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Original Article

Overexpression of galectin-1 indicates poor prognosis in resected non-small cell lung cancer patients

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Abstract: Galectin-1 overexpression is associated with the development and prognosis in several cancers. However, the prognostic significance of galectin-1 expression in NSCLC patients remains poor. We evaluated the prognostic value of galectin-1 expression by immunohistochemistry in resected non-small-cell lung cancer (NSCLC) patients. A total of 189 patients were enrolled in our study. Galectin-1 expression was positive in 67 out of 189 lung cancer samples (35.4%). We found that galectin-1 was significantly associated with gender, smoking, T stage, lymph node metastasis, and TNM stage (All P<0.05). The overall survival for galectin-1 positive patients was significantly poorer than that for galectin-1 negative patients. Patients with positive galectin-1 expression had worse survival than those with negative expression levels in adenocarcinoma (ADC), whereas the difference did not exist in the squamous cell carcinoma (SCC). Multivariate analysis showed the presence of visceral pleural invasion (VPI) (HR: 1.711; 95% CI: 1.008-2.905, P=0.047), the p-TNM stage (III-IV/I-II/) (HR: 1.049; 95% CI: 1.025-1.074 P<0.001), and galectin-1 positive expression (HR: 1.827; 95% CI: 1.099-3.035 P=0.020) were independent prognostic indicators of poor OS for resected lung cancer patients. In summary, our results have shown that galectin-1 expression was associated with lymph node metastasis and tumor progression, and was an independent prognostic factor for poor survival in NSCLC patients, especially in patients with adenocarcinoma.

Keywords: Non-small cell lung cancer, Galectin-1, prognosis

Introduction

Lung cancer is the most common type, and the leading cause of cancer death all over the world. About 85% of Lung cancer is non-small cell lung cancer (NSCLC) [1]. The prognosis remains poor despite significant advances made in diagnosis and treatment for non-small cell lung cancer patients [2, 3]. Therefore, finding some biologic and molecular targets may help to evaluate and improve prognosis in NSCLC patients.

Galectin-1 (14.5 kDa) encoded by the LGALS1 (lectin galactoside binding soluble 1) gene is located on chromosome 22 p12 [4]. Galectin-1 is the first protein discovered in the galectins family, and is a beta-galactoside binding protein. Accumulating evidence clearly shows that it is associated with cancer biology including proliferation [5], cell cycle regulation, apoptosis [6], cell adhesion [7], migration and invasion [8]. Furthermore, OTX008 (a selective small-molecule inhibitor of galectin-1) can down-regulates cancer cells proliferation, invasion and tumor angiogenesis [9]. In addition, Previous studies have demonstrated that galectin-1 contributes to tumor evasion of immune evasion [10, 11]. Moreover, Galectin-1 has been reported to be overexpressed in several cancers, and has been studied as a poor prognostic factor in several cancers, including colorectal cancer [12], cutaneous head and neck cancer [13], breast cancer [14], epithelial ovarian cancer [15], squamous cervical cancer [16], gastric cancer [17].

However, there are few studies evaluating the galectin-1 expression in lung cancer. A previous study indicated galectin-1 overexpression in lung cancer tissues [18]. However, the importance of galectin-1 expression for clinicopathological characteristics and prognostic value in NSCLC patients remains limited. In our study, we estimated the expressions of galectin-1 by immunohistochemistry in resected NSCLC pa-

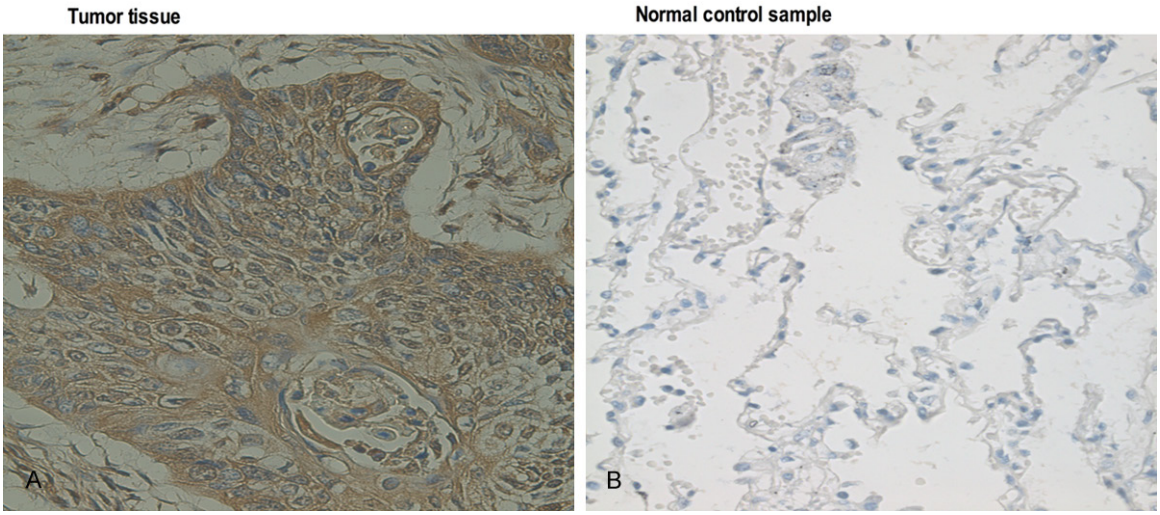

Figure 1. The positive galectin-1 expression in tumor tissue (A) and compared normal control sample (B) (magnification: ×400).

tients. We aim to assess whether the expression of galectin-1 was correlated with the clinicopathological features and survival.

Material and methods

Patients and tumor specimens

Patients with previous lung cancer or other malignancy, incomplete clinical records, previous radiotherapy and chemotherapy were excluded. From January 2008 to December 2011, A total of 189 resected NSCLC patients who undergwent surgery from West China Hospital were enrolled in our study. 189 tumor samples and their compared normal control tissue sample adjacent to the tumor tissue were obtained. We recorded age, gender, smoking status, the presence of viseral plural invasion (VPI), T stage (T1, T2, T3, or T4), lymph node metastasis (Yes or No) and TNM stage (I-II or III-IV stage) according to the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer [19], and differentiation (well/moderate or poor) and the histologic type (adenocarcinoma, squamous cell carcinoma and others) according to the World Health Organization classification for NSCLC [20], retrospectively.

Immunohistochemistry

All samples were obtained with patients completing written informed consents. All of the specimens were fixed in 4% formaldehyde in PBS immediately after removal and embedded in paraffin within 12-24 h after surgery. All paraffin tissues were made of 4 μm slices. The instruction of Envision two-step immunohistochemical staining was according to the previous literature [18]. Antigen retrieval treatment was done at 95°C for 16 min in sodium citrate buffer (pH 6.0). Primary antibody was rabbit monoclonal antibody Galectin-1 (1:2500 dilution Abcam) at 4°C overnight, Secondary antibodies of Dako Envision were purchased from Dako Corporation. Negative controls replaced the primary antibody by phosphate-buffered saline (PBS) showed no immunoreactivity.

Quantification of galectin-1 expression

We used dual-rate semi-quantitative method according to the literature [18, 21]. Two independent pathologists without knowledge of the patients' clinical status carried out evaluation separately. Galectin-1 is present both inside and outside cells and has both intracellular and extracellular functions [4], and we evaluated the expression of galectin-1 in the tumor cells and in the tumor stroma (cells and extracellular matrix). The score was defined: 0, ≤5% of tumor cells or stroma; 1, 6% to 25% of tumor cells or stroma; 2, 26% to 50% of tumor cells or stroma; and 3, >50% of tumor cells or stroma. The intensity score was defined as follows: 0, no appreciable staining; 1, barely detectable yellow staining; 2, brown staining; and 3, dark brown. The total score included stained area and staining intensity of the tumor cell and stoma. Thus, the final immunohistochemistry (IHC) score ranged from 0 to 9. While in our study, the total score more than 1 was defined as a positive expression.

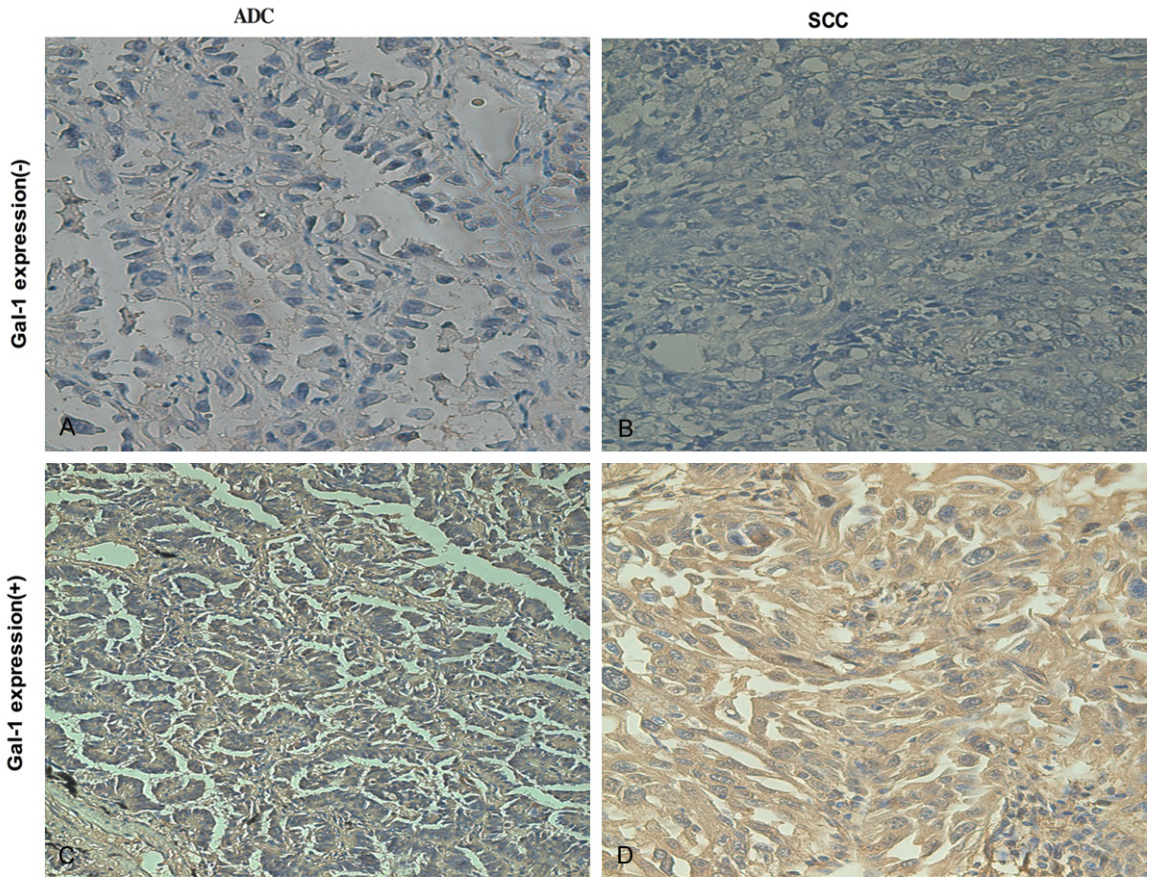

Figure 2. Galecint-1 (Gal-1) is overexpressed in NSCLC. Gal-1 presents negative expression in adenocarcinoma (A) and squamous cell carcinoma (B), and positive expression in in adenocarcinoma (C) and squamous cell carcinoma (D) (magnification: ×400).

Statistical analysis

All statistical calculations were performed using SPSS 19.0 for Windows (SPSS Inc., Chicago, III) and Graphpad Prism 6. The χ^2 test was used to analysis the association of clinical characteristics with galectin-1 expression. The Kaplan-Meier method was used to evaluate survival with the log-rank test. Independent prognostic factors of survival were identified with a multivariate Cox regression analysis. *P* values <0.05 were considered statistically significant.

Results

Galectin-1 expression in lung cancer tissue and controlled normal samples

Figure 1 showed galectin-1 staining in lung cancer tissues and compared normal control tissue in the same patient. We found galectin-1 was expressed in some lung cancer tissues but not expressed in compared normal control tissues. **Figure 2** showed positive and negative expression of galectin-1 expression in NSCLC patients. Galectin-1 expression was positive in 67 out of 189 lung cancer samples (35.4%) and negative in the remaining 122 samples (64.6%).

Correlation between galectin-1 expression and clinicopathological features

The correlation between galectin-1 expression and clinicopathological features was shown in **Table 1**. We found that galectin-1 was significantly associated with gender, smoking, T stage, lymph node metastasis, and TNM stage (All P<0.05). However, it was not significantly correlated between galectin-1 expression and other clinical features.

The galectin-1 expression and patients' survival

All patients underwent follow-up until cancer-related death or more than five years after tumor resection. The cumulative overall surviv-

Table 1. Baseline characteristics of Study Subjects According to galectin-1 expression

Characteristic	Negative (n=122)	Positive (n=67)	*P* Value
Age, y			*.502*
≤60	76	41	
>60	46	26	
Gender			*.003**
Male	76	55	
Female	46	12	
Smoking status			*.017**
Yes	57	20	
No	65	47	
Histology			*.149*
Adenocarcinoma	72	32	
Squamous cell	41	32	
Other	9	3	
Differentiation			.494
Poor	64	36	
Moderate/well	58	31	
VPI			.471
Presence	64	34	
Absence	58	33	
T stage			*.016**
T1	26	5	
T2	74	40	
T3	15	18	
T4	7	4	
TNM stage			
I-II	92	42	*.048**
III-IV	30	25	
LN metastasis			*.024**
No	83	35	
Yes	39	32	

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; VPI, visceral plural invasion; LN: lymph node; *Statistically significant.

al (OS) and progress-free survival (PFS) rates were determined. The 5-years overall survival rate was 52.4% for galectin-1-positive patients and 72.2% for galectin-1-negative patients, and the overall survival for galectin-1-positive patients was significantly poorer than that for galectin-1-negative patients (P=0.004, **Figure 3A**). Nevertheless, there was no significant correlation between galectin-1 and progress-free survival (PFS) (P=0.193, **Figure 3B**).

More interestingly, our results showed that patients with positive galectin-1 expression had worse survival than those with negative expression levels in adenocarcinoma (ADC) (all P<0.001, **Figure 4A**), whereas the difference did not exist in the squamous cell carcinoma (SCC) (P=0.766, **Figure 4B**).

Univariate and multivariate analysis

The Univariate and multivariate analysis of 189 lung cancer patients were showed in **Table 2**. Univariate Cox regression analysis showed that gender, T stage, lymph node metastasis, p-TNM stage, presence of VPI, and galectin-1 positive expression were significantly associated with the overall survival (all P<0.05). Furthermore, multivariate analysis showed the presence of VPI (HR: 1.711; 95% CI: 1.008-2.905, P=0.047), the p-TNM stage (III-IV/I-II/) (HR: 1.049; 95% CI: 1.025-1.074 P<0.001), and galectin-1 positive expression (HR: 1.827; 95% CI: 1.099-3.035 P=0.020) were independent prognostic indicators of poor OS for resected lung cancer patients.

Discussion

Galectin-1 is a member of the Galectins gene family that are overexpressed in a variety of cancer cells and have been associated with cell growth [5], apoptosis [6], cellular adhesion process [7], invasiveness [8], and metastasis [10]. Moreover, Galectin-1 levels showed correlations with other protein' expression such as VEGF [22] and mRNA levels such as MMP-9 [8] and CXCR4 expression [23]. Chen, J et al. indicated that positive expression of VEGF was associated with high Galectin-1 levels in gastric cancer [17, 22]. Zhu, X., et al. showed that Galectin-1 knockdown inhibits migration and invasion by modulating MMP-9 expression in human MDA-MB-231 breast cancer cells [8]. Galectin-1 knockdown decreased CXCR4 expression levels in kidney cancer cells [23]. The expression of galectin-1 is regulated by hypoxia-inducible factor-1 (HIF-1) [24] and it plays important pro-tumorigenic roles within the tumor microenvironment [25]. Furthermore, galectin-1 suppresses T cell-mediated cytotoxic immune responses in several cancer cells [26-28].

Recent evidence has demonstrated that galectin-1 expression was correlated with tumor invasiveness and metastasis in several other tumors including breast [8, 29, 30], colon cancer [31], pancreatic cancer [5], cervical cancer

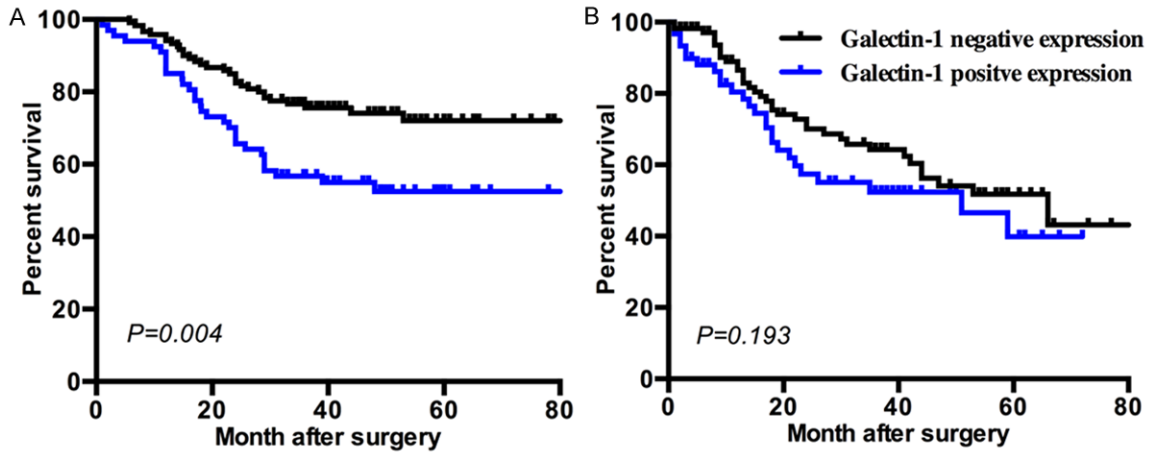

Figure 3. The prognostic value of galectin-1 protein expression in resected NSCLC patients. The survival analysis showed that the OS of galectin-1 negative patients was significantly better than that of galectin-1-positive patients (log-rank test P=0.004, A), the difference did not exist in progress-free survival (PFS) (P=0.193, B).

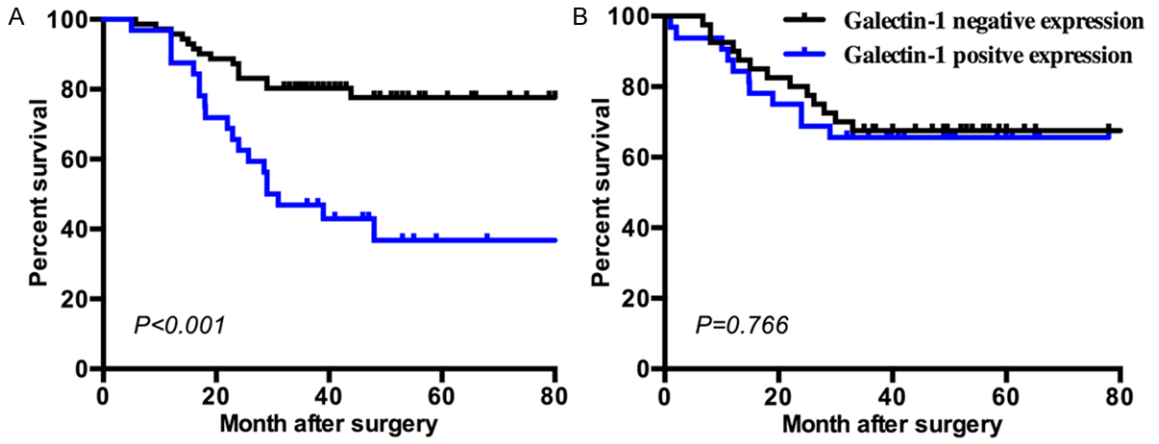

Figure 4. Kaplan-Meier curves for patients' survival was stratified by galectin-1-positive and galectin-1-negative expression in Adenocarcinoma (A) and Squamous cell carcinoma (B).

[32]. With regards to lung cancer, Hsu, Y.L, et al. showed that Galectin-1 promoted lung cancer tumor metastasis by potentiating integrin α6β4 and Notch 1/Jagged 2 signaling pathway in tumor cells and Animal model [33]. Chung, L.Y., et al. suggested Galectin-1 promoted lung cancer progression and chemoresistance by up-regulating p38 MAPK, ERK, and cyclooxygenase-2 in tumor cells and animal model [34]. In our study, we examined 189 NSCLC samples for the galectin-1 expression just by immunohistochemistry, and we found that galectin-1 was significantly associated with T stage, lymph node metastasis, and TNM stage, suggesting that galectin-1 may participate in tumor progression in lung cancer.

Interestingly, our result suggested galectin-1 was significantly associated with lymph node metastasis in resected NSCLC patients. Previous study has indicated that galectin-1 expression was strongly associated with vessels of tumor compared to the normal tissue (P<0.0001) [18], but there was no evidence with lymphatic invasion ever before. Galectin-4 is encoded by LGALS4, is another one of the identified 15 Galectins, and Hayashi, T. et al. demonstrated that galectin-4 might be a useful biomarker for predicting LN metastasis [35]. But there was no precious study to report the relationship between galectin-1 and LN metastasis in lung cancer. Our study showed that galectin-1 was significantly associated with

Table 2. The Univariate and multivariate analysis of 189 lung cancer patients

Variable	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (>60/≤60)	1.400	0.849-2.309	0.188			
Gender (male/female)	0.484	0.258-0.909	*0.024**			
Smoking status (Yes/No)	1.561	0.916-2.660	0.101			
Histology (SCC/ADC)	0.959	0.626-1.467	0.846			
Differentiation (well/moderate or poor)	0.665	0.399-1.110	0.118			
VPI status (present vs. absent)	1.812	1.082-3.024	*0.024**	1.711	1.008-2.905	*0.047**
Lymph node metastasis (Yes/No)	2.585	1.554-4.299	*<0.001**			
TNM stage (I-II/III-IV/)	1.057	1.033-1.082	*<0.001**	1.049	1.025-1.074	*<0.001**
Galectin-1 (positive/negative)	2.070	1.258-3.407	*0.004**	1.827	1.099-3.035	*0.020**

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; VPI, visceral plural invasion; *Statistically significant.

lymph node metastasis; it may be a marker for prediction of lymph node metastasis. Further studies are required to determine the mechanism between Galection-1 and LN metastasis in lung cancer.

High galectin-1 expression has been shown to be correlated with poor survival in several types of cancers including gastric cancer [17, 22], colorectal cancer [36], prostate [37], and head and neck cancer [13], and brain cancer [38]. Previous studie had reported that positive expression of galectin-1 in lung cancer correlated with cancer progression [28] and poor prognosis. Carlini, M. et al. reported that galectin-1 expression evaluated in 103 tumor tissue samples by immunohistochemistry was a useful biomarker for better prediction of the clinical outcome and management of NSCLC patients, showed that galectin-1 positive expression had a significant worse survival compared the galectin-1 negative expression (P= 0.033) [18]. And Schulkens, et al. reported the same results among 87 patients diagnosed with early stage (stage I/II) NSCLC, and also identified Galectin-1 as a possible prognostic marker by both univariate analysis and multivariate analysis [39], Our result showed the overall survival rate of patients with positive galectin-1 expression was significantly shorter than that of patients with negative galectin-1 expression. Univariate analysis showed that increased galectin-1 expression in lung cancer tissues was significantly associated with poor overall survival rate. Moreover, multivariate analysis demonstrated that galectin-1 expression, together with TNM stage and the presence of VPI were independent prognostic factors in resected NSCLC patients. Moreover, patients' overall survival was stratified by galectin-1 positive and negative expression in adenocarcinoma and squamous cell carcinoma, and we found that patients with positive galectin-1 expression had a significantly worse overall survival than patients with negative galectin-1 expression in adenocarcinoma, rather than patients with squamous cell carcinoma. Therefore, our results, taken together with those previous studies, suggesting galectin-1 can be used as a novel prognostic marker in NSCLC patients, especially in patients with adenocarcinoma.

In summary, our results have shown that galectin-1 expression was associated with lymph node metastasis and tumor progression, and was an independent prognostic factor for poor survival in NSCLC patients, especially in patients with adenocarcinoma. Therefore, galectin-1 can be used as a novel prognostic marker in NSCLC patients.

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Disclosure of conflict of interest

None.

Abbreviations

NSCLC, Non-small cell lung cancer; VPI, visceral pleural invasion; OS, overall survival.

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