



## Prognostic significance of blood and lymphatic vessel invasion in pathological stage IA lung adenocarcinoma in the 8th edition of the TNM classification<sup>\*</sup>



Joji Samejima<sup>a,\*</sup>, Tomoyuki Yokose<sup>b</sup>, Hiroyuki Ito<sup>a</sup>, Haruhiko Nakayama<sup>a</sup>, Takuya Nagashima<sup>a</sup>, Masaki Suzuki<sup>b</sup>, Rurika Hamanaka<sup>c</sup>, Kouzo Yamada<sup>d</sup>, Munetaka Masuda<sup>e</sup>

<sup>a</sup> Kanagawa Cancer Center, Department of Thoracic Surgery, 2-3-2 Nakao, Asahi, Yokohama, Kanagawa, 241-8515, Japan

<sup>b</sup> Kanagawa Cancer Center, Department of Pathology, 2-3-2 Nakao, Asahi, Yokohama, Kanagawa, 241-8515, Japan

<sup>c</sup> Kanagawa Cancer Center, Division of General Thoracic Surgery, Department of Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa, 259-1193, Japan

<sup>d</sup> Kanagawa Cancer Center, Department of Thoracic Oncology, 2-3-2 Nakao, Asahi, Yokohama, Kanagawa, 241-8515, Japan

<sup>e</sup> Kanagawa Cancer Center, Department of Surgery, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa, Yokohama, Kanagawa, 236-0004, Japan

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### ABSTRACT

**Objectives:** The prognostic significance of blood and lymphatic vessel invasion in the 8th edition of the Tumor, Node, Metastasis (TNM) classification remains unclear. Therefore, this study aimed to evaluate the prognostic significance of blood and lymphatic vessel invasion in p-stage IA lung adenocarcinoma in the 8th edition of the TNM classification.

**Materials and methods:** We retrospectively examined patients with p-Stage 0-IA lung adenocarcinoma, reclassified according to the 8th edition of the TNM classification. Blood and lymphatic vessel invasion were evaluated using hematoxylin-eosin and Elastica van Gieson and hematoxylin-eosin and anti-podoplanin antibody staining, respectively. Combined blood and lymphatic vessel invasion constituted tumor vessel invasion (TVI).

**Results:** Overall, 306 patients were evaluated. The median follow-up period was 98.0 (range: 10–216) months. The 5-year recurrence-free survival differed significantly among patients with and without TVI in p-stage IA1 (TVI–: 100%, TVI+: 88.9%,  $P = 0.007$ ) and IA2 (TVI–: 94.6%, TVI+: 80.8%,  $P = 0.012$ ) but not in p-stage IA3 (TVI–: 66.7%, TVI+: 75.0%,  $P = 0.598$ ). The 5-year lung cancer-specific survival also differed significantly among those with and without TVI in p-stage IA1 (TVI–: 100%, TVI+: 88.9%,  $P < 0.001$ ) and IA2 (TVI–: 98.2%, TVI+: 88.7%,  $P = 0.043$ ) but not in p-Stage IA3 (TVI–: 66.7%, TVI+: 75.0%,  $P = 0.858$ ). No recurrence and lung cancer-specific deaths occurred in p-stage IA1 patients without TVI. On multivariate analysis, the presence of TVI was independently associated with recurrence and lung cancer-specific death in patients with p-stage IA1-2 lung adenocarcinoma. TVI did not affect the prognosis of those with p-stage IA3 adenocarcinoma. **Conclusion:** TVI is a prognostic factor in patients with p-stage IA1-2 lung adenocarcinoma. P-stage IA1 lung adenocarcinoma without TVI may therefore be classified as minimally invasive.

### 1. Introduction

Numerous studies have found tumor vessel invasion (TVI), which includes blood and lymphatic vessels, to be an independent prognostic factor for recurrence in patients with pathological stage (p-stage) IA (T1a-1bN0M0 based on the Union for International Cancer Control Tumor, Node, Metastasis [TNM] Classification of Malignant Tumours, 7th edition [1]) lung adenocarcinomas measuring  $\leq 3$  cm in diameter

[2–11]. We have also reported on the prognostic significance of blood and lymphatic vessel invasion in patients with p-stage I non-small cell lung cancer, classified according to the 7th edition [12]. However, in the 7th edition, the presence of blood and lymphatic vessel invasion did not relate to stage. In the 8th edition, size of invasion was used as a pathological T descriptor; however, the presence of blood and lymphatic vessel invasion was not included [13,14].

The prognostic impact of blood and lymphatic vessel invasion in the

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<sup>\*</sup> Corresponding author.

E-mail address: [g\\_samej@kcch.jp](mailto:g_samej@kcch.jp) (J. Samejima).

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8th edition remains unclear. In the 8th edition, the pathological T descriptor is based on size of invasion; therefore, signs of more extensive infiltration such as TVI may be of particular value as a prognostic factor. Therefore, the present study aimed to clarify the prognostic significance of blood and lymphatic vessel invasion in p-stage IA lung adenocarcinoma according to the 8th edition of the TNM classification. We speculated that blood and lymphatic vessel invasion could be a prognostic factor in p-stage IA1, IA2, and IA3 lung adenocarcinomas according to the 8th edition.

## 2. Materials and methods

### 2.1. Patients and study design

We retrospectively reviewed patients who underwent lobectomy for p-stage 0-IA lung adenocarcinoma between 2000 and 2005 at the Kanagawa Cancer Center. All the patients did not receive pre- or postoperative treatment. The tumor stage was reclassified according to the 8th edition of the Union for International Cancer Control-Tumor, Node, Metastasis (UICC-TNM) classification for malignant tumors. In the 8th edition of this classification, Tis refers to carcinoma in situ, while T1mi refers to minimally invasive adenocarcinoma. Tumors with diameters of  $\leq 3$  cm are classified as T1a, T1b, or T1c, according to the pathological invasive size. Specifically, p-Stage 0 corresponds to TisN0M0, while p-stages IA1, IA2, and IA3 correspond to T1miN0M0 or T1aN0M0, T1bN0M0, and T1cN0M0, respectively.

This study was approved by the ethical committee of the Kanagawa Cancer Center (2018-41), and written informed consent was obtained from all patients.

### 2.2. Pathological evaluation

The excised lung was distended and fixed by injecting and retaining 10% formalin for 24 h. Paraffin-embedded tissue blocks were divided into 4- $\mu$ m thick sections. In all cases, the pathological invasive size was measured according to the World Health Organization Classification of Tumours of the Lung, Pleura, Thymus, and Heart (4th Edition) definition [14,15]. In summary, the pathological invasive size was measured on the maximal cut surface of the primary tumor, and the sample was then stained with hematoxylin-eosin (HE) and Elastica van Gieson (EvG). One researcher (J.S.) examined each case, and cases that were difficult to evaluate were discussed with another researcher (T.Y.).

With respect to lymphatic vessel invasion, positivity was defined as tumor cells floating in lymphatic vessels on HE- and anti-podoplanin antibody (clone D2-40)-stained specimens (Fig. 1A and B). Positive

blood vessel invasion was defined as the destruction of the vascular wall or invasion to the vascular lumen on HE- and EvG-stained specimens (Fig. 1C and D). We evaluated 1–5 slides (mean: 1.5 slides per patient) of the largest tumor sections per patient. Positive lymphatic vessel invasion and blood vessel invasion collectively represented tumor vessel invasion (TVI). Each sample was independently and microscopically examined by two researchers (T.Y. and R.H.), and cases with conflicting results were re-evaluated using a multi-headed microscope until a consensus was attained.

### 2.3. Follow-up protocol

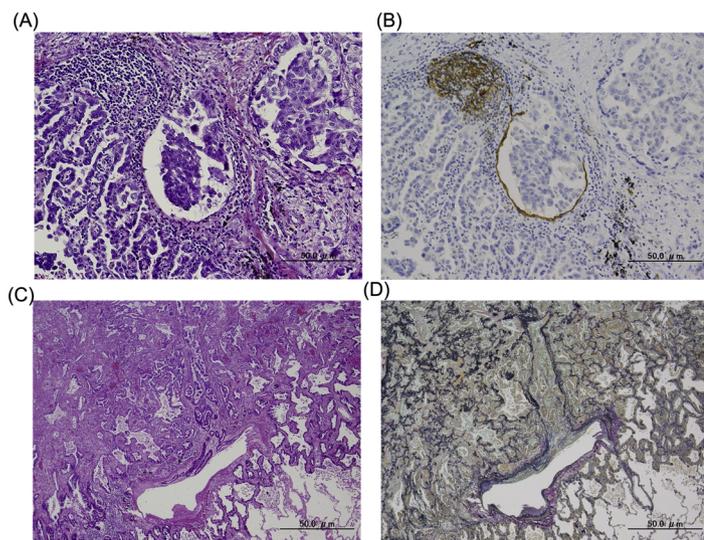
All patients were followed up once every 6 months for 5 years, and annually thereafter. The follow-up examination included physical examination, chest radiography, chest computed tomography, and blood tests for carcinoembryonic antigen, a tumor marker. Positron emission tomography and brain magnetic resonance imaging were performed in cases where the patient complained of any symptoms.

### 2.4. Statistical analysis

The date of recurrence was defined as the date on which recurrence was confirmed by imaging. Recurrence-free survival was defined as the period from the date of surgery to the date of recurrence or the last known recurrence-free date. Lung cancer-specific survival was defined as the period from the date of surgery to the date of death from lung cancer recurrence, or survival confirmation. Survival curves were plotted using the Kaplan–Meier method, and the statistical significance of differences between the groups was determined by the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. All statistical analyses were conducted using the SPSS software version 23 (IBM, Armonk, NY, USA) package. All P values were two-sided, and values  $< 0.05$  were considered statistically significant.

## 3. Results

Overall, 306 patients were evaluated. Their clinicopathological characteristics are presented in Table 1. The median follow-up period was 98.0 (range: 10–216) months. A total of 63 (20.6%) patients had tumors measuring  $> 30$  mm; these are classified under clinical stage IB in the 8th edition. The pathological T stage in 15.0%, 22.5%, 26.1%, 30.7%, and 5.6% of patients was Tis, T1mi, T1a, T1b, and T1c, respectively. Positive lymphatic and blood vessel invasion were found in 10.5% and 14.1% of patients, respectively. TVI was determined in



**Fig. 1.** (A, B) Representative case of lymphatic vessel invasion. Tumor cells are floating in lymphatic vessels on (A) HE-stained and (B) antipodoplanin antibody (clone D2-40)-stained specimens (original magnification  $\times 200$ ). (C, D) Representative case of blood vessel invasion. Tumor cells infiltrate the vascular lumen on (A) HE- and (B) EvG-stained specimens (original magnification  $\times 40$ ).

**Table 1**  
Clinicopathological characteristics of the 306 patients.

Characteristic	Value
Median follow-up period (months)	98
Age (years), n (%)	
< 65	133 (43.5)
≥ 65	173 (56.5)
Median age (range), years	66 (38–86)
Sex, n (%)	
Male	142 (46.4)
Female	164 (53.6)
Smoking, n (%)	
Yes	134 (43.8)
No	172 (56.2)
Tumor size, n (%)	
≤ 30 mm	243 (79.4)
> 30 mm	63 (20.6)
Surgical procedure, n (%)	
Lobectomy	306 (100)
Lymphadenectomy, n (%)	
Systematic lymph node dissection	91 (29.8)
Lobe-specific lymph node dissection	54 (17.6)
Lymph node sampling	161 (52.6)
pT descriptor, n (%)	
Tis	46 (15.0)
T1mi	69 (22.5)
T1a	80 (26.1)
T1b	94 (30.7)
T1c	17 (5.6)
Lymphatic vessel invasion, n (%)	
Yes	32 (10.5)
No	274 (89.5)
Blood vessel invasion, n (%)	
Yes	43 (14.1)
No	263 (85.9)
Tumor vessel invasion, n (%)	
Yes	64 (20.9)
No	242 (79.1)

**Table 2**  
Distribution of lymphatic, blood, and tumor vessel invasion in patients with p-Stage IA1-IA3.

	IA1	IA2	IA3
Lymphatic vessel invasion, n (%)	12 (8.1)	16 (12.0)	4 (23.5)
Blood vessel invasion, n (%)	9 (6.1)	29 (30.9)	5 (29.4)
Tumor vessel invasion, n (%)	18 (12.1)	38 (40.4)	8 (47.1)

20.9% of patients. The distribution of positive lymphatic, blood, and tumor vessel invasion in patients with p-stage IA1-IA3 is shown in Table 2. The percentage of tumor vessel invasion in patients with p-stage IA1, IA2, and IA3 was 12.1%, 40.4%, and 47.1%, respectively. On subdividing the patients by the predominant subtype, TVI was most frequently observed in those with a predominantly solid tumor, followed by those with predominantly papillary and acinar tumors (Table A.1). Recurrence-free survival differed significantly depending on the presence or absence of TVI in patients with p-stage IA1 (P = 0.007) and IA2 (P = 0.012) tumors; however, this was not observed in p-stage IA3 (P = 0.598) (Fig. 2A). Lung cancer-specific survival also differed significantly depending on the presence or absence of TVI in patients with p-stage IA1 (P < 0.001) and IA2 (P = 0.043) tumors; this was not noted in p-stage IA3 (P = 0.858) (Fig. 2B). There were no recurrences and lung cancer-specific deaths in p-stage IA1 patients without TVI. On multivariate analysis (Tables 3 and 4), the presence of TVI and smoking history were independently associated with recurrence and lung cancer-specific deaths in patients with p-stage IA1-2 lung adenocarcinoma. In

patients with p-stage IA tumors, recurrence-free and lung cancer-specific survival differed significantly depending on the presence or absence of TVI (Fig. A1). The recurrence rates in patients with and without TVI have been detailed in Table B.1. Distant metastasis was more frequently observed in patients with TVI.

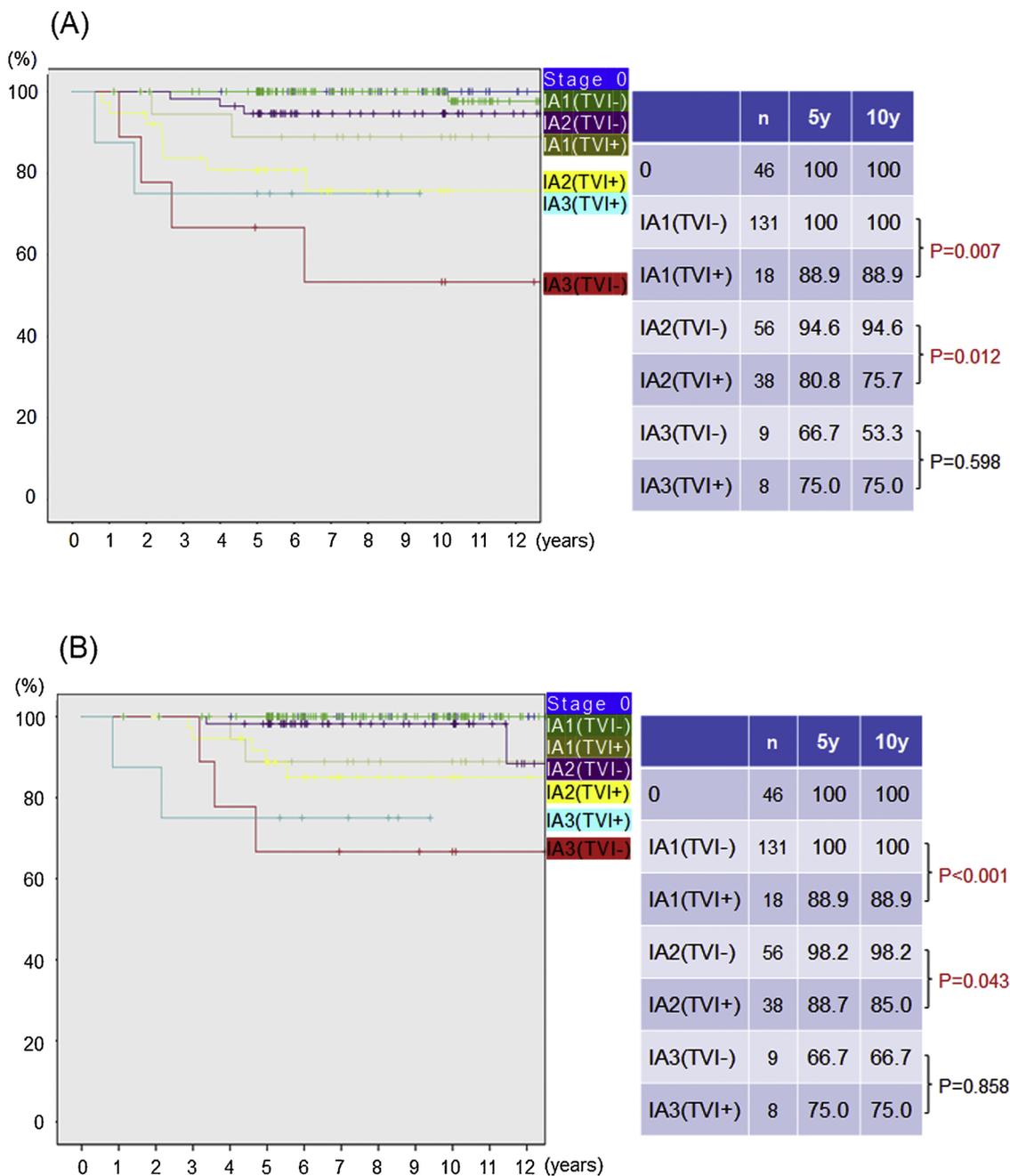
#### 4. Discussion

This study investigated the prognostic significance of blood and lymphatic vessel invasion in p-stage IA lung adenocarcinoma in the 8th edition of the TNM classification. Multivariate analysis showed that TVI was a significant predictor of recurrence and lung cancer-specific survival in patients with p-stage IA1-2 lung adenocarcinoma according to the 8th edition. There were no recurrences and lung cancer-specific deaths in p-stage IA1 patients without TVI.

We evaluated blood and lymphatic vessel invasion on EvG- and anti-podoplanin antibody (clone D2-40)-stained specimens [12]. The inclusion of anti-podoplanin antibody (clone D2-40) staining may aid in improving the detection of lymphatic vessel invasion. In this study, we confirmed that anti-podoplanin antibody (clone D2-40) should be employed to stain a representative section of the tumor to detect lymphatic vessel invasion. We believe that the presence or absence of TVI should be determined on several slides containing representative sections of the most extensive infiltration, or where HE-staining strongly suggests TVI. In previous studies that showed TVI to be an independent prognostic factor for recurrence, histologic types other than adenocarcinoma [2–11] (e.g., squamous cell carcinoma) were included, and accounted for 20%–30% of the cohort. In the 8th edition, invasive size is used as a pathological T descriptor, and stage migration is the largest for adenocarcinoma, as most cases with early lung adenocarcinoma contain a ground-glass opacity component. Therefore, we only selected patients with adenocarcinoma, and examined the effects of TVI on stage IA lung adenocarcinoma according to the 8th edition.

Previous reports included different stages of non-small cell lung cancer. Reports on patients with stage I [2–4,6,7,10,11], I-II [9], and all stage [5,8] tumors were based on the 7th edition or earlier. The number of patients with stage IA has been increasing in recent years; its prognosis may be improved by stratifying stage IA patients during treatment. Therefore, in the present study, we focused on patients with p-stage IA tumors according to the 8th edition. Our findings showed that patients with stage IA1 and IA2 tumors without TVI have a good prognosis, while those with stage IA1 and IA2 tumors with TVI have a significantly poorer prognosis than the former. This shows that post-operative adjuvant therapy may improve the prognosis of patients with stage IA1 and IA2 tumors with TVI.

In the present study, we defined TVI as a combination of positive lymphatic and blood vessel invasion. On examining lymphatic and blood vessel invasion separately, we obtained slightly different results; the recurrence-free survival outcomes differed significantly depending on the presence or absence of lymphatic and blood vessel invasion in patients with p-stage IA1 tumors (Fig. B.1A) and IA2 tumors (Fig. C.1A), respectively. In addition, the lung cancer-specific survival outcomes differed significantly depending on the presence or absence of lymphatic or blood vessel invasion in patients with p-stage IA1 (Fig. B.1B) or IA2 (Fig. C.1B) tumors, respectively. Certain previous studies have also evaluated lymphatic and blood vessel invasion in combination [2,4,9], while others have analyzed these separately [3,5–8,10,11]. In previous studies that investigated lymphatic and blood vessel invasion separately, either lymphatic vessel invasion [5,10], blood vessel invasion [3,6,8,11], or both (TVI) [7] were reported to be prognostic factors. Since we had previously reported that TVI was an important prognostic factor in patients with stage I tumors based on the 7th edition, we also analyzed its prognostic value in stage IA lung adenocarcinoma according to the 8th edition of the TNM classification. Combining lymphatic and blood vessel invasion into a single parameter, namely, TVI, will obviate the need for distinction, and will minimize



**Fig. 2.** (A) Recurrence-free survival curve in patients with p-Stage IA1, IA2, and IA3 according to the presence or absence of TVI. A significant difference was identified between patients with p-Stage IA1 and IA2, but not in p-Stage IA3. (B) Lung cancer-specific survival curve. There was a significant difference between patients with p-Stage IA1 and IA2, but not in p-Stage IA3. There were no recurrence and lung cancer-specific death in p-Stage IA1 patients without TVI. p-Stage, pathological stage; TVI, tumor vessel invasion.

**Table 3**  
Risk factors for recurrence in patients with p-Stage IA1-2 lung adenocarcinoma.

	Univariate		Multivariate
	p	Hazard ratio	95% CI
Age < 65/≥ 65 years	0.634		
Male/Female	0.736		
Non-smoker/Smoker	0.001	3.952	1.299-12.048
TVI-/+	< 0.001	4.871	1.959-12.112

p-Stage, pathological stage; TVI, tumor vessel invasion; CI, confidence interval.

observer bias.

Aokage et al. reported a 5-year survival rate of 95%, 84%, and 76% for patients with stage IA1, IA2, and IA3 tumours, respectively [16]. In the present study, the 5-year survival rates for stage IA1 and IA2 tumours without TVI were better than those reported previously. In particular, p-stage IA1 lung adenocarcinoma without TVI may be classified as minimally invasive (T1mi) since these patients demonstrated 100% recurrence-free and lung cancer-specific survival; T1mi is therefore defined as a pathologically invasive size ≤5 mm. However, we considered that a pathological invasive size of 5–10 mm without TVI would probably meet the criteria of T1mi. Only a small number of patients with p-stage IA3 adenocarcinoma was included in the present study as adenocarcinomas with consolidation measuring > 2 cm often shows

**Table 4**  
Risk factors for lung cancer-specific death in patients with p-Stage IA1-2 lung adenocarcinoma.

	Univariate		Multivariate	
	<i>p</i>	Hazard ratio	95% CI	<i>p</i>
Age < 65/≥ 65 years	0.561			
Male/Female	0.825			
Non-smoker/Smoker	0.006	5.82	1.276-26.540	0.023
TVI -/+	< 0.001	5.301	1.750-16.053	0.003

p-Stage, pathological stage; TVI, tumor vessel invasion; CI, confidence interval.

pleural invasion; our results showed that TVI did not affect the prognosis of these cases.

Our study had several limitations. First, it had a retrospective design and was performed in a single center; therefore, future validation cohort studies will be needed. Second, the prognostic significance of TVI in patients with p-stage IA3 adenocarcinomas was unclear as the included numbers in the present cohort were limited. The prognostic impact of TVI in patients with p-stage IA3 adenocarcinoma requires further investigation in large-scale cohorts. Third, lung cancer-specific survival was employed instead of overall survival (OS) for survival assessment. OS may have been preferable as it was used for survival assessment while developing the UICC-TNM classification; however, we used lung cancer-specific survival to exclude the influence of death from other causes. Fourth, the findings of the present study cannot be generalized for staging all histologies because we only evaluated adenocarcinoma. However, we speculate that since other histologic types do not have a ground-glass opacity component, and stage migration based on the 8th edition is not considerable, the results should not differ among patients staged according to the 7th edition, or with other histologic types.

## 5. Conclusions

TVI was found to be a prognostic factor in patients with p-stage IA1-2 lung adenocarcinomas. Those with p-stage IA1-2 tumors with TVI may be upstaged. In addition, p-Stage IA1 lung adenocarcinomas without TVI may be classified as minimally invasive as they achieved 100% recurrence-free survival and lung cancer-specific survival in this cohort. Further large prospective studies on larger and more diverse cohorts are needed to validate our findings.

## Declaration of Competing Interest

None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.lungcan.2019.09.022>.

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