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ORIGINAL ARTICLE

Preoperative biopsy does not affect postoperative outcomes of resectable non-small cell lung cancer

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Abstract

Objectives Preoperative diagnostic interventions such as transbronchial biopsy and/or computed tomography-guided biopsy inevitably disrupt the lung structures and may disseminate tumour cells into the airway, vessels, or pleural cavity. Therefore, these procedures may affect the postoperative outcomes. Thus, we aimed to compare the survival outcomes in patients diagnosed by transbronchial biopsy vs computed tomography-guided biopsy vs lung resection.

Methods In a single-institution retrospective analysis, data from consecutive patients with cTanyN0M0 lung cancer, who underwent surgery between January 2006 and December 2012, were extracted by chart review. The overall and recurrence-free survivals of patients diagnosed by transbronchial biopsy, computed tomography-guided biopsy, and lung resection were compared using the univariate and multivariate Cox proportional hazard models. A stepwise backward elimination method, with a probability level of 0.15, was used to select the most powerful sets of outcome predictors.

Results Transbronchial biopsy and/or computed tomography-guided biopsy were performed for larger and more advanced tumours, than lung resection (intra- or postoperative-diagnosis group). At crude analysis, transbronchial biopsy group and computed tomography-guided biopsy group showed higher probability of pleural dissemination, and worse prognosis than the lung resection group. At multivariate analysis, the diagnostic methods were not identified as independent risk factors of pleural dissemination, overall survival, or recurrence-free survival.

Conclusions Preoperative diagnostic interventions did not affect the relapse risk and prognosis, in this study cohort. Thus, preoperative diagnostic intervention is recommended if deemed necessary.

Keywords Preoperative diagnostic · Transbronchial biopsy · Computed tomography-guided biopsy · Multivariate analysis · Non-small cell lung cancer

Introduction

Lung cancer is one of the most common malignancies, as well as one of the leading causes of cancer deaths worldwide [1]. Preoperative diagnostic transbronchial biopsy (TBB) and computed tomography (CT)-guided biopsy are widely used for the diagnosis of lung cancer. Despite their short-term safety [2, 3], these procedures inevitably disrupt vascular, lymphatic, pleural, and parenchymal structures, and therefore, may potentially disseminate tumour cells into the airway, vessels, or pleural cavity; thus affecting the postoperative outcomes. However, whether preoperative biopsy affects the survival outcomes of the patients remains a controversial issue [4, 5].

In this study, we retrospectively compared the overall and recurrence-free survival outcomes of patients diagnosed by TBB, by CT-guided biopsy and by lung resection. To adjust for the possible bias inherent in the choice of diagnostic procedures, the univariate and multivariate Cox proportional hazard models with stepwise backward elimination method were performed.

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Materials and methods

Patients

We retrospectively reviewed consecutive patients who underwent surgery for cTanyN0M0 lung cancer from January 2006 to December 2012. Clinical and pathological staging was based on the 7th edition of the TNM classification of the Union for International Cancer Control [6]. Tumour histological classification was based on the World Health Organisation classification system [7]. The interval between follow-ups was 3 months for the first 2 years and then 6 months for up to 5 years. A full examination and chest X-ray were performed at each visit, and a CT scan was performed annually. Other investigations were performed when clinically indicated. We reviewed the clinical records of all patients. Before the study, the Research Review Board at our institution examined and approved our research protocol (#2015630); and our study was also conducted in accordance with the Declaration of Helsinki. The need for informed consent from the patients was waived provided the patient data remained anonymous.

Statistical methods

First, the following variables were compared among the TBB, CT-guided biopsy and by lung resection groups: preoperative covariates, including age, sex, body mass index (BMI) ($\leq 23/23 <$), smoking history (absent/present), carcinoembryonic antigen (CEA) ($\leq 5.0/5.0 <$), diabetes mellitus (absent/present), heart disease (absent/present), past history of malignancy (absent/present), percent vital capacity (%VC) ($\leq 80/< 80$), percent forced expiratory volume in 1 s (FEV1.0%) ($\leq 70/< 70$), solid tumor size (9) ($\leq 10/10 <. \leq 20/20 <. \leq 30/30 <. \leq 50/50 <$), and PET-CT SUV_{max} level. In addition, the operative and postoperative covariates, including surgical procedure (limited resection/lobectomy or pneumonectomy/exploration), pathological stage (IA/IB/IIA/IIB/IIIA/IIIB/IV), pathological type (adenocarcinoma/squamous cell carcinoma/others), vessel invasion (absent/present), lymphatic permeation (absent/present), pleural dissemination (absent/present), adjuvant chemotherapy (absent/present); and survival outcomes (including the recurrence-free survival and overall survival rates) were compared. In the 8th TNM staging for lung cancer, the solid component size of the tumour, not the whole tumour size, is defined as the T indicator, based on T-factor relevant studies [8–13]. However, the solid component size was not taken into consideration in previous studies, which might have influenced the obtained conclusions. Thus, we decided to include the solid tumor size in the present study. The solid component size was measured on the preoperative CT scan using the lung window setting.

The Kruskal–Wallis and Chi-square tests were used for comparing continuous and categorical covariates, respectively, between the groups. The survival curves were estimated using the Kaplan–Meier method, and the differences between the groups were compared using the log-rank test.

To overcome any bias caused by differing distributions of the covariates between the preoperative biopsy and lung resection groups, prognostic factors of pleural dissemination at the time of the lung resection were compared among groups: (TBB group, CT-guided biopsy group, and intra- or postoperative-diagnosis group), using the univariate and multivariate logistic regression analysis. The prognostic factors of overall and recurrence-free survival were also compared among groups (TBB group, CT-guided biopsy group, and intra- or postoperative-diagnosis group) using the univariate and multivariate Cox proportional hazard model. A stepwise backward elimination method with a probability level of 0.15 was used to select the most powerful sets of outcome predictors. All statistical analyses were performed using the statistical software packages Stata/SE 14.2 (StataCorp, College Station, TX, USA). For all analyses, a p value < 0.05 was considered statistically significant.

Results

Patient characteristics

The study included 397 patients (221, 71, and 105 patients were diagnosed by TBB, CT-guided biopsy, and lung resection, respectively); 90 deaths (60, 11, and 19 in the TBB, CT-guided biopsy, and lung resection groups, respectively); and 125 recurrences (81, 22, and 22 in the TBB, CT-guided biopsy, and lung resection groups, respectively). The baseline characteristics of all eligible cases ($n = 397$) are summarised in Table 1.

Crude analysis

The TBB and CT-guided biopsy groups tended to include greater CEA values ($p = 0.001$), solid tumour size ($p < 0.001$) and SUV_{max} ($p < 0.001$) than the lung resection group, whereas there were no significant differences in any other preoperative factors (Table 1; Figs. 1, 2). There was a significant difference between groups in terms of the operative procedure ($p < 0.001$) and pathological stage ($p < 0.001$); while TBB group tended to include more frequent vessel invasion and lymphatic permeation ($p < 0.001$ for both). The lung resection group showed a tendency of the highest overall survival and disease-free survival rates among the

Table 1 Patients' characteristics according to the groups

Variable (number of objectives)	Transbronchial biopsy ($n=221$)	CT-guided biopsy ($n=71$)	Lung resection ($n=105$)	p value
Pre-operative variables				
Age (years) (397)				0.571
< 68	104	35	56	
68 ≤	117	36	49	
Sex (397)				0.997
Male	139	45	66	
Female	82	26	39	
Body mass index (kg/m^2) (397)				0.357
≤ 23	123	33	59	
23<	98	38	46	
Smoking history (381)				0.364
Absent	65	27	34	
Present	148	41	66	
Carcinoembryonic antigen (ng/ml) (389)				0.001
≤ 5.0	140	52	87	
5<	81	19	18	
Diabetes mellitus (397)				0.423
Absent	175	54	88	
Present	46	17	17	
Heart disease (397)				0.470
Absent	207	64	95	
Present	14	7	10	
Past history of malignancy (397)				0.261
Absent	186	60	81	
Present	35	11	24	
% VC (%) (393)				0.804
80 ≤	212	69	102	
< 80	9	2	3	
FEV1.0% (%) (397)				0.283
70≤	164	51	69	
< 70	57	20	36	
Solid tumor size (mm) (396)				< 0.001
≤10	27	12	42	
10<. ≤ 20	91	37	40	
20<, ≤ 30	59	17	15	
30<. ≤ 50	35	3	8	
50<	9	2	0	
SUV_{max} (195) Mean (95% CI)	6.63 (5.85–7.41)	4.92 (3.33–6.50)	4.52 (3.34–5.70)	< 0.001
Operative and post-operative variables				
Procedure (397)				< 0.001
Limited resection	35	23	59	
Lobectomy or pneumonectomy	175	46	46	
Exploration	11	2	0	

Table 1 (continued)

Variable (number of objectives)	Transbronchial biopsy ($n=221$)	CT-guided biopsy ($n=71$)	Lung resection ($n=105$)	p value
pTNM (397)				< 0.001
IA	78	40	70	
IB	60	16	20	
IIA	18	4	3	
IIB	15	5	2	
IIIA	29	2	5	
IIIB	1	0	1	
IV	20	4	4	
Pathology (397)				0.936
Adenocarcinoma	164	51	79	
Squamous cell carcinoma	30	11	16	
Others	27	9	10	
Vessel invasion				< 0.001
Absent	42	25	46	
Present	166	44	56	
Lymphatic permeation				< 0.001
Absent	13	12	27	
Present	194	57	74	
Pleural dissemination				0.048
Absent	196	67	101	
Present	25	4	4	
Adjuvant chemotherapy (397)				0.479
Absent	202	68	97	
Present	19	3	8	

VC vital capacity, *FEV1.0* forced expiratory volume in 1 s, SUV_{max} the maximum standardized uptake value, *pTNM* pathological TNM stage

Chi-square test was used for categorical covariates

Kruskal–Wallis test was used for continuous covariates

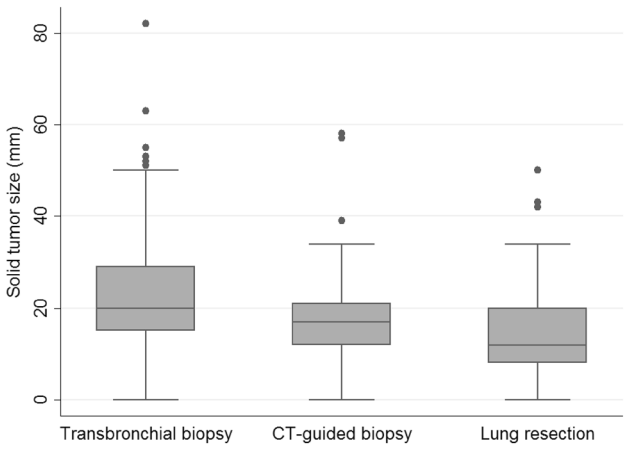

Fig. 1 Solid tumor size measured on preoperative computed tomography showed significant difference among groups (Kruskal–Wallis test: $p=0.0001$)

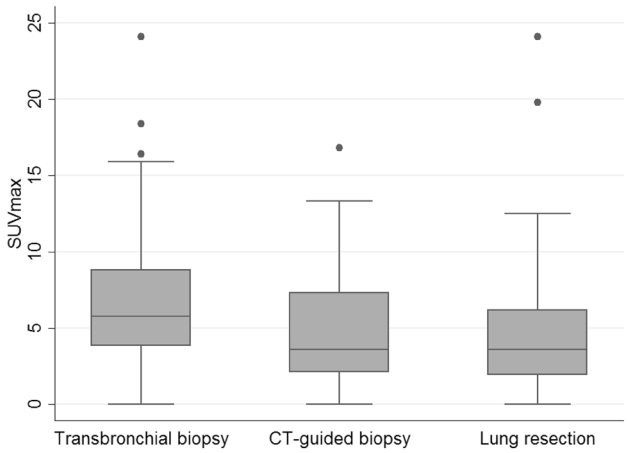

Fig. 2 The maximum standardized uptake value (SUV_{max}) measured by preoperative 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) showed significant difference among groups (Kruskal–Wallis test: $p=0.0001$)

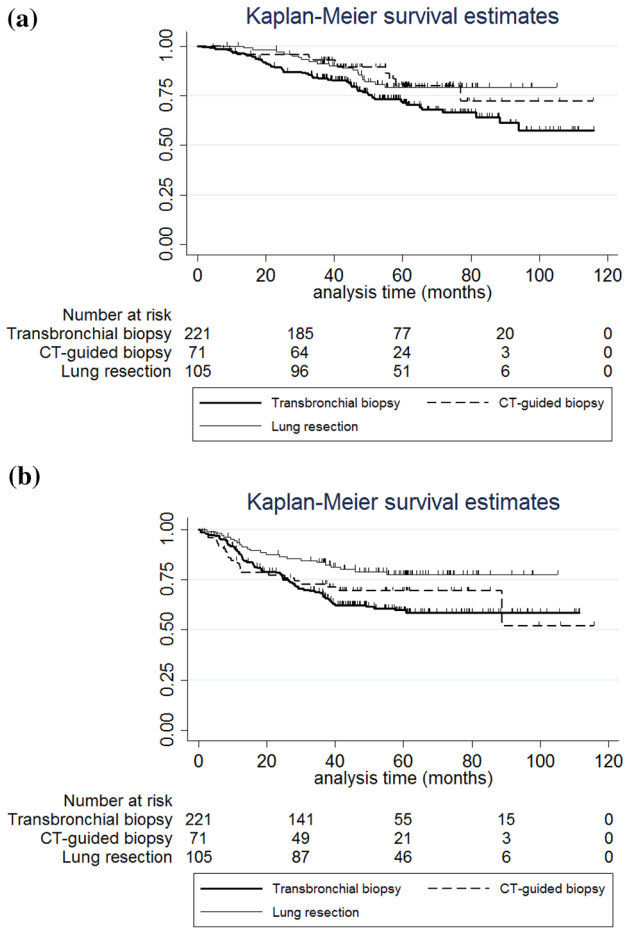

Fig. 3 Overall (**a**) and recurrence-free (**b**) survival curves according to the diagnostic methods. Overall survival: $p=0.0458$ (log-rank test). (Transbronchial biopsy vs CT-guided biopsy: $p=0.2508$, transbronchial biopsy vs Lung resection: $p=0.1173$, CT-guided biopsy vs Lung resection: $p=1.0000$). b Recurrence-free survival: $p=0.0101$ (log-rank test). (Transbronchial biopsy vs CT-guided biopsy: $p=1.0000$, transbronchial biopsy vs lung resection: $p=0.0059$, CT-guided biopsy vs lung resection: $p=0.2652$)

Table 2 Univariate and multivariate logistic regression analysis for pleural dissemination at the time of lung resection

Variable	Odds ratio	95% CI	*p* value
Univariate analysis			
Diagnosis method			
Transbronchial biopsy	1		
CT-guided biopsy	0.47	0.16–1.39	0.173
Lung resection	0.31	0.11–0.92	0.034
Age	2.38	1.10–5.14	0.028
Sex	2.19	1.07–4.48	0.033
BMI	0.56	0.27–1.20	0.136
Smoking history	0.56	0.27–1.16	0.117
CEA	1.20	0.56–2.56	0.636
%VC	0.84	0.11–6.66	0.872
FEV1.0%	0.94	0.42–2.08	0.874
Solid tumor size	1.51	1.08–2.10	0.015
SUV_{max}	1.07	0.96–1.20	0.202
pTNM	6.50	3.58–11.8	<0.001
Pathology			
Adenocarcinoma	1		
Squamous cell carcinoma	1.09	0.26–3.47	0.776
Other (non-adeno/non-squamous)	3.99	1.53–9.90	0.002
Vessel invasion	1.98	0.65–5.98	0.227
Lymphatic permeation	3.52	0.46–26.8	0.224
Multivariate analysis with the stepwise backward elimination method with a probability level of 0.15			
Diagnosis method	0.44	0.15–1.30	0.137
pTNM	7.35	3.72–14.5	<0.001
Pathology	2.94	1.19–7.25	0.019

Covariates with $p<0.05$ in the univariate analysis were entered into the multivariate model

BMI body mass index, *CEA* carcinoembryonic antigen, *VC* vital capacity, *FEV1.0* forced expiratory volume in 1 s, SUV_{max} the maximum standardized uptake value, *pTNM* pathological TNM stage

three groups ($p=0.0458$ and 0.010, respectively) (Fig. 3a, b). Moreover, the lung resection group showed significantly higher recurrence-free survival compared to transbronchial biopsy group ($p=0.0059$, Fig. 3b). Univariate analysis of pleural dissemination at the time of resection revealed that the following diagnostic methods: CT-guided biopsy vs TBB (odds ratio 0.47, $p=0.173$); lung resection vs TBB (odds ratio 0.31, 0.034); as well as age (odds ratio 2.38, $p=0.028$), sex (odds ratio 2.19, $p=0.033$), solid tumour size (odds ratio 0.56, $p=0.136$), pTNM (odds ratio 6.5, $p<0.001$), and non-adeno/ non-squamous pathology (odds ratio 3.99, $p=0.002$) were significant predictors (Table 2a). Univariate analysis of overall survival revealed that the diagnostic methods: CT-guided biopsy vs TBB (hazard ratio 0.57, $p=0.088$); lung resection vs TBB (hazard ratio 0.58, $p=0.041$), age (hazard ratio 1.87, $p=0.004$), sex (hazard ratio 0.43, $p=0.001$), smoking history (hazard ratio 2.35, $p=0.002$), CEA (hazard ratio 1.81, $p=0.005$), solid tumor size (hazard ratio 1.02, $p=0.005$), SUV_{max} (hazard ratio 1.09, $p=0.002$), procedure: exploration vs limited resection (hazard ratio 4.019, $p=0.003$), pTNM (hazard ratio 1.33, $p<0.001$), vessel invasion (hazard ratio 4.58, $p<0.001$), and lymphatic permeation (hazard ratio 4.83, $p=0.007$) were significant predictors (Table 3a). Univariate analysis of recurrence-free survival revealed that diagnostic methods: lung resection vs TBB (hazard ratio 0.48, $p=0.002$), age (hazard ratio 1.44, $p=0.044$), CEA (hazard ratio 1.62, $p=0.009$), solid tumor size (hazard ratio 1.32, $p=0.001$), SUV_{max} (hazard ratio 1.07, $p=0.003$), pTNM (hazard ratio 1.47, $p<0.001$), vessel invasion (hazard ratio 4.33, $p<0.001$), and lymphatic permeation (hazard ratio 3.56, $p=0.002$) were significant predictors (Table 4a).

Table 3 Univariate (a) and multivariate (b) Cox proportional hazard model for overall survival

Variable	Hazard ratio	95% CI	*p* value
Univariate analysis			
Diagnosis method			
Transbronchial biopsy	1		
CT-guided biopsy	0.57	0.30–1.09	0.088
Lung resection	0.58	0.35–0.98	0.041
Age	1.87	1.22–2.85	0.004
Sex	0.43	0.26–0.70	0.001
BMI	0.89	0.58–1335	0.572
Smoking history	2.35	1.36–4.04	0.002
CEA	1.81	1.19–2.75	0.005
%VC	2.21	0.90–5.47	0.085
FEV1.0%	1.52	0.99–2.33	0.057
Solid tumor size	1.02	1.01–1.04	0.005
SUVmax	1.09	1.03–1.14	0.002
Procedure			
Limited resection	1		
Lobectomy or pneumonectomy	0.72	0.46–1.14	0.160
Exploration	4.019	1.62–9.98	0.003
pTNM	1.33	1.21–1.47	< 0.001
Pathology			
Adenocarcinoma	1		
Squamous cell carcinoma	1.504	0.87–2.61	0.148
Other (non-adeno/non-squamous)	1.564	0.86–2.85	0.144
Vessel invasion	4.58	2.21–9.49	< 0.001
Lymphatic permeation	4.83	1.52–15.3	0.007
Adjuvant chemotherapy	0.94	0.45–1.95	0.859
Multivariate analysis with the stepwise backward elimination method with a probability level of 0.15			
Age	2.68	1.34–5.37	0.005
Sex	0.23	0.09–0.61	0.003
CEA	2.27	1.16–4.45	0.017
pTNM	1.62	1.34–1.94	< 0.001

Covariates with $p < 0.05$ in the univariate analysis were entered into the Cox model

BMI body mass index, *CEA* carcinoembryonic antigen, *VC* vital capacity, *FEV1.0* forced expiratory volume in 1 s, SUV_{max} the maximum standardized uptake value, *pTNM* pathological TNM stage

Multivariate analysis

At multivariate analysis, the following were observed as independent prognostic factors: pTNM (odds ratio 7.35, $p < 0.001$) and pathology (odds ratio 2.94, $p = 0.019$) for pleural dissemination at the time of resection (Table 2b); age (hazard ratio 2.68, $p = 0.005$), sex (hazard ratio 0.23, $p = 0.003$), CEA (hazard ratio 2.27, $p = 0.017$), and pTNM (hazard ratio 1.62, $p < 0.001$) for overall survival (Table 3b); as well as pTNM (hazard ratio 1.43, $p < 0.001$) and vessel invasion (hazard ratio 6.33, $p = 0.002$) for recurrence-free survival (Table 4b). Furthermore, in the multivariate analysis, diagnostic methods were not identified as independent risk factors for pleural dissemination, overall survival, or recurrence-free survival.

Discussion

In patients suspected of having lung cancer, it is recommended that the diagnosis of lung cancer be established before treatment. Gal concluded that TBB should be performed to avoid either open-lung biopsy or video-assisted thoracoscopic surgery biopsy [14]. Histological confirmation is crucial for the management of lung nodules suspected to be lung cancer, and transbronchial and fine-needle aspiration biopsies are regarded as the most important diagnostic tools for this purpose [15]. For central or endobronchial lesions, the overall sensitivity of flexible bronchoscopy for diagnosing lung cancer is 88%, although the diagnostic yield of bronchoscopy decreases for peripheral lesions [16]. For the diagnosis of peripheral lung cancer, the pooled sensitivity of transthoracic needle aspiration for the diagnosis of lung cancer was reported as 90% [16]. Gelbman et al. reported a false-negative rate with CT-guided biopsy of 10%, and recommended that benign fine-needle aspiration biopsies should have repeat imaging for at least 2 years, to document stability or resolution of the lesion [17]. It is conceivable that some lung tumors such as small pure ground glass attenuation, which occur in the central lesion adjacent to pulmonary vessels or major organs, may require operative approaches and not preoperative biopsy.

Despite the emphasis on pre-treatment biopsy, there has been some controversy regarding the need for performing preoperative pathologic diagnostic procedures, because pre-treatment biopsy inevitably disrupts the vascular and lymphatic structures of the bronchi and alveoli. They may also disseminate tumour cells into the airway, vessels, or pleural cavity; and may affect postoperative outcomes [4, 5, 18–22]. Although there are currently few reports about the risk of dissemination after transbronchial biopsy procedures, Nakajima et al. reported that transbronchial biopsy might worsen the prognosis of patients with resectable non-small cell lung carcinoma [4]. As for trans-pleural biopsy, there have been several conflicting reports. Inoue et al. reported that CT-guided percutaneous needle biopsy might increase the risk of pleural implantation [22]. On the other hand, Sawabata et al. and Matsuoka et al. reported that trans-pleural biopsy did not affect the risk of relapse and prognosis in patients and concluded that trans-pleural methods are advisable ways of diagnosing operable lung cancer [5, 21]. In addition, there have been several case reports pointing out the possible risk

Table 4 Univariate (a) and multivariate (b) Cox proportional hazard model for recurrence-free survival

Variable	Hazard ratio	95% CI	*p* value
Univariate analysis			
Diagnosis method			
Transbronchial biopsy	1		
CT-guided biopsy	0.82	0.51–1.32	0.422
Lung resection	0.48	0.30–0.77	0.002
Age	1.44	1.01–2.05	0.044
Sex	0.88	0.61–1.27	0.504
BMI	0.80	0.56–1.15	0.225
Smoking history	1.15	0.79–1.69	0.466
CEA	1.62	1.13–2.33	0.009
%VC	1.81	0.80–4.12	0.156
$FEV_1.0\%$	1.04	0.70–1.53	0.858
Solid tumor size	1.32	1.12–1.55	0.001
SUV_{max}	1.07	1.02–1.12	0.003
Procedure	0.98	0.69–1.41	0.929
Limited resection	1		
Lobectomy or pneumonectomy	0.75	0.5119–1.095	0.135
Exploration	2.49	1.158–5.355	0.020
pTNM	1.47	1.36–1.59	< 0.001
Pathology			
Adenocarcinoma	1		
Squamous cell carcinoma	0.59	0.31–1.10	0.094
Other (non-adeno/non-squamous)	1.53	0.94–2.48	0.084
Vessel invasion	4.33	2.43–7.71	< 0.001
Lymphatic permeation	3.56	1.56–8.10	0.002
Adjuvant chemotherapy	1.09	0.57–2.08	0.803
Multivariate analysis with the stepwise backward elimination method with a probability level of 0.15			
pTNM	1.43	1.26–1.63	< 0.001
Vessel invasion	6.33	1.96–20.4	0.002

Covariates with $p < 0.05$ in the univariate analysis were entered into the Cox model

BMI body mass index, *CEA* carcinoembryonic antigen, *VC* vital capacity, $FEV_1.0$ forced expiratory volume in 1 s, SUV_{max} the maximum standardized uptake value, *pTNM* pathological TNM stage

of dissemination of tumours other than lung cancer through the biopsy route after fine-needle aspiration biopsy [18–21]. Furthermore, in patients with sarcoma, Richardson et al. pointed out the risk of needle tract seeding after percutaneous biopsy [23].

During TBB or brushing, the neoplastic tissue is bluntly torn from the main tumour and, as a result, circulating tumour cells might be spread throughout the body. Sawabata et al. reported that the presence of clustered circulating tumour cells postoperatively indicated an unfavourable outcome [24]. Shiono et al. reported that the morphologic features of aerogenous spread with floating cancer cell clusters and vascular invasion at metastatic sites are prognostic factors for colorectal cancer patients who have undergone pulmonary metastasectomy [25]. Both studies pointed out the possibility of cancer spread by manipulation of the tumour. Fine-needle aspiration through the pleura, similar to TBB, has been reported as a potential risk factor associated with the spread of malignant cells to the pleural space [26]. However, although the possible risk of tumour dissemination by tumour manipulation from outside the body has been repeatedly pointed out, it remains unknown whether artificially disseminated malignant cells could mature into secondary tumour masses. Cancer metastasis is known to require complex and multi-step mechanisms. Artificial scattering of tumour cells might not always result in secondary tumour mass formation, as suggested by the "seed and soil" hypothesis [27]. Furthermore, the tumour may produce multitude of factors; depending on the type of stimuli, the cells in the tumour microenvironment can adopt different activation states, resulting in phenotypes ranging from tumour promotion to tumour suppression [28]. Thus, stimulus to tumour cells by TBB and CT-guided biopsy may not necessarily result in tumour promotion.

Study limitation

This study is a retrospective study conducted at a single institution; hence, the power of the retrieved results could be limited. Additionally, we could not retrieve all the data on the treatment regimen for recurrent disease because the majority of the recurrent case lack the data on their treatment. Thus, the potential impact of the treatment regimen for the recurrence on the overall survival could not be taken into consideration in our analysis, but should be assessed in future study. Further assessment in a larger cohort or in a prospective study will be necessary to confirm our conclusions.

Conclusion

In this study, by multivariate analysis, diagnostic methods were not identified as independent risk factors of pleural dissemination, overall survival, or recurrence-free survival. Preoperative diagnosis by TBB or CT-guided biopsy may help avoid exploratory surgery for the purpose of lung biopsy. It is desirable that lung cancer be diagnosed as early as possible to maximize the chance of recovery. Because preoperative diagnostic intervention does not appear to affect the risk of relapse and/or prognosis, preoperative diagnostic intervention is recommended if deemed necessary.

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest.

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