Effects of pre-operative biopsy on recurrence and survival in stage I lung adenocarcinoma patients in China

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Whether biopsy affects recurrence is controversial. Pre-operative biopsy was not associated with recurrence and survival in stage I lung adenocarcinoma patients. Biopsy might be safe for patients whose diagnosis is difficult to determine. https://bit.ly/3nWCysy

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Abstract

Background Whether pre-operative biopsy affects post-operative recurrence and metastasis of lung cancer patients is still controversial.

Methods In order to clarify these disputes, we collected relevant literature to conduct a meta-analysis. To validate the results of the meta-analysis, we retrospectively analysed 575 patients with stage I lung adenocarcinoma who underwent surgical resection at our centre from 2010 to 2018 using propensity score matching and competing risk models.

Results 5509 lung cancer patients from 11 articles were included in the meta-analysis. Summary analysis showed that the total recurrence rate of the biopsy group was higher than that of the nonbiopsy group (risk ratio 1.690, 95% CI 1.220–2.330; p=0.001). After propensity score matching, we found that there was no significant correlation between biopsy and total recurrence (risk ratio 1.070, 95% CI 0.540–2.120; p=0.850). In our cohort, of 575 stage I lung adenocarcinomas, 113 (19.7%) patients underwent pre-operative biopsy. During a median (interquartile range) follow-up of 71 (57–93) months, multivariable analyses showed pre-operative biopsy in the overall observation cohort (subdistribution hazard ratio (SHR) 1.522, 95% CI 0.997–2.320; p=0.051) and in the propensity score-matched cohort (SHR 1.134, 95% CI 0.709–1.810; p=0.600) was not significantly correlated with the risk of recurrence and metastasis. Moreover, the pre-operative biopsy did not affect disease-free survival (SHR 0.853, 95% CI 0.572–1.273; p=0.438) or overall survival (SHR 0.647, 95% CI 0.352–1.189; p=0.161).

Conclusion Pre-operative biopsy might not increase the risk of recurrence and metastasis, suggesting that these procedures might be safe for patients with stage I lung adenocarcinoma whose diagnosis is difficult to determine before surgery.

Introduction

The National Comprehensive Cancer Network (NCCN) guidelines state that if a nonlung cancer diagnosis is strongly suspected, or if intraoperative diagnosis appears difficult or very risky, a biopsy should be performed to confirm the diagnosis before surgery initially [1]. In clinical practice, bronchoscopic biopsy should be used for central nodules or intratracheal involvement [2]. Patients with peripheral nodules can be diagnosed with small specimens obtained by percutaneous transthoracic needle biopsy (PTNB) guided by computed tomography (CT) or ultrasound [3].

Multiple studies have shown that PTNB increases the risk of pleural recurrence after surgery in lung cancer [4, 5], but this view has been opposed by other studies [6]. The conclusion is still controversial. In addition, whether bronchoscopic biopsy increases a patient's risk of recurrence and affects prognosis has not been determined [7, 8].

We conducted a meta-analysis and retrospective cohort study to investigate whether pre-operative biopsy affects the recurrence and metastasis risk in stage I invasive lung adenocarcinoma patients whose nodules are difficult to determine before surgery. We present this article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist.

Methods

Search strategy and selection criteria

We conducted a systematic review in the following databases: PubMed, Web of Science, GeenMedical, the Cochrane Library, ScienceDirect, Embase, Scopus, Ovid MEDLINE and Google Scholar for eligible studies from 29 November 2012 to 29 November 2022 in order to find studies on the relationship between biopsy and recurrence in lung cancer. Keywords for the literature search included “lung cancer”, “biopsy”, “recurrence” and “metastasis”. We carried out the analysis in compliance with the PRISMA 2020 statement [9]. The inclusion criteria were as follows. 1) In the study, the influence of puncture on post-operative recurrence and metastasis of lung cancer patients was evaluated; 2) outcome events included overall recurrence, local recurrence, distant metastasis, combined recurrence and pleural recurrence [10]; 3) puncture included ultrasound-guided puncture, CT-guided puncture and bronchoscopic puncture. Reviews, letters, case reports, irrelevant studies, conference posters, incomplete studies, conference abstracts and seminars and repeated publications were excluded.

Data extraction and methodological quality assessment

The data included first author, publication year, country, period, tumour stage, sample size, histology, biopsy type, follow-up time, study type and baseline characteristics, recurrence indicator, *etc*. Two authors independently assessed the risk of bias for the included studies using the Cochrane Handbook [11]. The Cochrane Handbook clarified that the risk of bias needs to be assessed by the following criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of the participants and personnel (performance bias), blinding of the outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.

Study population

This study first collected lung adenocarcinoma patients who underwent surgical resection from May 2010 to August 2018. The inclusion criterion was lung adenocarcinoma diagnosed from surgical specimens. Exclusion criteria were pathological stage II–IV, adenocarcinoma *in situ* [12], minimally invasive adenocarcinoma [13] and invasive mucinous adenocarcinoma. Eligible patients were included in this study. This study was approved by the ethics committee of Beijing Chaoyang Hospital of Capital Medical University (2009-4 and 2016-79). All procedures were performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Diagnostic evaluation

The ultrasound- or CT-guided PTNB and transbronchial biopsy (TBB) were performed at Beijing Chaoyang Hospital by specialised pulmonologists and radiologists, respectively, using standard methods. For peripheral nodules, ultrasound- or CT-guided PTNB was used. CT was performed using a high-resolution 16-slice CT scanner (BrightSpeed Series CT systems; GE Healthcare, Milwaukee, WI, USA). PTNB was usually performed using the Supercore biopsy instrument 18 G 15 cm with optional co-axial needle MCXS1815LX (Argon Medical, Texas, TX, USA) or the Supercore biopsy instrument 18 G 9 cm with optional co-axial needle MCXS1809LX (Argon Medical).

A BF-260 video bronchoscopy (Olympus, Tokyo, Japan) was performed for intratracheal involvement or central-type nodules. Tumour samples were collected using conventional disposable biopsy forceps. Bbronchial ultrasound-guided biopsy can be used in patients whose lesions are not visible under bronchoscopy.

Follow-up strategy and assessment of recurrence and metastasis

During the first 3 years after surgery, patients underwent a general examination at least every 6 months. Whole-body examination included history-taking and physical examination, blood tumour markers, chest and abdomen CT, head magnetic resonance imaging and whole-body bone imaging. In the follow-up period, a full-body examination is performed once a year. Histological biopsy or positron emission tomography-CT can be further refined in patients with the potential for recurrence and metastasis. All recurrent and metastatic events were submitted to an independent adjudication committee including imaging and clinical experts. The adjudication committee determines the diagnosis of recurrence and metastasis through joint deliberation and comprehensive judgement.

Local recurrence is recurrence at the surgical margins, anastomotic or bronchial stump, tumour ipsilateral chest wall and pleura, ipsilateral lung or regional lymph nodes (grades 1–14). Distant metastases are defined as metastases to the contralateral lung or lymph nodes (neck or abdominal lymph node disease) or solid organs (head, abdominal organs, bones) [14–16]. Combined recurrence is the simultaneous detection of local recurrence and distant metastasis within 30 days [17]. Disease-free survival (DFS) was the time interval between diagnosis and the initial confirmation of local or distant recurrence, death or the end of follow-up. Overall survival was determined as the time from diagnosis to death or the end of follow-up [18].

Firstly, information on all patients was collected from the electronic case system of our hospital, focusing on recurrence, metastasis and prognosis. Secondly, all patients were followed-up by telephone on 1 April 2022. The examination results and prognosis of the patients in other hospitals were recorded in detail. The start time of follow-up in this study is the time of diagnosis of lung adenocarcinoma patients. If the patient died, the end time of follow-up was the time of death. If the patient survived, the end time of follow-up was 1 April 2022.

Statistical analysis

Risk ratios (95% CI) were used to analyse the recurrence rate. The degree of heterogeneity was determined by I^2 value. I^2>50% indicates obvious heterogeneity in which a random-effect model could be used to merge statistics. I^2<50% represents small heterogeneity; here we used a fixed-effect model to merge statistics. Funnel plots were used to explore publication bias.

Continuous and categorical variables were compared using the independent-samples t-test and Pearson's Chi-squared test or Fisher's exact test, respectively. Furthermore, to reduce possible selection bias, a propensity score matching (PSM) analysis was performed. Propensity scores were calculated using a multiple logistic regression model with variables including age, sex, tumour stage, tumour location, hospitalisation time and adjuvant chemotherapy. Matched at a 1:1 ratio, the caliper value is 0.01.

After the PSM analysis, a competing risk analysis was performed to determine the incidence of recurrence and metastasis. Death is treated as a competing event. Clinicopathological characteristics of subgroups of patients with and without recurrence were compared using Gray's test. Fine–Gray regression analysis was used to calculate risk factors for recurrence and metastasis, which were modelled as dependent variables in multivariable analysis. The selection of variables was based on the following criteria: 1) independent variables with $p<0.05$ in univariable analysis; 2) clinically important factors such as age, gender and tumour stage; 3) our main research objective in this study, which was pre-operative biopsy. All statistical tests were two-way and $p<0.05$ was considered statistically significant.

Review Manager (version 5.4; the Nordic Cochrane Centre) and STATA (version 15.0; Stata Corp) were used for meta-analysis. SPSS (version 25.0; IBM, Armonk, NY, USA) was used for PSM and other analyses. NCSS statistical software (version 12.0; NCSS, Kaysville, UT, USA) and R (version 3.4.4; R Foundation, Vienna, Austria) were used to perform Gray's test and Fine–Gray regression analysis. The study was reviewed by epidemiologists.

Results

Characteristics of included studies for meta-analysis

We screened 456 articles, and finally included 11 articles [8, 19–28] according to the inclusion and exclusion criteria. The literature screening is shown in supplementary figure S1. Three articles were from China, two from South Korea and six from Japan. The methodological quality assessment based on the Cochrane Handbook is listed in supplementary figure S2. In the included studies there were 5509 lung cancer patients in total, and their baseline characteristics and main data are listed in supplementary table S1. Funnel plots are symmetrical, indicating that there is no evidence of bias in publication (supplementary figure S3).

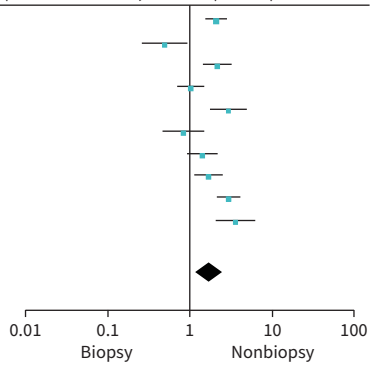
Influence of biopsy on recurrence and metastasis in meta-analysis

We compared the correlation between biopsy and total recurrence, local recurrence, distal recurrence, concurrent recurrence and pleural recurrence (figure 1). 10 studies compared the difference in the total recurrence rate between biopsy and nonbiopsy groups ($p<0.001$, $I^2=82\%$). Significant heterogeneity was found, so a random-effect model was used. The total recurrence rate of the biopsy group was higher than that of the nonbiopsy group (risk ratio 1.690 (95% CI 1.220–2.330; p=0.001). Four studies compared the difference in the local recurrence rate between biopsy and nonbiopsy groups ($p=0.003$, $I^2=79\%$). Significant heterogeneity was found, so a random-effect model was used. There was no significant difference between the biopsy and the nonbiopsy groups (risk ratio 1.370, 95% CI 0.500–3.740; p=0.540).

a)

Study or subgroup	Biopsy Events	Biopsy Total	Nonbiopsy Events	Nonbiopsy Total	Weight (%)	Risk ratio M–H, random (95% CI)
Ahn 2019	145	450	45	290	11.3	2.08 (1.54–2.80)
Asakura 2012	11	124	35	197	8.4	0.50 (0.26–0.95)
He 2021	35	186	47	544	10.5	2.18 (1.45–3.26)
Hu 2018	21	66	78	256	10.5	1.04 (0.70–1.56)
Huang 2020	46	229	19	280	9.6	2.96 (1.79–4.91)
Kashiwabara 2016	14	63	23	86	8.9	0.83 (0.47–1.48)
Moon 2017	58	243	25	149	10.3	1.42 (0.93–2.17)
Taniguchi 2019	103	292	22	105	10.5	1.68 (1.13–2.52)
Yasukawa 2018	90	236	38	295	11.0	2.96 (2.11–4.15)
Yasukawa 2021	25	104	18	267	9.1	3.57 (2.03–6.25)
Total (95% CI)		1993		2469	100.0	1.69 (1.22–2.33)
Total events	548		350			

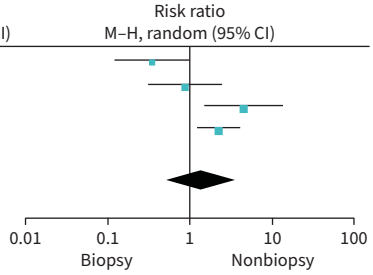
Heterogeneity: Tau²=0.22; Chi²=50.18, df=9 (p<0.00001); I²=82%
Test for overall effect: z=3.18 (p=0.001)



b)

Study or subgroup	Biopsy Events	Biopsy Total	Nonbiopsy Events	Nonbiopsy Total	Weight (%)	Risk ratio M–H, random (95% CI)
Asakura 2012	4	124	18	197	23.8	0.35 (0.12–1.02)
Hu 2018	4	66	18	256	23.9	0.86 (0.30–2.46)
Huang 2020	15	229	4	280	23.4	4.59 (1.54–13.62)
Moon 2017	45	243	12	149	28.9	2.30 (1.26–4.20)
Total (95% CI)		662		882	100.0	1.37 (0.50–3.74)
Total events	68		52			

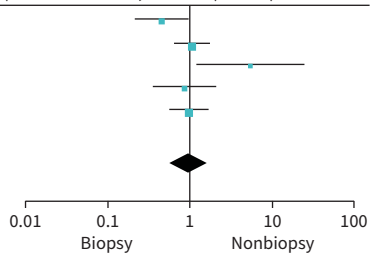
Heterogeneity: Tau²=0.81; Chi²=14.13, df=3 (p=0.003); I²=79%
Test for overall effect: z=0.61 (p=0.54)



c)

Study or subgroup	Biopsy Events	Biopsy Total	Nonbiopsy Events	Nonbiopsy Total	Weight (%)	Risk ratio M–H, random (95% CI)
Asakura 2012	8	124	28	197	20.5	0.45 (0.21–0.96)
Hu 2018	15	66	54	256	27.6	1.08 (0.65–1.78)
Huang 2020	9	229	2	280	8.5	5.50 (1.20–25.21)
Kashiwabara 2016	7	63	11	86	17.3	0.87 (0.36–2.12)
Moon 2017	29	243	18	149	26.1	0.99 (0.57–1.72)
Total (95% CI)		725		968	100.0	0.98 (0.59–1.61)
Total events	68		113			

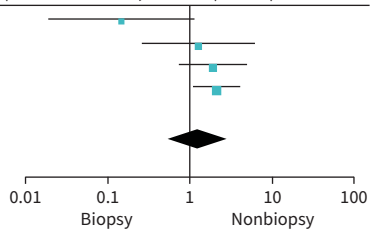
Heterogeneity: Tau²=0.17; Chi²=9.11, df=4 (p=0.06); I²=56%
Test for overall effect: z=0.10 (p=0.92)



d)

Study or subgroup	Biopsy Events	Biopsy Total	Nonbiopsy Events	Nonbiopsy Total	Weight (%)	Risk ratio M–H, random (95% CI)
Asakura 2012	1	124	11	197	12.9	0.14 (0.02–1.10)
He 2021	2	66	6	256	18.3	1.29 (0.27–6.26)
Hu 2018	7	186	11	544	30.9	1.86 (0.73–4.73)
Huang 2020	22	229	13	280	37.9	2.07 (1.07–4.02)
Total (95% CI)		605		1277	100.0	1.30 (0.56–3.05)
Total events	32		41			

Heterogeneity: Tau²=0.38; Chi²=6.56, df=3 (p=0.09); I²=54%
Test for overall effect: z=0.61 (p=0.54)



e)

Study or subgroup	Biopsy Events	Biopsy Total	Nonbiopsy Events	Nonbiopsy Total	Weight (%)	Risk ratio M–H, random (95% CI)
Ahn 2019	34	540	8	290	24.1	2.28 (1.07–4.87)
Asakura 2012	1	124	7	197	11.6	0.23 (0.03–1.82)
He 2021	1	186	2	544	9.7	1.46 (0.13–16.03)
Huang 2020	10	229	1	280	11.8	12.23 (1.58–94.81)
Kashiwabara 2016	7	63	5	86	20.4	1.91 (0.64–5.75)
Toyoda 2020	5	32	20	1015	22.4	7.93 (3.18–19.79)
Total (95% CI)		1174		2412	100.0	2.60 (1.04–6.50)
Total events	58		43			

Heterogeneity: Tau²=0.76; Chi²=14.31, df=5 (p=0.01); I²=65%
Test for overall effect: z=2.05 (p=0.04)

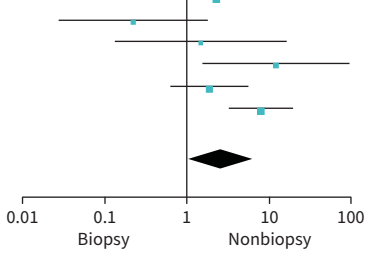


FIGURE 1 Forest plots for the risk ratio of a) total recurrence, b) local recurrence, c) distant metastasis, e) combined recurrence and f) pleural recurrence of the pre-operative biopsy group *versus* the non-pre-operative group of lung cancer patients. M–H: Mantel–Haenszel.

Five studies compared the difference in the distant metastasis rate between biopsy and nonbiopsy groups (p=0.060, I^2=56%). Significant heterogeneity was found, so a random-effects model was used. There was no significant difference between the biopsy and the nonbiopsy groups (risk ratio 0.980, 95% CI 0.590–1.610; p=0.920). Four studies compared the difference in the combined recurrence rate between biopsy and nonbiopsy groups (p=0.090, I^2=54%). Significant heterogeneity was found, so a random-effects model was used. There was no significant difference between the biopsy and the nonbiopsy groups (risk ratio 1.300, 95% CI 0.560–3.050; p=0.540). Six studies compared the difference in the pleural recurrence rate between biopsy and nonbiopsy groups (p=0.010, I^2=65%). Significant heterogeneity was found, so a random-effect model was used. The pleural recurrence rate of the biopsy group was higher than that of the nonbiopsy groups (risk ratio 2.600, 95% CI 1.040–6.500; p=0.040).

We further compared the total recurrence, combined recurrence and pleural recurrence in the biopsy group and the nonbiopsy group after propensity score matching (supplementary figure S4). Two studies compared the difference in the total recurrence rate between biopsy and nonbiopsy groups (p=0.830, I^2=0%). Significant heterogeneity was not found, so a fixed-effect model was used. There was no significant difference between the biopsy and the nonbiopsy groups (risk ratio 1.070, 95% CI 0.540–2.120; p=0.850). Two studies compared the difference in the combined recurrence rate between biopsy and nonbiopsy groups (p=0.830, I^2=0%). Significant heterogeneity was not found, so a fixed-effect model was used. There was no significant difference between the biopsy and the nonbiopsy groups (risk ratio 1.070, 95% CI 0.540–2.120; p=0.850). Two studies compared the difference in the pleural recurrence rate between the biopsy and nonbiopsy groups (p=0.790, I^2=0%). Significant heterogeneity was not found, so a fixed-effect model was used. There was no significant difference between the biopsy and the nonbiopsy groups (risk ratio 4.330, 95% CI 0.740–25.360; p=0.100).

Patient characteristics in our cohort

First, 963 patients with pathologically confirmed primary lung adenocarcinoma were screened from our electronic medical record system. The tumours of 229 patients were stage II–IV. Adenocarcinoma *in situ* was diagnosed in 106 patients; minimally invasive adenocarcinoma in 17 patients; and mucinous adenocarcinoma in 36 patients. All these patients were excluded (n=388). Finally, 575 stage I invasive lung adenocarcinoma patients treated surgically were included in this study (figure 2).

Of the 575 patients in the observational cohort, the median age was 61 years, and 249 (43.3%) were male. 272 (47.3%) patients had a body mass index <23.9 kg·m^{-2}. 187 (32.5%) patients had ever smoked. COPD was diagnosed in 106 (18.4%) patients. The tumour was located in the right thoracic cavity in 355 (61.7%)

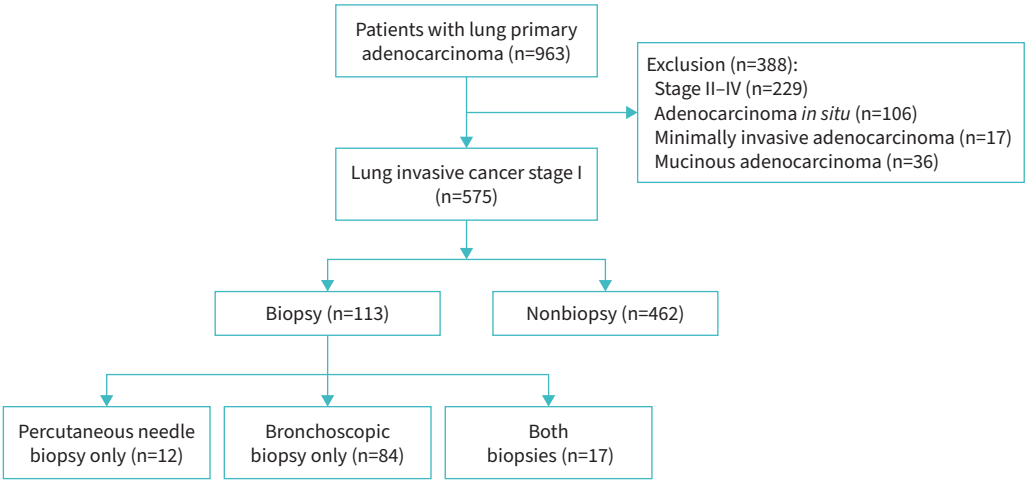


FIGURE 2 Study flow diagram.

patients. 33 (5.7%) patients underwent thoracotomy and 542 (94.3%) patients underwent video-assisted thoracoscopic surgery. In addition, 517 (89.9%) underwent lobectomy, and 58 (10.1%) underwent palliative surgery including segmentectomy and wedge resection.

This lung adenocarcinoma cohort of 575 cases included lepidic predominant (19.5%, n=112), acinar predominant (53.2%, n=306), papillary predominant (15.7%, n=90), micropapillary predominant (5.2%, n=30) and solid predominant (6.4%, n=37). Among all patients, 505 (87.8%) had pathological tumour stage IA, and 70 (12.2%) had stage IB. Vascular invasion was found in 85 (14.8%) patients according to the pathology report. 107 (18.6%) had pleural invasion. 122 (21.2%) patients received post-operative adjuvant chemotherapy (table 1).

TABLE 1 Characteristics of patients treated with biopsy and nonbiopsy in the observational dataset and propensity score-matched cohort

	Observational dataset				Propensity-score-matched dataset			
	Total	Biopsy	Nonbiopsy	p-value	Total	Biopsy	Nonbiopsy	p-value
Patients	575	113	462		226	113	113	
Age years				0.900				1.000
⩽61	288 (50.1)	56 (49.6)	232 (50.2)		112 (49.6)	56 (49.6)	56 (49.6)	
>61	287 (49.9)	57 (50.4)	230 (49.8)		114 (50.4)	57 (50.4)	57 (50.4)	
Gender				0.296				0.346
Male	249 (43.3)	44 (38.9)	205 (44.4)		95 (42.0)	44 (38.9)	51 (45.1)	
Female	326 (56.7)	69 (61.1)	257 (55.6)		131 (58.0)	69 (61.1)	62 (54.9)	
BMI kg·m^{-2}				0.924				0.690
<23.9	272 (47.3)	53 (46.9)	219 (47.4)		109 (48.2)	53 (46.9)	56 (49.6)	
⩾23.9	303 (52.7)	60 (53.1)	243 (52.6)		117 (51.8)	60 (53.1)	57 (50.4)	
Smoking history				0.401				0.204
Never	388 (67.5)	80 (70.8)	208 (66.7)		151 (66.8)	80 (70.8)	71 (62.8)	
Current and former	187 (32.5)	33 (29.2)	154 (33.3)		75 (33.2)	33 (29.2)	42 (37.2)	
COPD				0.162				0.322
No	469 (81.6)	87 (77.0)	382 (82.7)		180 (79.6)	87 (77.0)	93 (82.3)	
Yes	106 (18.4)	26 (23.0)	80 (17.3)		46 (20.4)	26 (23.0)	20 (17.7)	
Tumour location				0.035				0.790
Right	355 (61.7)	60 (53.1)	295 (63.9)		122 (54.0)	60 (53.1)	62 (54.9)	
Left	220 (38.3)	53 (46.9)	167 (36.1)		104 (46.0)	53 (46.9)	51 (45.1)	
Surgical approach				0.113				0.509
VATS	542 (94.3)	103 (91.2)	439 (95.0)		203 (89.8)	103 (91.2)	100 (88.5)	
Thoracotomy	33 (5.7)	10 (8.8)	23 (5.0)		23 (10.2)	10 (8.8)	13 (11.5)	
Extent of resection				0.890				0.404
Segmentectomy or wedge	58 (10.1)	11 (9.7)	47 (10.2)		26 (11.5)	11 (9.7)	15 (13.3)	
Lobectomy or pneumonectomy	517 (89.9)	102 (90.3)	415 (89.8)		200 (88.5)	102 (90.3)	98 (86.7)	
Predominant subtype								
Lepidic	112 (19.5)	19 (16.8)	93 (20.1)	0.425	26 (11.5)	19 (16.8)	7 (6.2)	0.012
Acinar	306 (53.2)	56 (49.6)	250 (54.1)	0.384	123 (54.4)	56 (49.5)	67 (59.3)	0.142
Papillary	90 (15.7)	21 (18.6)	69 (14.9)	0.339	42 (18.6)	21 (18.6)	21 (18.6)	1.000
Micropapillary	30 (5.2)	8 (7.1)	22 (4.8)	0.321	19 (8.4)	8 (7.1)	11 (9.7)	0.472
Solid	37 (6.4)	9 (8.0)	28 (6.1)	0.460	16 (7.1)	9 (8.0)	7 (6.2)	0.604
TNM stage				0.092				0.397
IA	505 (87.8)	94 (83.2)	411 (89.0)		183 (81.0)	94 (83.2)	89 (78.8)	
IB	70 (12.2)	19 (16.8)	51 (11.0)		43 (19.0)	19 (16.8)	24 (21.2)	
Vascular invasion				0.497				0.727
Absent	490 (85.2)	94 (83.2)	396 (85.7)		186 (82.3)	94 (83.2)	92 (81.4)	
Present	85 (14.8)	19 (16.8)	66 (14.3)		40 (17.7)	19 (16.8)	21 (18.6)	
Pleural invasion				0.782				0.029
Absent	468 (81.4)	93 (82.3)	375 (81.2)		172 (76.1)	93 (82.3)	79 (69.9)	
Present	107 (18.6)	20 (17.7)	87 (18.8)		54 (23.9)	20 (17.7)	34 (30.1)	
Adjuvant chemotherapy				0.071				0.466
No	453 (78.8)	82 (72.6)	371 (80.3)		159 (70.4)	82 (72.6)	77 (68.1)	
Yes	122 (21.2)	31 (27.4)	91 (19.7)		67 (29.6)	31 (27.4)	36 (31.9)	

Data are presented as n or n (%), unless otherwise stated. BMI: body mass index; VATS: video-assisted thoracic surgery; TNM: tumour, node, metastasis.

Recurrence and metastasis rates and mortality in our cohort

Of the 575 patients with stage I lung adenocarcinoma, 113 (19.7%) patients underwent pre-operative biopsy. Specifically, 12 (2.1%) patients underwent PTNB only; 84 (14.6%) patients underwent TBB only; and 17 (3.0%) patients underwent both biopsies.

38 (6.6%) patients were diagnosed in advance by finding lung adenocarcinoma cells in pre-operative biopsy samples. The detection rate of lung adenocarcinoma cells in pre-operative biopsy was 33.6%. Of the 12 patients who only received PTNB, only 10 (83.3%) patients found tumour cells in the puncture samples. Of the 84 patients who received TBB only, tumour cells were found in the tracheoscopic puncture samples in 15 (17.9%). Among the 17 patients who received both PTNB and TBB, tumour cells were found in PTNB samples of 12 patients, and tumour cells were found in TBB samples of three patients. Only one patient who underwent bronchoscopy had haemoptysis. Two patients who received PTNB developed pneumothorax.

During a median follow-up of 71 (57–93) months, 128 (22.3%) developed tumour recurrence or metastasis, and 105 patients died. Of the 226 patients in the PSM cohort, 74 (32.7%) developed tumour recurrence or metastasis, and 61 patients died. Detailed recurrence sites according to whether or not a puncture was performed are presented in table 2 and supplementary figure S5. Supplementary table S2 shows the recurrence and metastasis of different sites in patients who received different biopsy methods.

Of the 575 patients in the observational cohort, 462 patients did not undergo biopsy before surgery and 113 patients underwent needle biopsy. Of the 462 patients who did not undergo biopsy, 93 (20.1%) had recurrence or metastasis. Only local recurrence occurred in 44 (9.5%) patients. Only distant metastases occurred in 34 (7.4%) patients. 34 (7.4%) patients experienced combined recurrence. Pleural metastases occurred in 18 (3.9%) patients. Of the 113 patients who underwent biopsy, 35 (31.0%) had recurrence or metastasis. Only local recurrence occurred in 12 (10.6%) patients. Only distant metastases occurred in 10 (8.8%) patients. Combined recurrence occurred in 17 (15.0%) patients. Pleural metastases occurred in six (5.3%) patients (table 2 and supplementary figure S5).

In the PSM cohort, 113 patients did not undergo needle biopsy. Among them, 35 (31.0%) patients had recurrence or metastasis. Only local recurrence occurred in 15 (13.3%) patients. Only distant metastases occurred in 13 (11.5%) patients. Combined recurrence occurred in 16 (14.2%) patients. 10 (8.8%) patients developed pleural metastases (table 2 and supplementary figure S5).

Of the 12 patients who only underwent PTNB, six (50.0%) had recurrence or metastasis. Only local recurrence occurred in three (25.0%) patients. Only distant metastases occurred in one (8.3%) patient. Combined recurrence occurred in two (16.7%) patients. No patient had pleural metastasis (supplementary table S2).

Among the 84 patients who only received TBB, 24 (31.0%) had recurrence or metastasis Only local recurrence occurred in eight (9.5%) patients. Only distant metastases occurred in nine (10.7%) patients. Combined recurrence occurred in 11 (13.1%) patients. Two (2.4%) patients developed pleural metastases (supplementary table S2).

TABLE 2 Recurrence and metastasis patterns of patients in the observational dataset and propensity-score-matched cohort

	Observational dataset (n=575)		Propensity-score-matched dataset (n=226)	
	Biopsy	Nonbiopsy	Biopsy	Nonbiopsy
Patients	113	462	113	113
Recurrence and metastasis				
Overall	35 (31.0)	93 (20.1)	35 (31.0)	35 (31.0)
Only local	12 (10.6)	44 (9.5)	12 (10.6)	15 (13.3)
Only distant	10 (8.8)	34 (7.4)	10 (8.8)	13 (11.5)
Local and distant	17 (15.0)	34 (7.4)	17 (15.0)	16 (14.2)
Pleural	6 (5.3)	18 (3.9)	6 (5.3)	10 (8.8)

Data are presented as n or n (%).

Among the 17 patients who had received both PTNB and TBB, five (29.4%) had recurrence or metastasis Only local recurrence occurred in one (5.9%) patient. No patient had only distant metastases. Combined recurrence occurred in four (23.5%) patients. Four (23.5%) patients developed pleural metastases (supplementary table S2).

Risk factors for recurrence and metastasis before PSM in our cohort

In the observation before PSM cohort, univariable analysis showed that the risk factors for total recurrence were gender (p=0.002), smoking (p=0.003), biopsy (p=0.019) (figure 3a), the extent of resection (p=0.015), vascular invasion (p=0.001), pleural invasion (p=0.002) and adjuvant chemotherapy (p<0.001). In multivariable analysis, only adjuvant chemotherapy (subdistribution hazard ratio (SHR) 2.242, 95% CI 1.531–3.280; p<0.001) was significantly associated with total recurrence. Pre-operative biopsy was not significantly associated with total recurrence (SHR 1.522, 95% CI 0.997–2.320; p=0.051) (table 3).

Univariable analysis showed that the risk factors for local recurrence were gender (p=0.003), smoking (p=0.010), biopsy (p=0.038) (figure 3d), surgical approach (p=0.017), the extent of resection (p=0.034), vascular invasion (p=0.002), pleural invasion (p<0.001) and adjuvant chemotherapy (p<0.001). In multivariable analysis, only adjuvant chemotherapy (SHR 2.295, 95% CI 1.507–3.500; p<0.001) was significantly associated with local recurrence. Pre-operative biopsy was not significantly associated with local recurrence (SHR 1.500, 95% CI 0.948–2.370; p=0.094) (supplementary table S3).

Univariable analysis showed that the risk factors for distant metastasis were gender (p=0.004), smoking (p=0.027), biopsy (p=0.025) (figure 3e), the extent of resection (p=0.007), lepidic predominant subtype (p=0.013), vascular invasion (p<0.001), pleural invasion (p=0.001) and adjuvant chemotherapy (p<0.001). In multivariable analysis, vascular invasion (SHR 1.811, 95% CI 1.045–3.140; p=0.034) and adjuvant chemotherapy (SHR 2.315, 95% CI 1.491–3.590; p<0.001) were significantly associated with distant metastasis. Pre-operative biopsy was not significantly associated with distant metastasis (SHR 1.602, 95% CI 0.976–2.630; p=0.062) (supplementary table S4).

Univariable analysis showed that the risk factors for combined recurrence were biopsy (p=0.013) (figure 3f), surgical approach (p=0.018), lepidic predominant subtype (p=0.007), vascular invasion (p=0.002), pleural invasion (p<0.001) and adjuvant chemotherapy (p<0.001). In multivariable analysis, biopsy (SHR 1.912, 95% CI 1.026–3.560; p=0.041) and adjuvant chemotherapy (SHR 2.757, 95% CI 1.548–4.910; p=0.001) were significantly associated with combined recurrence (supplementary table S5).

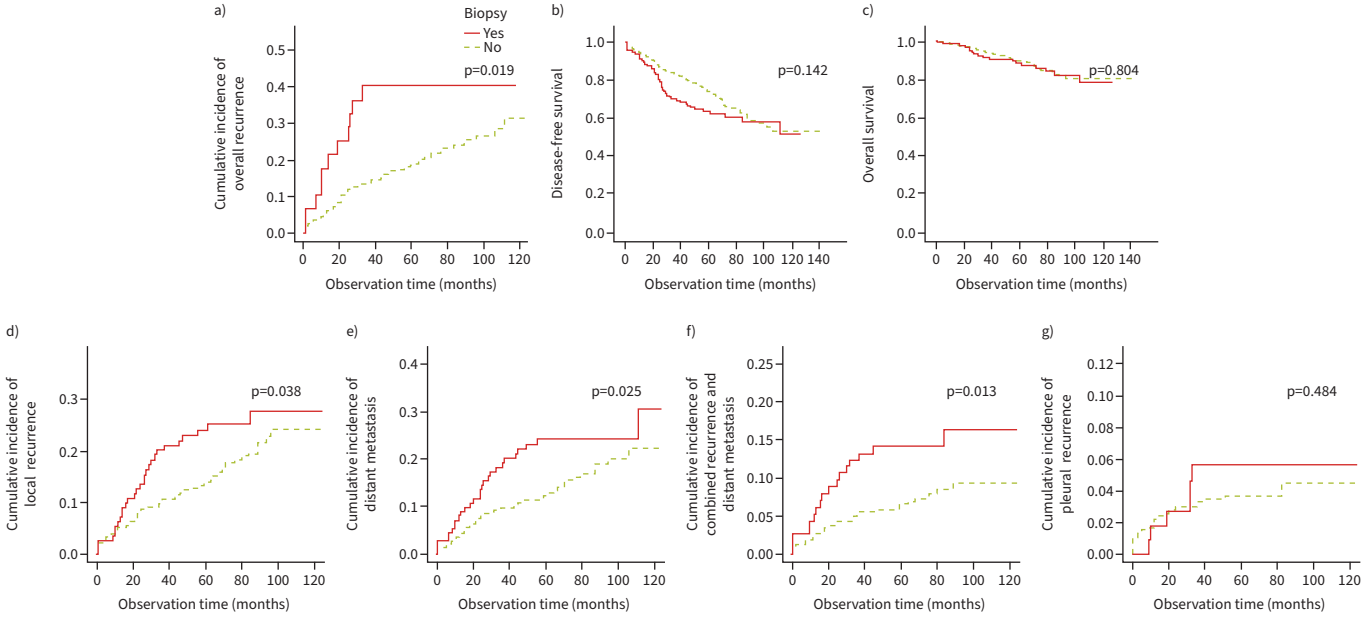


FIGURE 3 The effect of pre-operative biopsy on a) total recurrence, b) disease-free survival, c) overall survival, d) local recurrence, e) distant metastasis, f) combined recurrence and g) pleural recurrence in the observational dataset.

TABLE 3 Univariable and multivariable analyses of recurrence and metastasis in the observational dataset and propensity-score-matched cohort

	Observational dataset				Propensity-score-matched dataset			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	Chi-squared	p-value	SHR (95% CI)	p-value	Chi-squared	p-value	SHR (95% CI)	p-value
Patients n			575				226	
Age years								
⩽61	1		1		1		1	
>61	1.894	0.169	1.186 (0.822–1.710)	0.360	0.068	0.794	1.116 (0.694–1.790)	0.650
Gender								
Male	1		1		1		1	
Female	9.289	0.002	0.753 (0.487–1.160)	0.200	4.418	0.036	0.743 (0.399–1.380)	0.350
BMI kg·m^{-2}								
<23.9	1				1			
⩾23.9	1.179	0.278			0.716	0.398		
Smoking history								
Never	1		1		1		1	
Current and former	8.706	0.003	1.198 (0.775–1.850)	0.420	4.205	0.040	1.264 (0.668–2.390)	0.470
COPD								
No	1				1			
Yes	2.722	0.099			1.418	0.233		
Tumour location								
Right	1				1			
Left	2.484	0.115			1.980	0.159		
Biopsy								
No	1		1		1		1	
Yes	5.549	0.019	1.522 (0.997–2.320)	0.051	0.160	0.689	1.134 (0.709–1.810)	0.600
Surgical approach								
VATS	1				1			
Thoracotomy	3.052	0.081			1.597	0.206		
Extent of resection								
Segmentectomy or wedge	1		1		1			
Lobectomy or pneumonectomy	5.867	0.015	0.725 (0.402–1.310)	0.290	2.044	0.153		
Predominant subtype								
Lepidic	1.291	0.256			0.002	0.965		
Acinar	0.148	0.700			1.973	0.160		
Papillary	0.182	0.669			0.961	0.327		
Micropapillary	0.005	0.846			0.008	0.927		
Solid	3304	0.069			2.126	0.145		
TNM stage								
IA	1		1		1		1	
IB	2.318	0.128	1.014 (0.625–1.650)	0.950	0.254	0.615	0.981 (0.553–1.740)	0.950
Vascular invasion								
Absent	1		1		1			
Present	10.989	0.001	1.627 (0.994–2.660)	0.053	2.706	0.100		
Pleural invasion								
Absent	1		1		1			
Present	9.523	0.002	1.246 (0.781–1.990)	0.360	1.473	0.225		
Adjuvant chemotherapy								
No	1		1		1		1	
Yes	28.920	<0.001	2.242 (1.531–3.280)	<0.001	5.012	0.025	1.652 (1.002–2.720)	0.049

SHR: subdistribution hazard ratio; BMI: body mass index; VATS: video-assisted thoracic surgery; TNM: tumour, node, metastasis.

Univariable analysis showed that the risk factors for pleural recurrence were the extent of resection (p=0.002), vascular invasion (p=0.008), pleural invasion (p=0.003) and adjuvant chemotherapy (p<0.001). Pre-operative biopsy was not significantly associated with pleural recurrence (p=0.484) (figure 3g). In multivariable analysis, the extent of resection (SHR 0.277, 95% CI 0.128–0.600; p=0.001) and adjuvant chemotherapy (SHR 2.690, 95% CI 0.495–3.190; p=0.016) were associated with pleural recurrence. Pre-operative biopsy was not significantly associated with pleural recurrence (SHR 1.256, 95% CI 0.495–3.190; p=0.630) (supplementary table S6).

Cox univariable analysis revealed that age (p=0.012), gender (p=0.004), smoking history (p=0.003), surgical approach (p=0.005), the extent of resection (p=0.001), tumour, node, metastasis (TNM) stage (p=0.024), vascular invasion (p<0.001), pleural invasion (p=0.002) and adjuvant therapy (p<0.001) were significantly associated with DFS. Pre-operative biopsy (p=0.145) (figure 3b) and other indicators were unrelated to DFS. Cox multivariable analysis revealed that the extent of resection (hazard ratio (HR) 0.642, 95% CI 0.420–0.980; p=0.040), vascular invasion (HR 1.649, 95% CI 1.127–2.413; p=0.010) and adjuvant therapy (HR 1.656, 95% CI 1.201–2.284; p=0.002) were independent risk factors for DFS. Pre-operative biopsy was not significantly associated with DFS (SHR 1.179, 95% CI 0.833–1.670; p=0.352) (supplementary table S7).

Cox univariable analysis revealed that age (p=0.011), surgical approach (p=0.042), lepidic predominant subtype (p=0.020), TNM stage (p=0.008), vascular invasion (p<0.001) and pleural invasion (p<0.001) were significantly associated with overall survival. The pre-operative biopsy (p=0.805) (figure 3c) and other indicators were unrelated to OS. Cox multivariable analysis revealed that age (HR 1.732, 95% CI 1.093–2.742; p=0.019) and vascular invasion (HR 1.715, 95% CI 1.006–2.924; p=0.048) were independent risk factors for overall survival. Pre-operative biopsy was not significantly associated with overall survival (SHR 1.047, 95% CI 0.618–1.776; p=0.864) (supplementary table S8).

Risk factors for recurrence and metastasis after PSM in our cohort

In the observation cohort before PSM, univariable analysis showed that the risk factors for total recurrence were gender (p=0.036), smoking (p=0.040) and adjuvant chemotherapy (p=0.025). Biopsy (p=0.689) (figure 4a) was not significantly associated with total recurrence. In multivariable analysis, only adjuvant chemotherapy (SHR=1.652, 95% CI 1.002–2.720; p=0.049) was significantly associated with total recurrence. Pre-operative biopsy was not significantly associated with total recurrence (SHR 1.134, 95% CI 0.709–1.810; p=0.600) (table 3).

Univariable analysis showed that the risk factors for local recurrence were smoking (p=0.038), vascular invasion (p=0.040) and adjuvant chemotherapy (p=0.028). Biopsy (p=0.792) (figure 4d) was not significantly associated with local recurrence. In multivariable analysis, pre-operative biopsy was not significantly associated with local recurrence (SHR 1.143, 95% CI 0.677–1.930; p=0.620) (supplementary table S3).

Univariable analysis showed that the risk factors for lo distant metastasis were gender (p=0.024), vascular invasion (p=0.044), pleural invasion (p=0.005), adjuvant chemotherapy (p=0.002). Biopsy (p=0.906)

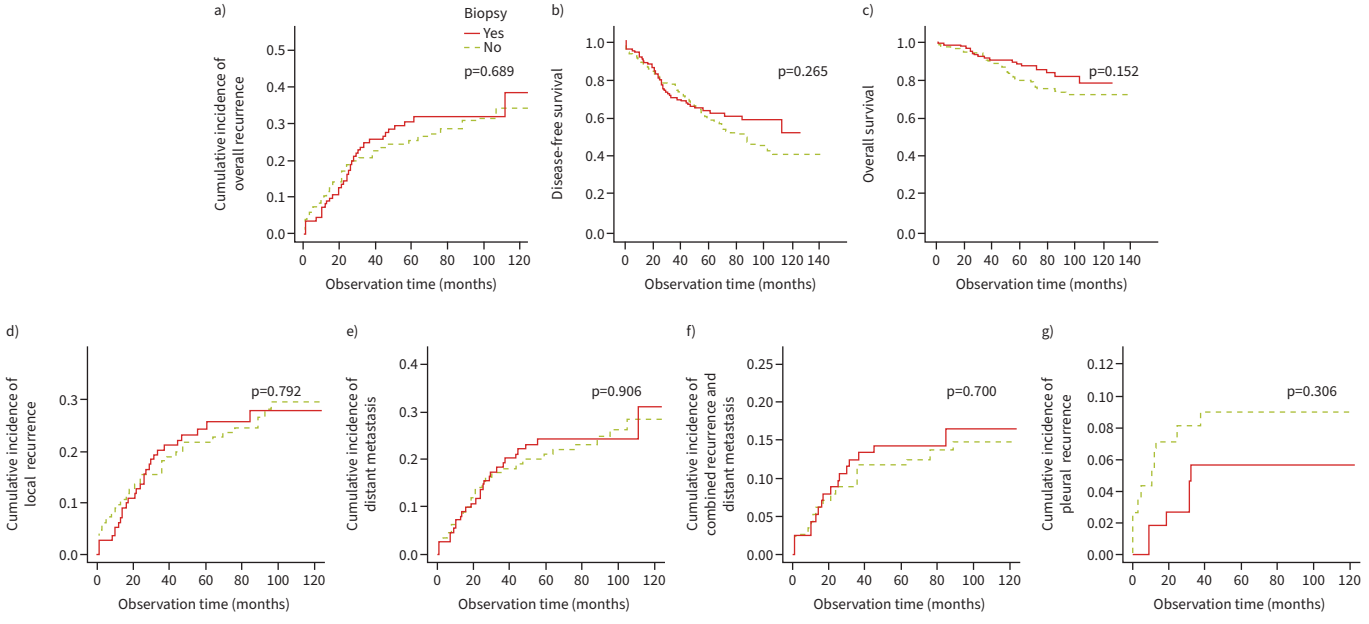


FIGURE 4 The effect of pre-operative biopsy on a) total recurrence, b) disease-free survival, c) overall survival, d) local recurrence, e) distant metastasis, f) combined recurrence and g) pleural recurrence in the propensity-score-matched cohort.

(figure 4e) was not significantly associated with distant metastasis. In multivariable analysis, adjuvant chemotherapy (SHR 1.983, 95% CI 1.134–3.470; p=0.016) was significantly associated with distant metastasis. Pre-operative biopsy was not significantly associated with distant metastasis. (SHR 1.203, 95% CI 0.686–2.110; p=0.520) (supplementary table S4).

Univariable analysis showed that the risk factors for combined recurrence were pleural invasion (p=0.008) and adjuvant chemotherapy (p=0.015). Biopsy (p=0.700) (figure 4f) was not significantly associated with combined recurrence. In multivariable analysis, pleural invasion (SHR 2.275, 95% CI 1.103–4.690; p=0.026) was significantly associated with combined recurrence. Pre-operative biopsy was not significantly associated with combined recurrence (SHR 1.303, 95% CI 0.652–2.600; p=0.450) (supplementary table S5).

Univariable analysis showed that the risk factors for pleural recurrence were the extent of resection (p=0.001). Pre-operative biopsy was not significantly associated with pleural recurrence (p=0.306) (figure 4g). In multivariable analysis, the extent of resection (SHR 0.193, 95% CI 0.076–0.485; p<0.001) was associated with pleural recurrence. Pre-operative biopsy was not significantly associated with pleural recurrence (SHR 0.633, 95% CI 0.234–1.709; p=0.370) (supplementary table S6).

Cox univariable analysis revealed that gender (p=0.021), smoking history (p=0.034), acinar predominant subtype (p=0.014) and vascular invasion (p=0.001) were significantly associated with DFS. Pre-operative biopsy (p=0.268) (figure 4b) and other indicators were unrelated to DFS. Cox multivariable analysis revealed that the acinar predominant subtype (HR 0.637, 95% CI 0.418–0.970; p=0.036) and vascular invasion (HR 2.018, 95% CI 1.284–3.170; p=0.002) were independent risk factors for DFS. Pre-operative biopsy was not significantly associated with DFS (SHR 0.853, 95% CI 0.572–1.273; p=0.438) (supplementary table S7).

Cox univariable analysis revealed that acinar predominant subtype (p=0.027), solid predominant subtype (p<0.001), vascular invasion (p<0.001) and pleural invasion (p=0.020) were significantly associated with overall survival. Pre-operative biopsy (p=0.156) (figure 4c) and other indicators were unrelated to overall survival. Cox multivariable analysis revealed that solid predominant subtype (HR 3.078, 95% CI 1.285–7.371; p=0.012) and vascular invasion (HR 2.502, 95% CI 1.346–4.652; p=0.004) were independent risk factors for overall survival. Pre-operative biopsy was not significantly associated with overall survival (SHR 0.647, 95% CI 0.352–1.189; p=0.161) (supplementary table S8).

Discussion

Meta-analysis showed that in the overall observation cohort, the total recurrence rate of the biopsy group was higher than that of the nonbiopsy group. However, after propensity score matching, we found that there was no significant correlation between biopsy and total recurrence. Furthermore, this cohort study in our centre verified that pre-operative biopsies, including PTNB and bronchoscopic biopsy, did not increase post-operative recurrence and metastasis rates in stage I lung adenocarcinoma patients before or after adjusting for clinicopathological features using PSM. Therefore, pre-operative diagnosis could be safely used for differential diagnosis when it was difficult to determine whether a nodule was malignant before surgery. In addition, patients who required adjuvant chemotherapy were at higher risk of recurrence and metastasis than those who did not.

Although pre-operative biopsy is very important for the diagnosis of cancer [29], whether it adversely affects the prognosis, recurrence and metastasis of lung cancer remains controversial. What is more, there are few studies on the impact of biopsy on the recurrence and metastasis of the early-stage lung adenocarcinoma after surgical resection. This study suggested that pre-operative biopsy did not affect the recurrence and metastasis rate of patients, and these procedures could be safely used for the diagnosis of stage I lung adenocarcinoma. This result was consistent with the previous studies [22]. The effect of PTNB on pleural metastases has been evaluated in several studies, but the conclusion is still controversial. Other individual retrospective studies have shown that PTNB was not associated with pleural recurrence [24, 28], and PTNB techniques [6] were not significantly associated with the risk of pleural recurrence and survival [30]. However, some studies have come to the opposite conclusion [4, 21, 31].

Other studies have evaluated the influence of bronchoscopy on recurrence and prognosis. Some studies have pointed out that pre-operative bronchoscopy diagnosis does not increase the risk of recurrence of stage IA nonsmall cell lung cancer (NSCLC) [7]. However, other studies have shown that pre-operative fibreoptic bronchoscopy with fluorescence imaging is a prognostic factor in NSCLC patients undergoing surgery [8]. Tumours diagnosed by bronchoscopy might have a worse prognosis [32].

The differences between this study and previous studies [8, 19–28] are that this study was an exhaustive real-world study to explore the impact of pre-operative biopsy, including ultrasound- or CT-guided lung biopsy, bronchial mucosa biopsy and transbronchial lung biopsy, on the overall recurrence, local recurrence, distant metastasis, combined recurrence, pleural recurrence, DFS and overall survival of patients with stage I lung adenocarcinoma after surgical resection.

So far, some researchers have considered the following possible reasons for recurrence of pre-operative biopsy. First, needle tract implantation rates for osteosarcoma biopsies have been reported to be as high as 20% [33]. PTNB might also cause lung cancer tumour cells to metastasize along the needle track. Thus, the biopsy tract and pleural cavity were implanted [34]. Second, bronchoscopy biopsy might cause spread through air spaces (STAS) or cause bronchial structural damage, leading to poor post-operative outcomes [35, 36]. Third, the tumour was rich in blood supply, and the mRNA levels of tumour markers increased after biopsy [37, 38]. Therefore, during the puncture process, tumour cells might enter the blood circulation and colonise other organs with the blood flow [39].

We found that the overall recurrence and metastasis rate of patients receiving only PTNB was higher than those receiving both TBB and PTNB and those receiving only TBB. This was a very interesting result. Combined with the results of PTNB and TBB puncture samples, we speculated that the reason for the higher recurrence and metastasis rate of patients receiving only PTNB might be related to its higher tumour detection rate. This result showed that during the puncture process, if the puncture needle punctured the tumour tissue and took out the pathological specimen, the possibility of tumour metastasis along the needle path or haematogenous metastasis would increase. In addition, patients receiving PTNB and TBB might have a special tumour location, which required two puncture methods to diagnose. Therefore, tumour location might also be an influencing factor. However, the number of patients in PTNB group was small, and the persuasiveness of analysis was limited. The above results could be verified by prospective studies of large samples in the future.

However, this theory has been refuted by some studies. First, prior studies have reported that the incidence of needle tract metastasis was 0.016–0.018% [40, 41]. No clear needle tract metastases were found in this study cohort. Therefore, a small number of needle tract metastases might not affect overall recurrence and metastasis. Secondly, prior studies have shown that STAS is a unique feature of tumour invasion, which is not affected by the biopsy procedures [42]. Pre-operative biopsy in patients with stage I NSCLC was not associated with an increased risk of STAS, nor did it affect STAS-related outcomes [43]. Third, in most cases, tumour cells that enter the blood circulation will undergo anoikis [44] or be recognised and eliminated by the body's immune system [45, 46]. And even with a few cells surviving in the bloodstream, successful metastatic colonisation was difficult to achieve [47].

Interestingly, compared with patients who did not require post-operative adjuvant chemotherapy, patients requiring adjuvant chemotherapy were more likely to develop recurrence and metastasis. We speculate that it might be due to the following reasons. NCCN guidelines recommend that when patients with stage I NSCLC have certain characteristics, such as poorly differentiated tumours (including lung neuroendocrine tumours but excluding well-differentiated neuroendocrine tumours), vascular invasion, wedge resection, tumours >4 cm, visceral pleural involvement and unknown lymph node status (NX), clinical experts should consider that they have high risk and need to receive adjuvant chemotherapy [1]. However, each individual risk factor might not be enough to affect recurrence and metastasis. The need for adjuvant chemotherapy could be considered as the sum of the overall risk factors and was significantly associated with the risk of recurrence and metastasis.

This study showed that tumour stage, vascular invasion and pleural invasion were not associated with the recurrence and metastasis risk. This was consistent with previous studies [48]. However, some studies have suggested that visceral pleural invasion, lymphatic invasion and vascular invasion are independent factors for recurrence-free survival in stage I NSCLC [49, 50]. These different findings might be due to differences in study design and patient baseline characteristics.

This study had some limitations. First, this was a single-centre retrospective study; patient selection bias was difficult to avoid. Second, there might be differences in the clinical and pathological characteristics of patients in the pre-operative biopsy group and the nonbiopsy group. Although we attempted to overcome selection bias by using PSM for covariance adjustment, not all independent variables were balanced across groups. Moreover, the reduced sample size of the cohort after PSM also reduces the validity of the interpretation of the results to a certain extent. In addition, the recurrence and metastasis in this study were

not all confirmed by histopathology, which might lead to overestimation of the incidence of recurrence and metastasis. Finally, this study only included patients with lung adenocarcinoma, not NSCLC patients.

Conclusions

Whether pre-operative biopsy including PTNB and bronchoscopic biopsy affects the recurrence and metastasis of lung cancer patients remains controversial. We found that pre-operative biopsy was not associated with an increased risk of post-operative recurrence and metastasis in stage I lung adenocarcinoma patients, either in the overall observation cohort or in the PSM cohort adjusting tumour and patient characteristics, which was consistent with other studies. Therefore, these diagnostic procedures can be safely used in patients with pulmonary nodules. However, relatively speaking, PTNB has a higher risk of recurrence and metastasis than TBB patients, because of its high tumour detection rate.

Provenance: Submitted article, peer reviewed.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

This study was approved by the ethics committee of Beijing Chao-Yang Hospital of Capital Medical University (numbers 2009-4 and 2016-79). All procedures were performed in accordance with the Helsinki Declaration. Informed consent was obtained from all individual participants included in the study.

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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