Original research

Pleural recurrence after transthoracic needle lung biopsy in stage I lung cancer: a systematic review and individual patient-level meta-analysis

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ABSTRACT

Introduction Conflicting results exist regarding whether preoperative transthoracic biopsy increases the risk of pleural recurrence in early lung cancer. We conducted a systematic, patient-level meta-analysis to evaluate the risk of pleural recurrence in stage I lung cancer after percutaneous transthoracic lung biopsy.

Methods A systematic search of OVID-MEDLINE, Embase and the Cochrane Database of Systematic Reviews was performed through October 2018. Eligible studies were original articles on the risk of pleural recurrence in stage I lung cancer after transthoracic biopsy. We contacted the corresponding authors of eligible studies to obtain individual patient-level data. We used the Fine-Gray model for time to recurrence and lung cancer-specific survival and a Cox proportional hazards model for overall survival.

Results We analysed 2394 individual patient data from 6 out of 10 eligible studies. Compared with other diagnostic procedures, transthoracic biopsy was associated with a higher risk for ipsilateral pleural recurrence, which manifested solely (subdistribution HR (sHR), 2.58; 95% CI 1.15 to 5.78) and concomitantly with other metastases (sHR 1.99; 95% CI 1.14 to 3.48). In the analysis of secondary outcomes considering a significant interaction between diagnostic procedures and age groups, reductions of time to recurrence (sHR, 2.01; 95% CI 1.11 to 3.64), lung cancer-specific survival (sHR 2.53; 95% CI 1.06 to 6.05) and overall survival (HR 2.08; 95% CI 1.12 to 3.87) were observed in patients younger than 55 years, whereas such associations were not observed in other age groups.

Discussion Preoperative transthoracic lung biopsy was associated with increased pleural recurrence in stage I lung cancer and reduced survival in patients younger than 55 years.

Key messages

What is the key question?

► Does preoperative transthoracic needle lung biopsy increase pleural recurrence in stage I lung cancer?

What is the bottom line?

► The preoperative transthoracic biopsy was associated with a higher risk for pleural recurrence manifested solely (subdistribution HR (sHR), 2.58; 95% CI 1.15 to 5.78) and concomitantly with other metastases (sHR 1.99; 95% CI 1.14 to 3.48) than other diagnostic procedures when considering death as a competing event for recurrence.

Why read on?

► This study reveals the association between preoperative transthoracic biopsy and increased pleural recurrence in stage I lung cancer, highlighting a cautious application of transthoracic biopsy for the diagnosis of early lung cancer for which curative treatment is anticipated.

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide.[1] Surgical resection is a primary curative treatment for lung cancer, but it was previously inapplicable to a considerable proportion of lung cancers, which were found at an advanced stage.[2] Low-dose CT screening for lung cancer has successfully enabled the early detection of lung cancer at stage I,[3 4] thereby contributing to reduced mortality.[5] Screening-detected early-stage lung cancer is predominantly located in peripheral regions of the lung owing to the capability of screening CT to detect small peripheral lesions[6] and a shift in the location of smoking-related lung cancer to the lung periphery.[7]

Percutaneous transthoracic needle lung biopsy is a commonly used diagnostic procedure for pulmonary lesions suspected to be lung cancer, particularly those with a peripheral location.[8] Percutaneous biopsy was the second most commonly used diagnostic procedure in a lung cancer screening programme.[9] Furthermore, percutaneous biopsy provided accurate diagnoses for lung cancer, with a pooled sensitivity and specificity of 90% and 97%, respectively.[8] Nevertheless, percutaneous biopsy can be accompanied by complications up to 38.8%,[10] and pneumothorax is the most common complication.[11] Tumour implantation along the needle track is a potential long-term complication of percutaneous biopsy. As of 2018, 4 studies with 1323

patients reported that transpleural biopsy increased the risk of pleural recurrence in stage I lung cancer,[12–15] whereas opposite results were reported in 6 other studies with 1726 patients.[16–21] These discrepancies may have resulted from the limited number of cases with pleural recurrence in single-institutional studies, as well as differences in study populations and statistical analyses.

We conducted a systematic, patient-level meta-analysis to evaluate the risk of pleural recurrence in stage I lung cancer after percutaneous transthoracic needle lung biopsy.

METHODS

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data statement.[22] The study protocol was registered in the PROSPERO database (registration number: CRD42018110279) on 8 October 2018, when the preliminary searches and piloting of the study selection process with eligibility criteria started, but before formal screening and data collection began.

Search strategy and eligibility criteria

We searched OVID-MEDLINE, Embase and the Cochrane Database of Systematic Reviews to identify relevant publications. The search terms consisted of keywords related to 'lung cancer', 'biopsy' and 'pleural recurrence'. The search was current as of 24 October 2018, without any language limit. The search was further supplemented by screening the bibliographies of the retrieved studies.

We applied the following criteria to determine eligibility: (1) studies or subsets thereof investigating the risk of pleural recurrence in pathologically proven stage I lung cancer after preoperative percutaneous transthoracic biopsy in comparison with other diagnostic procedures, (2) a study population comprising 30 adult patients or more and (3) studies reporting time-to-event data regarding plural recurrence or death according to either transthoracic biopsy or other diagnostic procedures. Transpleural intraoperative needle lung biopsy was regarded as percutaneous transthoracic lung biopsy. The other diagnostic procedures included sputum cytology, bronchoscopy, wedge resection of the lung or curative surgical resection without a definitive diagnosis. We excluded review articles, abstracts, editorials, letters, case reports and guidelines.

Definition of outcomes

The primary outcomes were time to isolated ipsilateral pleural recurrence and time to concomitant ipsilateral pleural recurrence during postoperative follow-up according to whether transthoracic biopsy or another diagnostic procedure was performed. Ipsilateral pleural recurrence was considered to have occurred when any of the three following findings newly manifested in the ipsilateral hemithorax: malignant pleural effusion proven by pleural cytology; pleural seeding proven by pleural biopsy; or increasing number and size of pleural nodules and masses on chest CT scans or hypermetabolism on ^{18}F-deoxyglucose positron emission tomography. As pleural recurrence can occur alone or simultaneously with recurrence at another site (eg, contralateral pleural recurrence or lymph node or distant metastasis), a distinction was made between isolated pleural recurrence and concomitant pleural recurrence and they were analysed separately. Secondary outcomes included time to recurrence, lung cancer-specific survival and overall survival during postoperative follow-up. Lung cancer-specific survival was defined as the time from the date of surgery to the last follow-up or cancer-related death. Death after recurrence was regarded as cancer-related death.

Data acquisition

The corresponding authors of all eligible studies were contacted and asked to participate in anonymized patient-level data sharing of the final data in their publications. The data from the participating authors were obtained after receiving an institutional review board approval using a standardised Excel file: age, sex, preoperative diagnostic procedures, surgical operation, pathological findings (lobar location; size; microscopic pleural, vascular or lymphatic invasion of lung cancer; 'tumor, node, metastasis' (TNM) descriptors; stage), CT findings (lesion consistency, pleural contact of lung cancer), recurrence status, time to recurrence, recurrence type, survival status and time to death during follow-up. The T descriptor was reassessed according to the eighth TNM staging system for lung cancer.[23] The internal consistency of data was assessed with respect to descriptive statistics in the publications, where possible. Also, logical errors among covariates such as pathological findings and outcomes were examined. For example, the value on tumour stage was compared with its pathological T descriptor and the length of time to recurrence was compared with time to death. Any discrepancies were resolved by asking clarification from the corresponding authors. There were some cases where studies had not obtained information on overall survival originally, and the researchers additionally collected the relevant information in a retrospective way from the electronic medical records for the current study.

Risk of bias assessment

Two authors independently assessed the risk of bias for the included studies using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool.[24] The ROBINS-I tool evaluates the following seven domains: confounding, population selection, classification of intervention, deviation from the intended intervention, missing data, outcome measurement and selective reporting. Discrepancies were resolved through consensus.

Statistical analysis

Baseline demographic and clinical characteristics of patients undergone the two diagnostic procedures, preoperative transthoracic needle lung biopsy and others, were summarised and compared using t-test or Wilcoxon rank sum test for continuous variables and χ^2 test or Fisher's exact test for categorical variables.

One-stage approach for individual participant data meta-analysis was used because the number of patients experiencing ipsilateral pleural recurrence was expected to be small and many adjustment factors were considered in the planning stage.[25]

For the analysis of lung cancer-specific survival and time to recurrence, the Fine-Gray model, which extends the Cox proportional hazards model to competing-risks data by considering the hazard of cumulative incidence, was employed[26] and death before the onset of recurrence was considered as a competing event. Overall survival was analysed using a Cox proportional hazards model. All analyses were stratified by study to allow for differences in the baseline hazards among the included studies. Heterogeneity in treatment effects across studies was explored using visual assessment of cumulative incidence plots. Variables significant at 0.1 in the univariable analysis were considered as candidate covariates for the multivariable analysis. Age and pathological tumour size were kept in the final model regardless of their statistical significance, and pathological tumour stage and T descriptor were not included in the multivariable analysis

Table 1 Baseline characteristics, follow-up period, and outcomes according to diagnostic procedures

	All	Transthoracic needle biopsy	Other diagnostic procedures	
	(N=2329)	(N=1158)	(N=1236)	P value
Age (years), mean±SD	63.6±9.9	62.8±9.9	64.4±9.9	<0.0001
Male, n (%)	1403 (58.6)	654 (56.5)	749 (60.6)	0.0407
Lobar location, n (%)*				
Right upper lobe	772 (32.2)	403 (34.8)	369 (29.9)	0.0048
Right middle lobe	145 (6.1)	63 (5.4)	82 (6.6)	
Right lower lobe	497 (20.8)	239 (20.6)	258 (20.9)	
Left upper lobe	562 (23.5)	248 (21.4)	314 (25.4)	
Left lower lobe	363 (15.2)	187 (16.1)	176 (14.2)	
Lesion composition on CT, n (%)*				
Solid	1242 (51.9)	714 (61.7)	528 (42.7)	<0.0001
Subsolid	595 (24.9)	303 (26.2)	292 (23.6)	
Pleural contact on CT, n (%)*	895 (37.4)	483 (41.7)	412 (33.3)	<0.0001
Type of surgery, n (%)				
Sublobar resection	198 (8.3)	55 (4.7)	143 (11.6)	<0.0001
Lobectomy or pneumonectomy	2196 (91.7)	1103 (95.3)	1093 (88.4)	
Histological subtype, n (%)				
Adenocarcinoma	1808 (75.5)	917 (79.2)	891 (72.0)	<0.0001
Squamous cell carcinoma	456 (19.0)	177 (15.3)	279 (22.6)	
Other subtypes	130 (5.4)	64 (5.5)	66 (5.3)	
Pathological T descriptor, n (%)				
T1a	184 (7.7)	52 (4.5)	132 (10.7)	<0.0001
T1b	750 (31.3)	345 (29.8)	405 (32.8)	
T1c	589 (24.6)	304 (26.3)	285 (23.1)	
T2a	717 (29.9)	382 (33.0)	335 (27.1)	
T2b	154 (6.4)	75 (6.5)	79 (6.4)	
Pathological tumour stage, n (%)				
1A	1523 (63.6)	701 (60.5)	822 (66.5)	0.0024
1B	871 (36.4)	457 (39.5)	414 (33.5)	
Pathological tumour size, n (%)				
≤1 cm	196 (8.2)	55 (4.7)	141 (11.4)	<0.0001
1< to ≤2 cm	890 (37.2)	421 (36.4)	469 (37.9)	
2< to ≤3 cm	760 (31.7)	416 (35.9)	344 (27.8)	
3< to ≤4 cm	394 (16.5)	191 (16.5)	203 (16.4)	
4< to ≤5 cm	154 (6.4)	75 (6.5)	79 (6.4)	
Microscopic pleural invasion, n (%)	484 (20.2)	300 (25.9)	184 (14.9)	<0.0001
Microscopic vascular invasion, n (%)*	166 (6.9)	47 (4.1)	119 (9.6)	<0.0001
Microscopic lymphatic invasion, n (%)*	294 (12.3)	161 (13.9)	133 (10.8)	<0.0001
Follow-up for recurrence (months) median (min, max)	62.6 (0.3, 300.9)	59.5 (0.4, 239.6)	62.6 (0.3, 300.9)	<0.0001
Follow-up for overall survival (months) median (min, max)	84.5 (0.6, 300.9)	87.6 (2.3, 239.6)	80.8 (0.6, 300.9)	0.0087
Ipsilateral isolated pleural recurrence, n (%)	57 (2.4)	45 (3.9)	12 (1.0)	<0.0001
Ipsilateral concomitant pleural recurrence, n (%)	102 (4.3)	73 (6.3)	29 (2.3)	<0.0001
All recurrence, n (%)	448 (18.7)	247 (21.3)	201 (16.3)	0.0015
Lung cancer-specific death, n (%)	257 (10.7)	140 (12.1)	117 (9.5)	0.0382
Death, n (%)	574 (24.0)	279 (24.1)	295 (23.9)	0.8970

*Following information was missing in data: lobar location, 2.3% (all), 1.6% (transthoracic biopsy), 3.0% (other procedures); lesion composition on CT, 23.3% (all), 12.2% (transthoracic biopsy), 33.6% (other procedures); pleural contact on CT, 14.8% (all), 11.3% (transthoracic biopsy), 18.0% (other procedures); microscopic vascular invasion, 14.7% (all), 9.4% (transthoracic biopsy), 19.6% (other procedures) and microscopic lymphatic invasion, 15.5% (all), 9.8% (transthoracic biopsy), 20.9% (other procedures).

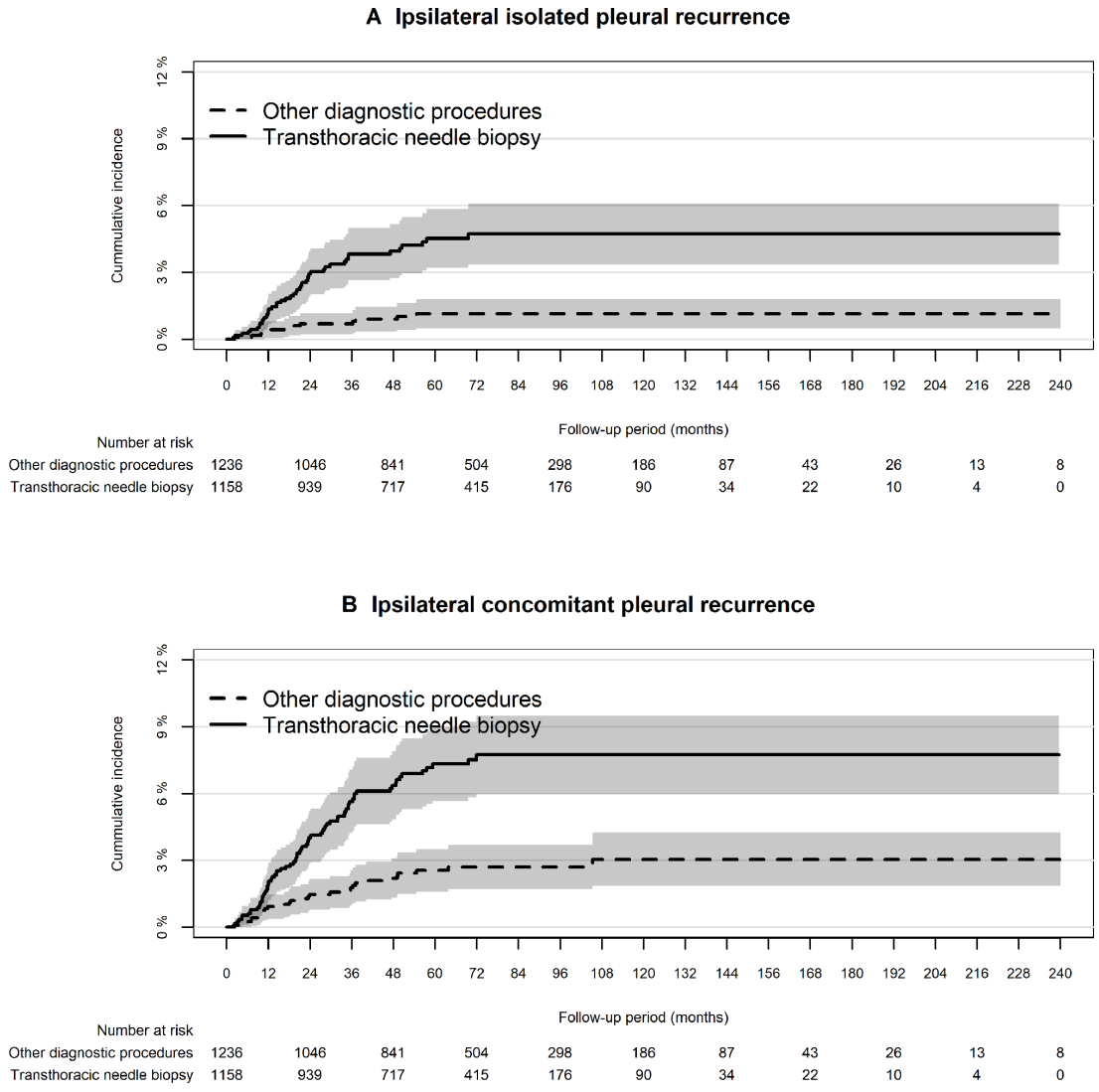

Figure 1 Cumulative incidence plots for (A) ipsilateral isolated and (B) concomitant pleural recurrence according to transthoracic needle biopsy.

due to strong collinearity with tumour size. Also, lesion composition and pleural contact in the CT findings were not included in the multivariable analysis due to missing information in some studies. We explored whether the effect of the diagnostic procedure differed according to patients' characteristics by examining a cumulative incidence plot or Kaplan-Meier plot for each level of the covariates and the significance of interaction terms between the diagnostic procedure and covariates. Statistically as well as clinically significant interactions were included in the final model. The assumption of proportionality was checked by the use of time-varying covariate effects and Schoenfeld residual plots.

Subgroup analyses were performed by histological subtype, pathological stage, the country of the included studies, lesion composition on CT and subpleural cancers that contacted the pleura on CT. Sensitivity analyses were conducted to evaluate the robustness of our findings as follows: (1) adjustments for different covariates, (2) analyses using multiply imputed data and (3) analyses using propensity score-matched data. Details of the missing data imputation and propensity score matching can be found in online supplemental material.

All statistical analyses were performed using SAS V.9.4 (SAS Institute) and R V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Data acquisition

Of the 1432 references identified, 10 studies with 3049 participants with stage I lung cancer were considered eligible (online supplemental eFigure 1). We obtained data from 6 studies and 2456 participants, corresponding to the majority of eligible studies (60.0%) and participants (80.5%) published through October 2018. The eligible studies for which data could not be obtained were similar to those for which data were obtained (online supplemental eTable 1). Additionally, an updated search in January 2020 indicated that at least two studies reporting inconsistent results (a study with 509 patients[27] reporting an elevated risk and a study with 284 subset patients[28] reporting no risk) had been published after data collection and were potentially eligible (online supplemental eTable 1). Even when considering these additional studies, the present meta-analysis covers half of the eligible studies (50.0%) and two-thirds of the eligible participants (63.9%; 2456 of 3842). We excluded 62 patients with lung cancer higher than stage I in the eighth TNM staging system, resulting in a final study population of 2394 patients.

Study description and risk of bias

The study populations ranged from 130 to 822 patients (online supplemental eTable 1). The included studies were retrospective

Table 2 Univariable and multivariable analysis for time to ipsilateral recurrence

	Time to isolated ipsilateral recurrence				Time to concomitant ipsilateral recurrence			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	sHR (95% CI)	P value	sHR (95% CI)	P value	sHR (95% CI)	P value	sHR (95% CI)	P value
Diagnostic procedures (Ref: other)								
Transthoracic needle biopsy	3.58 (1.79 to 7.14)	0.0003	2.58 (1.15 to 5.78)	0.0215	2.50 (1.60 to 3.90)	<0.0001	1.99 (1.14 to 3.48)	0.0156
Age (Ref: <55)								
55≤ to <75	0.75 (0.40 to 1.38)	0.3496	0.72 (0.38 to 1.38)	0.3258	0.81 (0.51 to 1.31)	0.3940	0.75 (0.45 to 1.25)	0.2679
75≤	1.58 (0.68 to 3.65)	0.2856	1.76 (0.73 to 4.20)	0.2057	1.71 (0.92 to 3.21)	0.0925	1.61 (0.82 to 3.20)	0.1688
Sex (Ref: female)								
Male	1.05 (0.62 to 1.78)	0.8471			1.14 (0.77 to 1.70)	0.5072		
Lobar location (Ref: left lower lobe)*								
Left upper lobe	0.78 (0.34 to 1.79)	0.5625			0.98 (0.50 to 1.90)	0.9409		
Right lower lobe	0.75 (0.33 to 1.74)	0.5084			1.08 (0.56 to 2.08)	0.8174		
Right middle lobe	1.45 (0.53 to 3.92)	0.4678			1.54 (0.68 to 3.54)	0.3038		
Right upper lobe	0.68 (0.31 to 1.51)	0.3438			0.99 (0.53 to 1.85)	0.9787		
Lesion composition on CT (Ref: subsolid)*								
Solid	1.91 (0.98 to 3.73)	0.0581			2.60 (1.49 to 4.52)	0.0007		
Pleural contact on CT (Ref: no)*								
Yes	2.61 (1.49 to 4.58)	0.0009			2.07 (1.37 to 3.14)	0.0006		
Type of surgery (Ref: sublobar resection)								
Lobectomy or pneumonectomy	1.38 (0.41 to 4.66)	0.6040			1.92 (0.69 to 5.36)	0.2105		
Histological subtype (Ref: adenocarcinoma)								
Squamous cell carcinoma	0.55 (0.25 to 1.21)	0.1356			0.60 (0.33 to 1.09)	0.0954		
Others	0.69 (0.17 to 2.80)	0.5999			0.98 (0.39 to 2.43)	0.9601		
Pathological T descriptor†								
T1b	–				3.66 (0.48 to 28.16)	0.1236		
T1c	1.94 (0.83 to 4.52)	0.1264			7.08 (0.93 to 53.82)	0.0586		
T2a	4.47 (2.21 to 8.24)	<0.0001			17.64 (2.41 to 129.01)	0.0047		
T2b	1.25 (0.28 to 5.68)	0.7702			9.81 (1.19 to 80.94)	0.0034		
Pathological stage (Ref: 1A)								
1B	2.87 (1.69 to 4.88)	<0.0001			3.53 (2.35 to 5.32)	<0.0001		
Pathologic tumour size (Ref: ≤1 cm)								
1< to ≤2 cm	5.22 (0.69 to 39.38)	0.1089	2.68 (0.33 to 21.39)	0.3534	3.55 (0.84 to 15.07)	0.0864	2.08 (0.49 to 8.95)	0.3236
2< to ≤3 cm	6.09 (0.80 to 46.42)	0.0813	2.28 (0.27 to 19.41)	0.4493	4.93 (1.16 to 21.07)	0.0312	2.06 (0.46 to 9.17)	0.3414
3< to ≤4 cm	7.51 (0.95 to 59.53)	0.0563	2.09 (0.23 to 19.29)	0.5163	9.53 (2.22 to 41.01)	0.0025	3.05 (0.66 to 14.05)	0.1533
4< to ≤5 cm	2.87 (0.26 to 31.98)	0.3914	1.11 (0.09 to 13.37)	0.9351	5.27 (1.07 to 25.83)	0.0407	1.63 (0.30 to 9.00)	0.5749
Microscopic pleural invasion (Ref: no)								
Yes	3.94 (2.30 to 6.74)	<0.0001	3.45 (1.77 to 6.70)	0.0003	4.26 (2.86 to 6.36)	<0.0001	3.48 (2.15 to 5.64)	<0.0001
Microscopic vascular invasion (Ref: no)*								
Yes	2.14 (0.79 to 5.82)	0.1343			1.28 (0.52 to 3.15)	0.5845		
Microscopic lymphatic invasion (Ref: no)*								
Yes	3.02 (1.63 to 5.60)	0.0004	2.29 (1.20 to 4.34)	0.0116	3.22 (2.04 to 5.09)	<0.0001	2.27 (1.42 to 3.65)	0.0007

*Fifty-five subjects (2.3%), 557 subjects (23.3%) and 354 subjects (14.8%) were missing for the information on a lobar location, lesion composition on CT, and pleural contact on CT respectively. Three hundred and fifty-two subjects (14.7%) were missing for a presence of microscopic vascular invasion and 371 subjects (15.5%) were missing for a presence of microscopic lymphatic invasion.
†For time to isolated ipsilateral recurrence, categories T1a and T1b were considered as a reference category since no event was observed in T1a. For time to concomitant ipsilateral recurrence, T1a was considered as a reference category.
sHR, subdistribution HR.

cohort studies in Japan (four studies) and Korea (two studies). All independent variables significantly differed according to the diagnostic procedure, but the differences were within 10% (table 1) except for visceral pleural invasion (transthoracic biopsy, 25.9%; other diagnostic methods, 14.9%). During the median follow-up of 60.7 months, isolated and concomitant

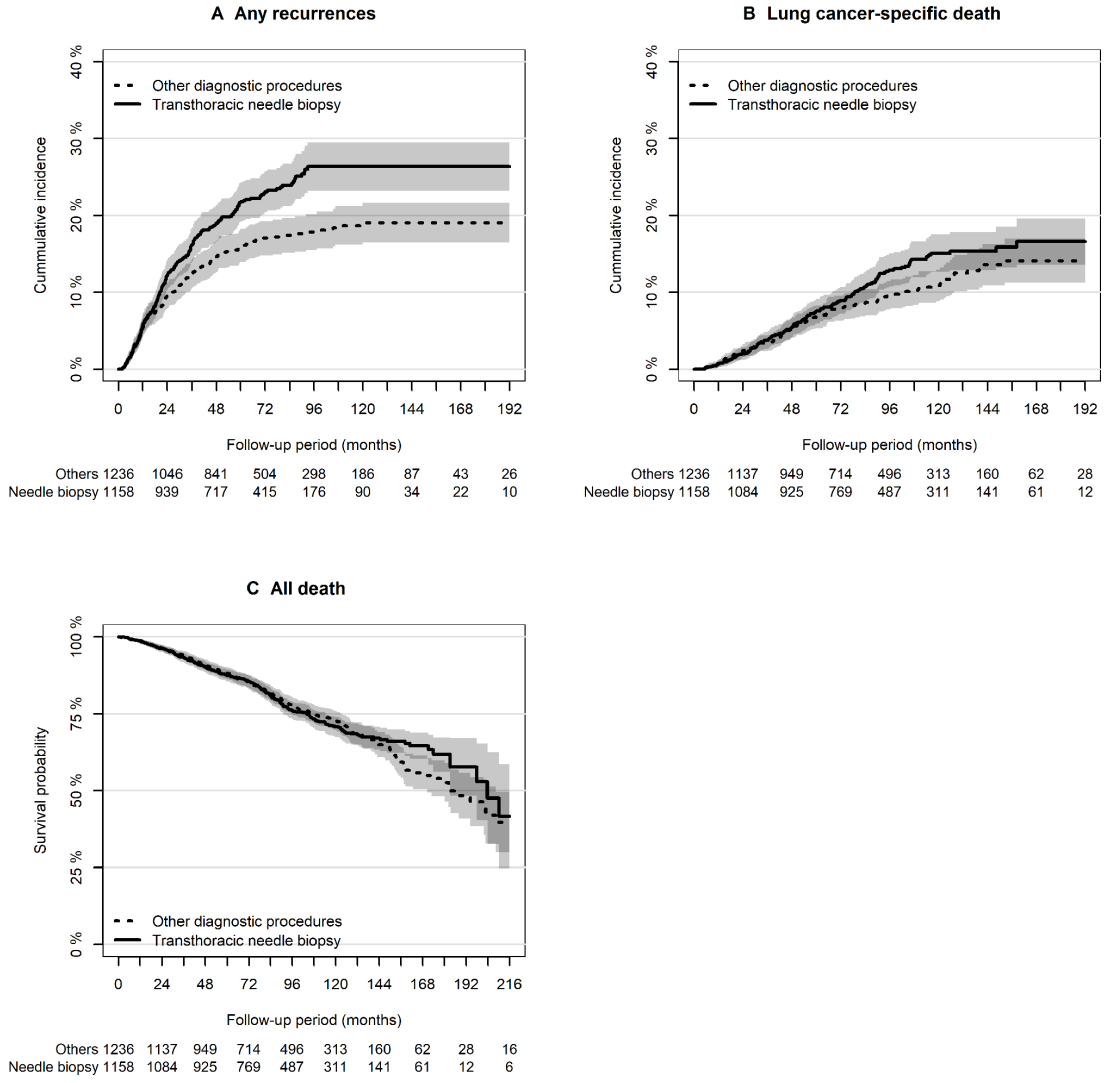

Figure 2 Cumulative incidence plots for (A) any recurrence and (B) lung cancer-specific death and Kaplan-Meier curve for (C) overall survival according to transthoracic needle biopsy.

pleural recurrence occurred in 2.4% and 4.3% of patients, respectively, and recurrence of any type occurred in 18.7% of patients. During the median follow-up of 84.5 months, lung cancer-specific and overall deaths occurred in 10.7% and 24.0% of patients, respectively. No critical issues were identified in checking the internal consistency of patient-level data.

When assessed by the ROBINS-I tool, the included studies had a moderate risk of bias due to confounding, as transthoracic biopsy was preferentially applied to peripheral lung cancer if bronchoscopic biopsy had failed or was difficult to perform. The studies had a low risk of bias in the other six domains (online supplemental eTable 2).

Primary outcomes

The incidence of ipsilateral pleural recurrence in the transthoracic biopsy group was higher than those in other diagnostic procedures group for both isolated and concomitant recurrence (figure 1). The cumulative incidences of ipsilateral pleural recurrences varied across studies, however, the incidence in the transthoracic biopsy group was consistently higher than the other group in most of the studies, where enough number of events occurred (online supplemental eFigures 2 and 3). Compared with other diagnostic procedures, transthoracic biopsy increased the risk of ipsilateral pleural recurrence, which manifested solely (subdistribution HR (sHR), 2.58; 95% CI 1.15 to 5.78; p=0.0215) and concomitantly with other metastases (sHR 1.99; 95% CI 1.14 to 3.48; p=0.0156) after adjusting for important prognostic factors (table 2). There were no statistically significant interactions between diagnostic procedures and other prognostic factors in the analysis of the primary outcomes.

While no significant subgroup difference was observed, most subgroup analyses showed a consistent tendency of higher risk in transthoracic biopsy compared with other diagnostic procedures (online supplemental eFigure 4). Transthoracic biopsy significantly increased the risk of isolated and concomitant pleural recurrence in stage IA lung cancer (sHRs 5.56; 95% CI 1.37 to 22.57 and 2.76; 95% CI 1.14 to 6.67, respectively) and adenocarcinoma (sHRs 2.41; 95% CI 1.04 to 5.57 and 1.96; 95% CI 1.06 to 3.64, respectively), in both Japanese (sHRs 5.63; 95% CI 1.77 to 17.87 and 2.22; 95% CI 1.04 to 4.76, respectively) and Korean cohorts (sHRs 2.29; 95% CI 0.97 to 5.41 and 2.20; 95% CI 1.12 to 4.33, respectively), and in subpleural cancers (sHRs 3.63; 95% CI 1.10 to 12.00 and 2.73; 95% CI 1.02 to 7.33, respectively). The results of sensitivity analyses were qualitatively similar to the primary analysis (online supplemental eFigure 4).

Table 3 Risk of transthoracic needle biopsy relative to other diagnostic procedures in secondary outcomes

	Age (years)	No of patients	Follow-up periods (months) median (range)	HR* (95% CI)	P value
Time to recurrence†	Any ages	2394	84.5 (0.6 to 300.9)	1.18 (0.95 to 1.47)	0.1332
	<55	439	95.2 (6.1 to 259.6)	2.01 (1.11 to 3.64)	0.0205
	55≤ to <75	1656	85.3 (0.7 to 300.9)	1.13 (0.88 to 1.45)	0.3463
	75≤	299	59.5 (0.6 to 194.3)	0.85 (0.51 to 1.43)	0.5514
Lung cancer-specific survival†	Any ages	2394	60.7 (0.3 to 300.9)	1.32 (0.97 to 1.78)	0.0753
	<55	439	67.6 (1.5 to 259.6)	2.53 (1.06 to 6.05)	0.0366
	55≤ to <75	1656	62.2 (0.3 to 300.9)	1.20 (0.85 to 1.70)	0.2985
	75≤	299	47.9 (0.6 to 194.3)	1.14 (0.56 to 2.31)	0.7158
Overall survival*‡	Any ages	2394	60.7 (0.3 to 300.9)	1.10 (0.90 to 1.34)	0.3623
	<55	439	67.6 (1.5 to 259.6)	2.08 (1.12 to 3.87)	0.0199
	55≤ to <75	1656	62.2 (0.3 to 300.9)	1.03 (0.82 to 1.28)	0.8207
	75≤	299	47.9 (0.6 to 194.3)	0.99 (0.64 to 1.54)	0.9812

*Subdistribution HR for time to recurrence and lung cancer-specific survival; HR for overall survival.
†Adjusted for age, histological subtype, pathological tumour size, microscopic pleural and lymphatic invasion.
‡Adjusted for age, sex, histological subtype, pathological tumour size, microscopic pleural and lymphatic invasion.

Secondary outcomes

The incidences of any recurrence and lung cancer-specific death in the transthoracic biopsy group were higher than those in other diagnostic procedures group (figure 2). In the multivariable analyses assuming the same effect of transthoracic biopsy across all ages, transthoracic needle biopsy tended to decrease time to recurrence (sHR 1.18; 95%CI 0.95 to 1.45) and lung-cancer specific survival (sHR 1.32; 95%CI 0.97 to 1.78), whereas overall survival did not significantly differ according to whether transthoracic biopsy was performed (HR 1.10; 95%CI 0.90 to 1.34) (table 3). The interaction terms between diagnostic procedure and age groups in the multivariable models were significant at 0.1. Cumulative incidence plots for recurrence, lung cancer-specific death and the Kaplan-Meier plots for overall survival differed across age groups (online supplemental eFigures 5–7). Accordingly, the interaction terms were included in the multivariable analyses, and the effect of transthoracic biopsy was estimated according to age group (<55, 55–74 and ≥75 years). When adjusted, transthoracic biopsy consistently decreased time to recurrence (sHR 2.01; 95%CI 1.11 to 3.64), lung cancer-specific survival (sHR 2.53; 95%CI 1.06 to 6.05) and overall survival (HR 2.08; 95%CI 1.12 to 3.87) in patients younger than 55 years, whereas such associations were not observed in other age groups (table 3).

In regard to disease-free and lung cancer-specific survival, similar tendencies across subgroups were observed in patients younger than 55 and patients between 55 and 74 years. However, in patients aged 75 or older, the effects of transthoracic biopsy were somewhat different by the stage and presence of subpleural cancers. The results of subgroup analysis for overall survival were qualitatively comparable to the primary analysis. The sensitivity analysis for the secondary outcomes showed consistent results (online supplemental eFigures 8–10).

DISCUSSION

This large-scale meta-analysis of participant-level data revealed that, compared with other diagnostic procedures, transthoracic biopsy increased the risk of ipsilateral pleural recurrence, which manifested solely (sHR, 2.58) and concomitantly with other metastases (sHR 1.99). The adverse effect of transthoracic biopsy on pleural recurrence was consistently observed in subgroup analyses, and the effect was observed in subgroups of stage IA lung cancer, adenocarcinoma, subpleural cancers, differing countries. Similar tendencies were observed in sensitivity analyses with propensity score-matching or missing value imputation. Furthermore, transthoracic biopsy independently decreased time to recurrence (sHR, 2.01), lung cancer-specific survival (sHR, 2.53) and overall survival (HR, 2.08) in patients younger than 55 years. The results support the introduction of surgical resection or non-surgical treatment instead of nonsurgical biopsy for pulmonary nodules with a high risk for malignancy (ie, >70%)[29] and the preferential use of bronchoscopic biopsy over transthoracic biopsy for the diagnosis of lung cancer and in the guidelines.[8 29]

Malignant cells in lung cancer can be dislodged into the pleural space or the soft tissue via the needle track after transthoracic biopsy.[30 31] The reported incidence of chest wall implantation after transthoracic biopsy was 0.06%–0.2%,[31 32] although the actual incremental incidence of pleural seeding due to the biopsy is unknown, as the pleural seeding by the biopsy cannot be distinguished from tumour dissemination itself. Besides, pleural penetration during the biopsy may make a route of direct tumour dissemination, particularly when the tumour attaches to a pleural surface. Indeed, patients who underwent transthoracic biopsy before surgery had a higher risk of pleural recurrence after adjusting for visceral pleural and lymphovascular invasion with pathological tumour size, which are the most critical for the pleural recurrence of lung cancer.[33 34]

Transthoracic biopsy non-significantly decreased lung cancer-specific survival (p=0.0753) and did not affect overall survival (p=0.3623) in analyses assuming the same effect of transthoracic biopsy across all ages. These results are in accordance with those in the SEER data.[35] Interestingly, transthoracic biopsy decreased lung cancer-specific (p=0.0366) and overall survival (p=0.0199) in patients younger than 55 years. The exclusive observation of the deleterious effect of transthoracic biopsy in younger patients may have resulted from comorbidities in older patients. Patients with lung cancer frequently have various comorbidities, including chronic pulmonary disease, diabetes and heart disease.[36] The prevalence of comorbidities and their impact on survival in stage I lung cancer increases with age as a competing event.[37] Indeed, patients between 55 and 74 years and those 75 years or older did not have a plateau

in survival curves despite the curative resection of lung cancer (online supplemental eFigure 7). We did not collect information about comorbidities; therefore, the impact of comorbidities on survival could not be incorporated into our analysis, potentially hindering the identification of the impact of transthoracic biopsy on survival in older patients.

The lack of association between transthoracic biopsy and impaired survival outcomes in patients between 55 and 75 years cannot ensure the use of transthoracic biopsy without concerning a deleterious effect of pleural recurrence in lung cancer screening. Transthoracic biopsy increased the risk of isolated and concomitant pleural recurrence in adenocarcinoma, a predominant subtype in lung cancer screening, and in stage IA lung cancer (online supplemental eFigure 4), where the early detection maximises survival benefits. Transthoracic biopsy may spoil the early detection of peripheral lung adenocarcinoma in lung cancer screening. Pleural recurrence might not dominantly contribute to reduced survival in patients 55 years or older frequently having comorbidities, but the recurrence can impair quality of life after curative treatment.[38] The adverse effect of transthoracic biopsy on pleural recurrence should be considered before the biopsy and cautiously balanced with the diagnostic benefit of the biopsy in lung cancer screening.

To overcome some limited aspects of the individual patient data meta-analysis that occurred by a lack of information in some studies, we conducted a few versions of sensitivity analyses. We considered an analysis that used the data fully as possible as the primary version. A propensity score matching was considered only for sensitivity analysis, due to a large portion of data loss after matching especially for the rare event of primary outcomes. Although the CT findings were statistically significant in the univariable analysis, these could not be included for adjustment in the primary analysis due to missing information in some studies. However, we attempted to adjust those variables in sensitivity analyses by including studies providing the relevant information.

The strengths of this study included its large sample size with individual patient data staged according to the latest TNM classification on the rare event of pleural recurrence. Furthermore, the median follow-up of 5 years was sufficient to observe a plateau in the incidence of pleural recurrence. Rigorous sensitivity analyses consistently showed the deleterious effect of transthoracic biopsy on pleural recurrence.

The main caveat of this study is a lack of adjustment for tumour location from the pleura. It remains unknown whether the proximity of lung cancer to the pleura may affect the risk of pleural recurrence. The risk of pleural recurrence might, therefore, differ between lung cancers that were diagnosed via transthoracic biopsy and those diagnosed via other diagnostic procedures. The former would be located more peripherally, whereas the latter would be located more centrally (proportion of pleural contact, 41.7% vs 33.3% in this study). Nevertheless, transthoracic biopsy increased isolated and concomitant pleural recurrences when confined to subpleural lung cancers that had the same proximity. Consistent results were observed in the propensity score matching analyses, which achieved balance in baseline characteristics, including the presence of pleural contact (online supplemental eFigures 4 and 11). Our result warrants a randomised controlled trial using either transthoracic biopsy or other diagnostic procedures for peripheral lung cancer.

Additional limitations exist in this study. The participating studies were retrospectively performed in Asian countries, and primary data from one-third of eligible participants were not included as of 2020. The postoperative follow-up duration was inhomogeneous across studies. Missing values for microscopic vascular or lymphatic invasion may have influenced the magnitude of the effect of transthoracic biopsy. Korean sites showed a stronger preference for transthoracic biopsy (around 60% vs 30%) and seemed to apply broader indications for transthoracic biopsy than Japanese sites. Nevertheless, the effect of transthoracic biopsy was consistent in sensitivity analyses according to the country of the study.

In conclusion, preoperative transthoracic needle lung biopsy was associated with increased pleural recurrence in stage I lung cancer and reduced survival in patients younger than 55 years. Transthoracic biopsy should be cautiously applied for the diagnosis of early lung cancer for which curative treatment is anticipated, particularly for patients younger than 55 years.

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