Prognostic factors including lymphovascular invasion on survival for resected non–small cell lung cancer

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ABSTRACT

Objectives: The aim of this study was to report on the influence of tumor lymphovascular invasion on overall survival and in patients with resected non–small cell lung cancer and identify prognostic factors for survival.

Methods: This is a retrospective observational study of a consecutive series of patients who had surgical resection of non–small cell lung cancer in a single institution. The study covers a 3-year period. Overall survival was estimated by Kaplan-Meier method and multivariate Cox regression analysis was used to evaluate the relationship of lymphovascular invasion and other clinicopathologic variables. A multivariate regression was used to assess the relationship between tumor lymphovascular invasion and other clinical and pathologic characteristics.

Results: A total of 524 patients were identified and included in the study. Two hundred twenty-five patients (43%) had tumors with lymphovascular invasion. Patients with tumor lymphovascular invasion had a lower overall survival ($P < .0001$). Tumor lymphovascular invasion was independently associated with visceral pleural involvement ($P < .0001$). In a multivariable model, lymphovascular invasion (hazard ratio [HR], 2.58; 95% confidence interval [CI], 1.63–4.09; $P < .0001$), parietal pleural invasion (HR, 45.4; 95% CI, 2.08–990; $P = .015$), advanced age (HR, 1.028; 95% CI, 1.009–1.048; $P = .004$), and N2 lymph node involvement (HR, 1.837; 95% CI, 1.257–2.690; $P = .002$) were independent prognostic factors for lower overall survival.

Conclusions: Lymphovascular invasion is associated with a worse overall survival in patients with resected non–small cell lung cancer regardless of tumor stage. Parietal pleural involvement, N2 nodal disease, and advanced age independently predict poor overall survival. (J Thorac Cardiovasc Surg 2018;156:785-93)

Guy's Hospital.

Central Message

Tumor lymphovascular invasion is associated with a worse overall survival in patients with resected NSCLC.

Perspective

This retrospective observational study of 524 patients with resected NSCLC shows that tumor lymphovascular invasion significantly influences overall survival. We found an association between tumor lymphovascular invasion and visceral pleural involvement as well as tumor size. Lymphovascular invasion may be a marker of subclinical tumor spread.

See Editorial Commentary page 794.

Surgical resection with lymph node dissection is the mainstay of treatment of early stage (T1, T2, or T3; N0 or N1) non–small cell lung cancer (NSCLC). Pathologic stage is the most important prognostic factor for survival following resection and is the basis of guideline recommendations for adjuvant therapies. Adjuvant chemotherapy is offered to patients with pathologically confirmed lymph node

involvement on the basis of evidence of survival benefit from randomized trial data.^{1–4} Analysis of data from a subgroup of patients with node-negative NSCLC suggests that there may be a survival benefit for adjuvant chemotherapy in larger tumors.⁵ The role of adjuvant radiotherapy after resection of NSCLC is less well defined but is generally recommended for patients with incompletely removed involved mediastinal lymph nodes and positive resection margins.⁶ Survival for lung cancer, especially in the

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Received for publication May 16, 2017; revisions received Feb 6, 2018; accepted for publication Feb 15, 2018; available ahead of print May 10, 2018.

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0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2018.02.108>

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Abbreviations and Acronyms

LVI	= lymphovascular invasion
NSCLC	= non-small cell lung cancer
OS	= overall survival

presence of lymph node involvement, remains poor. Better understanding of a number of tumor biological factors may help better stratify patients beyond current staging and identify patients at risk of early recurrence who may require adjuvant therapies to mitigate this risk.

Lymphovascular invasion (LVI) has been shown to independently predict early recurrence following resection of NSCLC.⁷⁻¹² Some authors have proposed that in the presence of lymphovascular invasion adjuvant therapies should be considered even in node-negative disease, as is the case for a number of gynecologic and head and neck epithelial malignancies.^{6,13-16} The purpose of this study was to report on the influence of tumor lymphovascular invasion on overall survival (OS) in patients with NSCLC who have undergone resection and to identify prognostic factors for overall survival.

MATERIALS AND METHODS

This was a retrospective observational study of a consecutive series of patients with NSCLC who underwent surgical resection for stage T1 through T3 N0 through N2 M0 disease at a single institution over a 3-year period. All staging was according to the seventh edition of the joint American Joint Committee on Cancer and the International Union for Cancer Control. Patients were excluded if they had carcinoid tumors, if they had a prior history of lung cancer, or if they received preoperative chemotherapy and/or radiotherapy. Ethical approval for this study was obtained from the institutional review board. LVI was defined by detecting the tumor emboli within vascular channels lined by single layer of endothelial cells in the resected primary tumor following staining with hematoxylin and eosin. Results were reported by 2 dedicated thoracic histopathologists.

Patients

All patients were discussed at dedicated lung cancer multidisciplinary team meetings before referral for surgery. A standard preoperative workup was performed for each patient according to established guidelines.¹⁷ Individual patient data were obtained from a prospective surgical database and patient case notes. Data on mortality were obtained from a national register of deaths.

Statistical Analysis

Continuous data are reported as median and range, and categorical data are reported as count and percentage. Survival was measured from the date of surgery. Survival and prognostic factors were analyzed by the Kaplan-Meier method. Univariate analysis of data was performed using χ^2 test, log rank test, Fisher exact test, unpaired *t* test, and analysis of variance, where appropriate. Factors that significantly influenced survival in univariate analysis (at $P < .10$) were tested for their independent role in multivariate analysis using the Cox proportional hazards model. The stepwise backward procedure based on the likelihood ratio was used to assess the significance of covariates included in the model. Colinearity was assessed using a correlation matrix of coefficients in the Cox regression model. Any variables with coefficient >0.75 or <-0.75 were considered colinear. No

colinearity of variables was observed in the final multivariable model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. All analyses were conducted using SPSS software version 18 (IBM-SPSS Inc, Armonk, NY).

RESULTS

Patient Characteristics

Between April 2011 and March 2013, a total of 524 patients had lung resection for pathologic stage T1, T2, or T3 N0, N1, or N2 M0 NSCLC at our institution and are included in this study. The median age was 73 years (range, 37-95 years) and 240 (46%) were men. Baseline characteristics of the study population are summarized in Table 1.

Operative Procedures and Staging

The majority of patients had a lobectomy and lymphadenectomy as the surgical procedure. Bilobectomy was performed in 28 (5%). Pneumonectomy was performed in 31 patients (6%) (Table 1). Stage distribution is summarized in Table 1. Three quarters of operations were performed

TABLE 1. Baseline characteristics of the study population

Parameter	Result
Age, y	73 (37-95)
Gender, male	240 (46)
Type of operation	
Lobectomy	461 (78)
Sleeve lobectomy	50 (10)
Bilobectomy	18 (3)
Pneumonectomy	31 (6)
Segmentectomy	14 (3)
Surgical approach	
Thoracotomy	399 (76)
Video-assisted thoracoscopic surgery	125 (24)
Histology	
Adenocarcinoma	301 (57)
Squamous cell carcinoma	195 (37)
Large cell neuroendocrine carcinoma	16 (3)
Sarcomatoid	10 (1.9)
Small cell	2 (0.38)
pTNM stage	
In situ	4 (0.76)
IA	138 (26)
IB	141 (27)
IIA	81 (15)
IIB	59 (11)
IIIA	100 (19)
IIIB	1 (0.19)
IV	0 (0)
Lymphovascular invasion	
Positive	225 (43)
Negative	299 (57)

Values are presented as median (range) or n (%).

TABLE 2. Table comparing baseline characteristics of patients with lymphovascular invasion (LVI) to those without LVI

Characteristic	Patients with tumor LVI (n = 225)	Patients without tumor LVI (n = 299)	P value
Age, y	73 (57, 67, 73, 79, 86)	73 (58, 68, 73, 79, 85)	.844
Male sex	93 (41)	147 (49)	.075
Tumor size	38.9 ± 20.6	34.7 ± 23.2	.033
Smoking status			
Nonsmoker	3	6	.743
Exsmoker	73	132	.092
Current smoker	32	34	.058
Unknown	117	127	.030
Type of operation			
Lobectomy	192 (85)	259 (87)	.673
Bilobectomy	12 (5)	16 (5)	.993
Pneumonectomy	14 (6)	17 (6)	.797
Segmentectomy	7 (3)	7 (2)	.588
Pleural involvement			
Visceral	128 (57)	95 (32)	<.0001
Parietal	22 (10)	17 (6)	.077
Surgical approach			
Thoracotomy	179 (80)	220 (74)	.112
Video-assisted thoracoscopic surgery	46 (20)	79 (26)	.112
Histology			
Adenocarcinoma	130 (58)	177 (59)	.744
Squamous cell carcinoma	87 (39)	112 (38)	.778
Large cell neuroendocrine carcinoma	4	1	.093
Small cell	1	1	.840
Other*	3	7	.404
pTNM stage			
In situ	0 (0)	4 (1)	.082
IA	34 (15)	104 (35)	<.0001
IB	58 (26)	83 (28)	.613
IIA	40 (18)	41 (14)	.203
IIB	26 (12)	33 (11)	.852
IIIA	66 (29)	34 (11)	<.0001
IIIB	1 (0.44)	0 (0)	.24
IV	0 (0)	0 (0)	–

Values are presented as median (5th, 25th, 50th, 75th, and 95th percentiles), mean ± standard deviation, or n (%). *Sarcomatoid lung cancer or small cell lung cancer

by thoracotomy (n = 399; 76% vs video-assisted thoracoscopic surgery n = 125; 24%).

Lymphovascular Invasion and Histologic Subtype

The histologic distribution of patients with tumor LVI is summarized in Table 2. There was no correlation of tumor histologic subtype and LVI (χ^2 for adenocarcinoma vs all other tumors and LVI was 0.1066; $P = .744$).

Lymphovascular Invasion and Pleural Involvement

The presence of LVI was significantly associated with visceral pleural involvement with tumor ($P < .0001$). LVI was not significantly associated with parietal pleural involvement ($P = .077$) (Table 2).

OS

The OS of the study group was 86.5% (95% CI, 83.2-89.1) at 1 year, 73.9% (95% CI, 69.9-77.4) at 2 years, 65.9% (95% CI, 61.6-69.8) at 3 years, and 62.6% (95% CI, 58.0-66.8) at 4 years with a median follow-up of 36.5 months (range, 3-55 months). As expected, OS was worse with increasing T stage, lymph node involvement (N2 indicates worst OS, N0 indicates best OS), and TNM stage (stage III indicates worst OS and stage IA indicates best OS) (Figures 1 and 2).

The presence of tumor LVI was associated with a worse overall survival. Patients with no LVI demonstrated 89.3% (95% CI, 85.2-92.3), 82.6% (95% CI, 77.8-86.5), 75.3% (95% CI, 69.9-79.8), and 72.8% (95% CI, 67.1-77.6) OS at 1, 2, 3, and 4 years, respectively. Patients with LVI

FIGURE 1. Kaplan-Meier curve comparing overall survival of patients with tumor lymphovascular invasion (LVI) to those without in stages I and IIA. CI, Confidence interval.

demonstrated significantly worse OS ($\chi^2 = 29.51$; $P < .0001$), corresponding to 82.7% (95% CI, 77.1-87.0), 62.2% (95% CI, 55.5-68.2), 53.3% (95% CI, 46.5-59.6), and 48.7% (95% CI, 41.0-55.9) at 1, 2, 3, and 4 years, respectively [Figure 3](#).

The OS of patients with LVI was significantly different only for patients with stage IIA disease ([Figures 1 and 2](#)).

Prognostic Factors for OS

Univariate and multivariate Cox regression models were fitted to test for individual factors contributing to OS. The individual factors entered into the univariate analysis with their corresponding P values are summarized in [Table 3](#). Each variable was assessed for violation of proportionality assumption through Schoenfeld residuals. No significant violation of this assumption was identified ([Table 3](#)).

Multivariate Cox regression showed a significant interaction between the variables of advanced age and parietal pleural invasion; LVI and visceral pleural invasion; and LVI and parietal pleural invasion. Confirmation that the proportional hazards assumption was met was assessed through Schoenfeld residuals. Results for each independent regression variable are shown in [Table 3](#). Results of a global test of proportional hazards assumption for the adjusted multivariable model revealed $\chi^2 = 18.30$ with $P > \chi^2 = 0.436$ suggesting no violation of the proportional hazards assumption ([Table 4](#)).

A Cox proportional hazards model was used to test the variables in [Table 3](#) for their significance in a multivariate model. The fully adjusted model taking into account interactions is shown in [Table 4](#). Of these only age (≥ 70 years) ($P = .004$), N2 nodal involvement ($P = .002$), LVI ($P < .0001$), and parietal pleural

FIGURE 2. Kaplan-Meier curve comparing overall survival of patients with tumor lymphovascular invasion (LVI) to those without in stages IIB and III. CI, Confidence interval.

FIGURE 3. Kaplan-Meier curve comparing overall survival of patients with tumor lymphovascular invasion (LVI) to those without in stages I and IIA. CI, Confidence interval.

involvement ($P = .015$) were statistically significant independent variables (Table 4).

DISCUSSION

Our results show that tumor LVI is associated with a worse OS in patients with resected NSCLC. In addition there was an association between tumor LVI and lymph node involvement as well as visceral pleural involvement.

Surgical resection remains the treatment of choice for patients with early stage (I and II as well as selected stage IIIA) NSCLC. There remains a high rate of relapse in these patients with 5-year survival of resected lung cancer varying between 73% for stage IA NSCLC and 24% for stage IIIA¹⁸ This pattern is borne out in our data showing near identical overall survival data especially in patients with no LVI, albeit at 4 years.

The role of platinum-based adjuvant chemotherapy for NSCLC was first defined by the International Adjuvant Lung Cancer Trial and subsequently confirmed by the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis of 5 adjuvant chemotherapy trials.^{2,4} Survival benefit from adjuvant chemotherapy remains limited, ranging from 5% to 8% at 5 years.⁴ There is, therefore, a need to define novel variables to better stratify patients likely to benefit from adjuvant treatment. This will not only help to inform prognosis, but also the need for adjuvant therapies. Adjuvant chemotherapy is offered to patients with involvement of

intrathoracic lymph nodes as well as patients with no lymph node involvement but with larger tumors. It may be that the real value of LVI as a potential marker of tumor metastatic potential by local lymphatic invasion is in the group of patients with no nodal involvement (ie, stage I lung cancer patients). Whilst our results showed the OS of patients with stage I lung cancer and LVI was not statistically significantly worse than those without ($P = .06$) (Figure 1) this may be an area of future study and may be of value in evaluation of adjuvant therapies.

The presence of tumor LVI has been shown to confer a poor prognosis in multiple studies to date.⁶⁻¹² (Table 5). Our results show the overall survival of patients with tumors having LVI was worse in the whole cohort and in the various stages (stage I-IIIa). This effect is more marked in patients with early stage NSCLC (stage I and IIA) than in locally advanced disease (stage IIB and IIIa). It is possible that in patients with smaller tumors, the presence of LVI is an early sign of subclinical tumor spread and therefore increases the risk of recurrence (Video 1). Tumor microscopic metastases begin with local invasion of surrounding tissue stroma and proceeds to penetrate lymphatic or blood vessel.³⁶ Micrometastases then result from the clonal growth of tumor subpopulations with highly metastatic potential that then invade locoregional lymph nodes.³⁷ This may explain the correlation of tumor LVI and presence of lymph node spread that we found in this study and has

TABLE 3. Individual variables entered into the univariate model to test for their significance with corresponding *P* values*

Variable	Cox regression model			Proportional hazards testing based on Schoenfeld residuals
	95% confidence		<i>P</i> value	<i>P</i> value
	Hazard ratio	interval		
Gender	0.854	0.64-1.14	.286	.7174
Access (video-assisted thoracoscopic surgery vs thoracotomy)	0.749	0.52-1.08	.119	.9396
Lymphovascular invasion	2.16	1.62-2.90	<.0001	.7331
Visceral pleural invasion	1.87	1.40-2.49	<.0001	.0656
Parietal pleural involvement	3.19	2.13-4.79	<.0001	.8708
T category				
1a	Base	Base	Base	Base
1b	1.087	0.59-2.02	.791	.2445
2a	1.480	0.89-2.45	.128	.8539
2b	2.706	1.54-4.77	.001	.7253
3a	3.211	1.90-5.42	<.0001	.7272
3b	4.133	1.88-9.09	<.0001	.0505
Global test	–	–	–	.2068
N category				
1	Base	Base	Base	Base
2	1.483	0.99-2.22	.055	.6055
3	2.178	1.53-3.09	<.0001	.4456
Global test	–	–	–	.7047
Extent of resection				
Lobectomy	Base	Base	Base	Base
Bilobectomy	0.766	0.38-1.56	.463	.6462
Sementectomy	1.471	0.69-3.14	.318	.4342
Pneumonectomy	1.428	0.84-2.43	.188	.4833
Global test	–	–	–	.7562
Histology				
Large cell neuroendocrine	Base	Base	Base	Base
Adenocarcinoma	0.765	0.19-3.10	.708	.8682
Squamous cell	1.013	0.25-4.12	.985	.9023
Small cell	1.854	0.17-20.5	.614	.1372
Other	2.511	0.52-12.1	.251	.6513
Global test	–	–	–	.1834
TNM stage				
IA	Base	Base	Base	Base
IB	1.512	0.93-2.47	.099	.3457
IIA	2.059	1.22-3.48	.007	.5919
IIB	3.667	2.20-6.13	<.0001	.5837
IIIA	4.079	2.59-6.43	<.0001	.7914
Global test	–	–	–	.6339
Skip lesions†	0.77	0.40-1.51	.452	.1552
Age ≥ 70 y	1.015	1.00-1.03	.094	–
Tumor size, ≥ mm	1.014	1.01-1.10	<.0001	–

*Univariate analysis significant at *P* = .1. †Involvement of mediastinal lymph nodes (N2, N3) without N1 nodal involvement.

previously been reported.^{6,37,38} Tumor LVI has been noted to correlate with the development of distant metastatic disease on follow-up.⁶ Again, this probably relates to the

metastatic potential of these tumors demonstrated by local lymphatic and vascular invasion with subsequent dissemination of tumor cells via the respective vessels. We did

TABLE 4. Multivariable cox regression model*

Variable	Hazard ratio	P value	95% confidence interval	Test of proportional hazards based on Schoenfeld residuals
				P value
Age	1.03	.004	1.01-1.05	.410
T Stage (base 1a)				
1b	0.764	.421	0.397-1.47	.310
2a	0.910	.749	0.511-1.62	.819
2b	1.78	.070	0.954-3.33	.378
3a	1.35	.383	0.689-2.64	.377
3b	1.88	.144	0.805-4.40	.053
N Stage (base N0)				
N1	1.26	.289	0.819-1.95	.993
N2	1.83	.002	1.26-2.69	.885
Lymphovascular invasion	2.58	<.001	1.63-4.09	.350
Visceral pleural invasion	0.953	.833	0.607-1.50	.758
Parietal pleural invasion	45.4	.015	2.08-990.5	.330
Histology (base large cell neuroendocrine)				
Adenocarcinoma	0.891	.875	0.214-3.72	.924
Squamous cell	1.07	.928	0.255-4.48	.794
Small cell	6.07	.149	0.523-70.4	.098
Other	3.10	.173	0.608-15.9	.821
Interaction variables				
Lymphovascular invasion and parietal pleural invasion	1.73	.235	0.701-4.27	.231
Lymphovascular invasion and visceral pleural invasion	1.72	.102	0.898-3.29	.127
Parietal pleural invasion and age	0.954	.034	0.913-0.996	.403

*(Breslow method for ties): Overall model (with hazard ratios) – Number of subjects = 519; 187 failures. Likelihood ratio $\chi^2 = 101.15$; $df = 19$; probability $> \chi^2 < .00001$.

not have data on disease recurrence in our cohort of patients owing to a large majority of patients in our institution coming from various referral centers where their subsequent follow-up is done.

Our data did not show tumor subtype (adenocarcinoma vs squamous cell carcinoma) to predict the presence of LVI. Previous reports have noted an association between LVI and death or developing distant metastatic disease in patients with adenocarcinoma histology but not squamous cell carcinoma.⁶ No explanation was offered for this correlation by the authors.

The proportion of patients with tumor LVI in our study is relatively high (43%). However, in their meta-analysis of studies reporting patients with tumor LVI, Wang and colleagues³⁷ found a median of 32% of tumor samples were reported to contain tumor LVI with a range of 2.8% to 70.9%. It is not clear why there is such wide variability in tumor LVI. However, it has been noted that whilst hematoxylin and eosin staining is the most common means of reporting LVI in tumors, it can have a false negative rate of 13.85% to 18% and a false-positive rate of 4% to 11.1%.^{39,40} The use of the

monoclonal antibody D2-40, a marker of lymphatic endothelium to identify tumor emboli in lymph vessels may improve accuracy in identifying LVI.⁴¹ However, there are concerns about the immunoreactivity of D2-40 to the basal cell layer of the squamous epithelium, stromal myofibroblasts, mesothelial cells, and lung cancer cells that may confound results.^{19,42}

There are a number of limitations of this study. Firstly, it contains data from a single institution, which may influence applicability to other patient populations. Secondly, the period of follow-up is limited, which may influence the ability to detect variables significantly influencing survival due to small number of events that occur during the follow-up period, especially in the multivariate model. Thirdly, we have not included in the multivariate model data on lung function, patient comorbidity, and postoperative adjuvant therapy, factors that are known to influence survival in surgical patients undergoing lung resection. These data were incomplete and hence unreliable, owing to patients in our institution being followed-up by the referring physicians in various regional hospitals and we do not have access to those records.

TABLE 5. Summary of studies reporting on the impact of tumor lymphovascular invasion (LVI) on overall survival (OS) in resected non-small cell lung cancer (NSCLC) over the past decade

First author	Year	Country	n	LVI positive	Stage	Histology	OS	
							Univariate analysis	Multivariate analysis
Moon and colleagues ¹⁹	2017	Korea	271	71	IA	NSCLC	N/A	NS
Kinoshita and colleagues ¹²	2015	Japan	629	85	I-III	NSCLC	NA	S
Al-Alao and colleagues ²⁰	2014	Ireland	457	25	I-II	NSCLC	NS	NA
Tao and colleagues ²¹	2013	Japan	142	22	I-II	NSCLC	S	S
Yanagawa and colleagues ⁹	2013	Japan	433	41	I-III	NSCLC	S	S
Higgins and colleagues ⁶	2012	USA	1559	352	I-III	NSCLC	S	S
Maeda and colleagues ²²	2012	Japan	1070	233	IA	NSCLC	S	S
Hanagiri and colleagues ⁸	2011	Japan	226	70	I	NSCLC	S	NS
Araki and colleagues ²³	2011	Japan	26	7	IB	NSCLC	NS	N/A
Funai and colleagues ²⁴	2011	Japan	229	32	IA	NSCLC	S	S
Sakai and colleagues ²⁵	2011	Japan	548	265	I-IV	NSCLC	N/A	S
Harada and colleagues ²⁶	2011	Japan	610	225	I	NSCLC	S	S
Maeda and colleagues ²⁷	2011	Japan	434	134	IB	NSCLC	NS	NS
Shimada and colleagues ²⁸	2010	Japan	1000	244	I-IV	NSCLC	S	N/A
Kawachi and colleagues ²⁹	2009	Japan	226	13	I	NSCLC	N/A	S
Kawachi and colleagues ³⁰	2009	Japan	376	90	I-IV	NSCLC	N/A	S
Sun and colleagues ³¹	2009	China	82	46	I-III	NSCLC	S	NS
Hashizume and colleagues ³²	2009	Japan	221	92	IA	NSCLC	S	S
Higashiyama and colleagues ³³	2009	Italy	679	327	I-IV	NSCLC	S	S
Bodendorf and colleagues ³⁴	2009	Germany	112	41	IIB-III	NSCLC	S	N/A
Matsuguma and colleagues ³⁵	2008	Japan	455	69	I	NSCLC	N/A	NS

LVI, Lymphovascular invasion; OS, overall survival; N/A, not available or not applicable; NS, no significant relationship between LVI and survival; S, statistically significant relationship between LVI and survival.

CONCLUSIONS

We believe that this study, which had a large number of patients, carries an important message: Patients with tumor LVI have a lower overall survival compared with those with no LVI in resected NSCLC. We believe that the presence of

tumor LVI could be tested as a variable for offering patients with resected NSCLC adjuvant therapies.

Conflicts of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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VIDEO 1. Drs Bille, Okiror, and Harling discuss the key findings of this articles with particular focus on the prognostic implications of lymphovascular invasion on overall and stage-specific survival. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)30935-8/fulltext](https://www.jtcvs.org/article/S0022-5223(18)30935-8/fulltext).

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Key Words: lymphovascular invasion, non-small cell lung cancer, overall survival