2510
v (+ vs −)	1.738 (0.639–4.539)	0.2361	0.3440 (0.097–1.220)	0.0983
ly (+ vs −)	5.832 (2.245–15.817)	< 0.0001	6.420 (2.140–19.300)	0.0009
Tumor size (> 20 mm vs ≤ 20 mm)	3.424 (1.353–8.910)	0.00649	2.500 (0.910–6.850)	0.0756
Histology (Ad vs non-Ad)	3.546 (1.376–9.355)	0.00502	2.530 (0.879–7.300)	0.0851
Surgical margin (> 20 mm vs ≤ 20 mm)	1.991 (0.696–5.414)	0.1987	1.860 (0.616–5.610)	0.2720

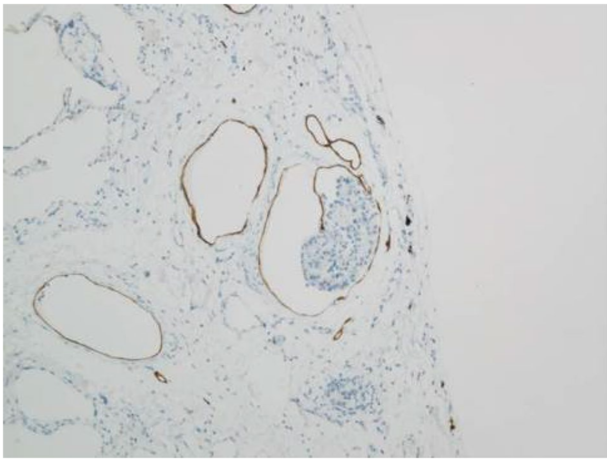

Fig. 3 Immunohistochemical staining of a case with lymphatic vessel invasion and recurrence along the stapler line. Tumor cells were identified in the lymph duct just beneath the visceral pleura

after securing a sufficient surgical margin (i.e., exceeding tumor size) at wedge resection and finding no pathological evidence of residual tumor at the surgical margin, a considerable number of patients develop local recurrence. We, therefore, investigated correlations between sub-pleural lymphatic flow and local recurrence.

Various factors that regulate the prognosis of early-stage lung cancer have been reported, including preoperative serum level of CEA, tumor size, histological grade, intratumoral vascular or lymphatic invasion, and visceral pleural invasion [5–11]. Among these, the presence of vascular and/or lymphatic invasion has been reported as a significant prognostic factor [7–11]. In the present study, both OS and RFS for patients with LVI/BVI were significantly lower than those of patients without LVI/BVI. Both LVI and BVI may be strong prognostic factors. Although BVI was related to recurrence and survival, LVI was more strongly related to local recurrence. In the present study, proportions of all recurrence and local recurrence were significantly higher among LVI patients than among those without LVI ($p < 0.0001$). Furthermore, multivariate logistic regression analysis demonstrated only LVI (OR = 6.420, $p = 0.0009$) as a significant predictor of local recurrence. With LVI, there is the possibility of local recurrence even if sufficient surgical margins are secured. This may be due to cancer cells migrating with lymph flow from the tumor toward the visceral pleura. Immunohistochemical staining of a case with LVI and recurrence along the stapler line is shown in Fig. 3. Tumor cells were identified in the lymph duct just beneath the visceral pleura. This may be a cause of local recurrence.

Under the current TNM classification system, lymphatic invasion is not adopted as the degree of progress. This is probably because this pathology can only be diagnosed after surgery and there are variations due to facilities. However, LVI correlates strongly with recurrence and may require additional treatment even for early-stage lung cancer. The accumulated evidence of numerous studies has led to postoperative adjuvant chemotherapy being recognized as standard treatment for localized NACLC [12–14]. However, the risks of chemotherapy have been shown to exceed the benefits for some stages of the disease [15]. Postoperative adjuvant therapy for stage-IA NSCLC has not been performed, but in cases where LVI is observed as a pathological outcome after limited surgery, some adjuvant therapy may need to be considered if the condition of the patient permits.

Conclusion

Intratumoral lymphatic invasion represents a major cause of local recurrence. Mean tumor diameter in cases of local recurrence can be as small as 15.4 mm, and tumor diameter thus cannot be considered a safe excision margin even for small lung cancer. Although we should try to perform radical surgery whenever possible, when limited surgery is inevitably necessary in some cases, postoperative adjuvant treatment may need to be considered for patients showing lymphatic invasion, even in early-stage disease.

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