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Original Article

Development of the Korean Association for Lung Cancer Clinical Practice Guidelines: Recommendations on Radial Probe Endobronchial Ultrasound for Diagnosing Lung Cancer - An Updated Meta-Analysis

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Purpose Radial probe endobronchial ultrasound (RP-EBUS) accurately locates peripheral lung lesions (PLLs) during transbronchial biopsy (TBB). We performed an updated meta-analysis of the diagnostic yield of TBB for PLLs using RP-EBUS to generate recommendations for the development of the Korean Association of Lung Cancer guidelines.

Materials and Methods We systematically searched MEDLINE and EMBASE (from January 2013 to December 2022), and performed a meta-analysis using R software. The diagnostic yield was evaluated by dividing the number of successful diagnoses by the total lesion number. Subgroup analysis was performed to identify related factors.

Results Forty-one studies with a total of 13,133 PLLs were included. The pooled diagnostic yield of RP-EBUS was 0.72 (95% confidence interval [CI], 0.70 to 0.75). Significant heterogeneity was observed among studies (χ^2=292.38, p < 0.01, I^2=86.4%). In a subgroup analysis, there was a significant difference in diagnostic yield based on RP-EBUS findings (within, adjacent to, invisible), with a risk ratio of 1.45 (95% CI, 1.23 to 1.72) between within and adjacent to, 4.20 (95% CI, 1.89 to 9.32) between within and invisible, and 2.59 (95% CI, 1.32 to 5.01) between adjacent to and invisible. There was a significant difference in diagnostic yield based on lesion size, histologic diagnosis, computed tomography (CT) bronchus sign, lesion character, and location from the hilum. The overall complication rate of TBB with RP-EBUS was 6.8% (bleeding, 4.5%; pneumothorax, 1.4%).

Conclusion Our study showed that TBB with RP-EBUS is an accurate diagnostic tool for PLLs with good safety profiles, especially for PLLs with within orientation on RP-EBUS or positive CT bronchus sign.

Key words Bronchoscopy, Lung neoplasms, Meta-analysis, Pulmonary nodule, Radial probe endobronchial ultrasound

Introduction

The National Lung Cancer Screening Trial (NLST) demonstrated a 20% reduction of mortality in lung cancer by low-dose computed tomography, which led to an increased detection rate of peripheral lung lesions (PLLs) (1.5 million PLLs per 5 million U.S. population annually) [1,2]. However, only 5.2% of PLLs were finally diagnosed with lung cancer, implying that most PLLs were benign [1]. Because most of them are benign, it is necessary to select the target patients who need invasive examination carefully. To this end, positron emission tomography–computed tomography can be considered in the intermediate risk group, and even if biopsy is performed, non-surgical biopsy is recommended [3].

The most common non-surgical procedures to diagnose PLLs are bronchoscopic transbronchial biopsy (TBB) and transthoracic needle biopsy (TTNB) [3,4]. TBB using the conventional bronchoscope showed a suboptimal diagnostic yield for malignancy ranging from 0.34-0.63 in the diagnosis of PLLs [3]. To overcome this issue, radial probe endobronchial ultrasound (RP-EBUS) has been introduced, providing a circumferential ultrasound image of the surrounding lung, confirming the accurate location of PLLs [5]. RP-EBUS with a guide sheath (GS) is a commonly performed TBB procedure enabling access to and detection of PLLs through the bronchoscope's working channel [6]. After the detection of PLLs by RP-EBUS with GS, RP-EBUS is withdrawn, leaving the GS near PLLs as an extended working channel. Then, biopsy instruments are inserted through GS for tissue acquisition.

Although safe, a previous meta-analysis by Wang Memoli

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et al. [7] reported that the pooled diagnostic yield of TBB using RP-EBUS for PLLs is 71%, which is lower than that of TTNB (90%). To increase the diagnostic yield of TBB, newer technologies, such as virtual bronchoscopic navigation (VBN) [8], electromagnetic navigation bronchoscopy (ENB) [9], and ultrathin bronchoscopes [10], have been introduced with increasing frequency over the last decade, in addition to previous technology such as fluoroscopy (Flu) [3]. However, there is a lack of systematic research reflecting the current status of TBB performance using RP-EBUS.

Thus, we aimed to evaluate the updated meta-analysis of the diagnostic yield of TBB for PLLs using RP-EBUS based on recently published articles in the last 10 years and to generate recommendations for the development of the Korean Association of Lung Cancer guidelines on RP-EBUS. Furthermore, we evaluated the factors affecting the diagnostic yield and associated complications.

Materials and Methods

1. Literature search

We performed a meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The study protocol is registered with the PROSPERO database (Identifier: CRD42022378949). We searched MEDLINE and EMBASE (from January 2013 to December 2022) to identify all studies that employed RP-EBUS to evaluate PLLs using a predetermined protocol (Table 1). A manual search of references cited in original and review papers was done for relevant studies, which might have been missed by the electronic search.

2. Selection of studies

All articles identified by the search strategy were independently assessed by four authors (S.H.K., H.S.C., I.K., and J.S.E.). Discordance was resolved by consensus. Abstracts were initially examined, and studies were selected for inclusion only after all reviewers assessed the full-text articles.

Table 1. Search strategy for meta-analysis

	Search strategy
1	"Endobronchial ultrasound AND lung AND nodule(s)"
2	"Endobronchial ultrasound AND lung AND lesion(s)"
3	"Endobronchial ultrasound AND lung AND cancer(s)"
4	"Endobronchial ultrasound AND pulmonary AND nodule(s)"
5	"Endobronchial ultrasound AND pulmonary AND lesion(s)"
6	"Endobronchial ultrasound AND pulmonary AND cancer(s)"
7	"Endobronchial ultrasound AND peripheral AND nodule(s)"
8	"Endobronchial ultrasound AND peripheral AND lesion(s)"
9	"Endobronchial ultrasound AND peripheral AND cancer(s)"
10	"Endobronchial ultrasonograph(y) AND lung AND nodule(s)"
11	"Endobronchial ultrasonograph(y) AND lung AND lesion(s)"
12	"Endobronchial ultrasonograph(y) AND lung AND cancer(s)"
13	"Endobronchial ultrasonograph(y) AND pulmonary AND nodule(s)"
14	"Endobronchial ultrasonograph(y) AND pulmonary AND lesion(s)"
15	"Endobronchial ultrasonograph(y) AND pulmonary AND cancer(s)"
16	"Endobronchial ultrasonograph(y) AND peripheral AND nodule(s)"
17	"Endobronchial ultrasonograph(y) AND peripheral AND lesion(s)"
18	"Endobronchial ultrasonograph(y) AND peripheral AND cancer(s)"
19	"Radial probe AND lung AND nodule(s)"
20	"Radial probe AND lung AND lesion(s)"
21	"Radial probe AND lung AND cancer(s)"
22	"Radial probe AND pulmonary AND nodule(s)"
23	"Radial probe AND pulmonary AND lesion(s)"
24	"Radial probe AND pulmonary AND cancer(s)"
25	"Radial probe AND peripheral AND nodule(s)"
26	"Radial probe AND peripheral AND lesion(s)"
27	"Radial probe AND peripheral AND cancer(s)"

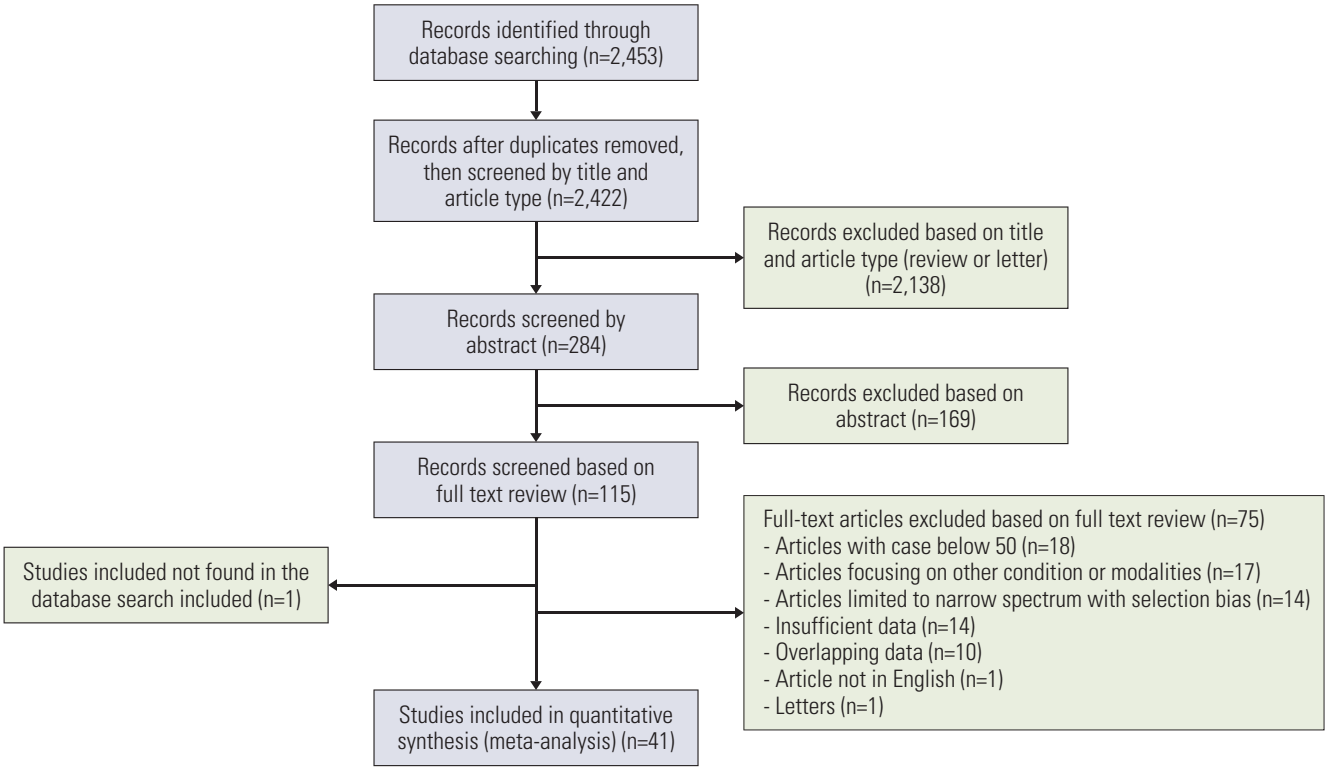

Fig. 1. Flow diagram of search and study selection.

Criteria for inclusion were as follows: (1) RP-EBUS for diagnosis of PLL providing a diagnostic yield, (2) diagnosis confirmed histologically or by close clinical follow-up, and (3) studies where at least 50 patients were enrolled.

We excluded review articles, meta-analysis articles, letters, case reports with fewer than 50 patients, articles not available in English, articles focusing on modalities other than RP-EBUS, or articles only limited to PLLs with a narrow spectrum (e.g., malignant lesion, ground-glass opacity lesion [GGO]). Furthermore, articles focusing on cone-beam computed tomography (CT) or robotic bronchoscopy were also excluded due to the high risk of selection bias. When two or more studies were published by the same author(s), the methods sections were reviewed to check for overlapping study periods. If so, we included only one publication with the greatest number of patients to prevent duplication of the study cohorts.

3. Data extraction

All data were independently extracted by S.H.K., H.S.C., and I.K., followed by a comparison of extracted data. Disagreements were resolved by further discussion with the other investigator (J.S.E.). The following were retrieved: author, year of publication, study design (randomized controlled trial, prospective, retrospective, or unknown), total number of lesions, number of successful diagnoses, type of bronchoscope (standard bronchoscope, thin bronchoscope, ultrathin bronchoscope), use of guidance modalities (e.g., GS, VBN, Flu, ENB), biopsy methods (e.g., forceps biopsy, cryobiopsy), mean lesion size, prevalence of malignancy, RP-EBUS findings, histologic diagnosis, presence of CT bronchus sign, lesion character (solid, part-solid, GGO), distance from the hilum (central, inner third; intermediate, middle third; peripheral, outer third in the lung field on CT scan) [12], complications, and reference standard.

The quality of selected studies was evaluated by S.H.K., H.S.C., and I.K., using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [13]. This validated tool contains 14 signaling questions to evaluate four main components (patient selection, index test, reference standard, and flow and timing) in two categories (risk of bias and applicability concerns). Disagreements were resolved by further discussion with the other investigator (J.S.E.).

4. Statistical analysis

Meta-analysis was performed using the meta package of R statistical software (ver. 4.0.5, http://www.R-project.org). A p-value of < 0.05 was considered statistically significant. The

primary outcome was the diagnostic yield with a 95% confidence interval (CI), calculated by dividing the number of successful diagnoses by the total number of lesions. Inverse variance weighting across selected studies was applied to evaluate the pooled diagnostic yield, where the weight of each study was based on the number of lesions.

Subgroup analysis was performed to identify the factors associated with diagnostic yield. Stratified analysis on diagnostic yield was based on lesion size (≤ 20 mm vs. > 20 mm), histologic diagnosis (malignant vs. benign), RP-EBUS findings (within vs. adjacent to vs. invisible), CT bronchus sign (present vs. absent), lesion character (solid vs. part-solid vs. GGO), and distance from the hilum (peripheral vs. non-peripheral [central and/or intermediate]). In addition, subgroup analysis based on adjunctive modalities (ENB, GS, Flu, VBN), bronchoscope types (standard, thin, ultrathin bronchoscope), and use of cryobiopsy were evaluated. A subgroup meta-analysis was performed using the Mantel-Haenszel risk ratio (RR) [14,15]. RR > 1 was in favor of the former variable for the diagnostic yield, while RR < 1 was in favor of the latter variable.

Study heterogeneity was assessed using the Cochran Q test (χ^2 test) and quantified by the I^2 index [16]. Statistical heterogeneity was indicated in cases of $p < 0.01$ in the χ^2 test [16], and I^2 index values of > 50% indicated significant heterogeneity [17]. Random-effect models with the inverse variance method were applied to reflect the variability of effect sizes among included studies with diversity in adjunctive modalities [18]. Publication bias was evaluated using funnel plot asymmetry [19] based on the Egger and Begg tests [20,21]. We used funnel plots of standard error or diagnostic yield (logit transformed).

Results

1. Literature search and study selection

After removing duplicates, the search algorithm revealed 2,422 potentially relevant papers (Fig. 1). Following the abstract review, 115 articles were selected for full-text review. Of these, 75 articles were excluded according to the exclusion criteria, and one study missed in the database search was added [22]. Therefore, 41 studies formed the basis of our systematic review [22-62].

2. Study description

A total of 13,133 PLLs were included. Table 2 lists the study characteristics and summarizes their features [22-62]. Overall, 13 studies were randomized controlled trials, seven were prospective, and 21 were retrospective studies. The prevalence of malignancy was reported in 35 studies (median, 78%; interquartile range, 68 to 83). Among them, 15 studies showed a prevalence of malignancy ≤ 75%, whereas 20 studies showed > 75%. There was variation in additional guidance devices used among included studies, such as GS (31 studies), Flu (26 studies), VBN (16 studies), ultrathin bronchoscopy (5 studies), and ENB (1 study). S1 Table provides a quality assessment of all included studies based on QUADAS-2. The overall analysis showed good performance in the patient selection and index test criteria. However, it showed poor performance in the reference standard in addition to flow and timing criteria, which indicates the potential for significant bias. The funnel plot (Fig. 2) was not asymmetric, with both Egger's (p=0.156) and Begg's tests (p=0.103) showing insignificant p-values, indicating the absence of publication bias.

3. Test performance: meta-analysis

The inverse variance weighted overall diagnostic yield was 0.72 (95% CI, 0.70 to 0.75) (Fig. 3) [22-62]. The diagnostic yield among studies ranged from 0.49 to 0.94. The χ^2 value of 293.38 ($p < 0.01$) and I^2 index of 86.4% indicated substantial heterogeneity across studies. The pooled sensitivity and specificity for malignant PLLs in 30 studies were 0.76 (95% CI, 0.72 to 0.79) and 0.98 (95% CI, 0.96 to 0.99), respectively [22-25,29,31-35,37-46,48,49,51,55-57,59-62].

The factors related to diagnostic yield were further evaluated by subgroup meta-analysis. Regarding trichotomous variables (Table 3), there were significant differences in the pooled diagnostic yield based on RP-EBUS findings, where RR was 1.45 (95% CI, 1.23 to 1.72) between within and adjacent to in 12 studies, 4.20 (95% CI, 1.89 to 9.32) between within and invisible in five studies, and 2.59 (95% CI, 1.32 to 5.01) between adjacent to and invisible in five studies (Fig. 4A-C) [28,31,38,42,45-47,52,53,55,61,62]. As for lesion characters (Table 3), there was a significant difference in the pooled diagnostic yield between solid and part-solid, where RR was 1.15 (95% CI, 1.03 to 1.28) in seven studies. However, there was a difference in the pooled diagnostic yield without significance in the other variables, where RR was 1.40 (95% CI, 0.93 to 2.11) between solid and GGO in three studies, and 1.39 (95% CI, 0.93 to 2.11) between part-solid and GGO in two studies (S2A-S2C Fig.) [22,34,42,53,55,56,60,61].

Regarding dichotomous variables (Table 3), the pooled diagnostic yield was significantly different based on lesion size in 21 studies (≤ 20 vs. > 20 mm: RR, 0.78; 95% CI, 0.73 to 0.83) (S3A Fig.) [22,24,26,27,31-35,37,41,42,45,46,48,53,55,59-62], histologic diagnosis in 30 studies (malignancy vs. benign: RR, 1.30; 95% CI, 1.12 to 1.52) (S3B Fig.) [22-25,29,31-35,37-46,48,49,51,55-57,59-62], CT bronchus sign in 14 studies (present vs. absent: RR, 1.683; 95% CI, 1.32 to 2.14) (S3C Fig.) [22,27,28,30,33-35,40,45,53,56,60-62], and distance from the

Table 2. Study characteristics

No.	Author/ year	Study design	Selection criteria	No. of lesions	Diagnostic yield	Prevalence of malignancy (%)	Additional guidance	Biopsy method	Bronchoscope	Complications	Reference/ Comparison test
1	Fuso 2013 [23]	Retrospective	PLL not visible on routine bronchoscopy	447	0.77	80.3	None	Forceps	Standard	2 Bleed, 8 PNX	Histology by alternative means or clinical/radiologic surveillance (12 mo)
2	Tamiya 2013 [24]	Prospective	PLL ≤ 30 mm	68	0.78	63.2	GS, Flu, VBN	Brush, forceps, needle	Thin	NE	Histology by alternative means or clinical/radiologic surveillance (6 mo)
3	Tay 2013 [25]	Retrospective	PLL not visible on routine bronchoscopy	196	0.56	68.9	GS, Flu	Brush, forceps	NE	NE	Histology by alternative means or clinical/radiologic surveillance
4	Chen 2014 [26]	Retrospective	NE	467	0.69	NE	GS	Brush, forceps, needle	NE	6 Bleed, 13 PNX (7 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance
5	Evison 2014 [27]	Retrospective	PLL not visible on routine bronchoscopy	117	0.69	82.9	GS	Forceps	Standard	6 Bleed 1 PNX (1 requiring chest tube), 2 poor tolerance to bronchoscope	Clinical/radiologic surveillance (6 mo)
6	Kuo 2014 [28]	Retrospective	PLL without endobronchial lesion, extrinsic compression, submucosal infiltration, or orifice narrowing	271	0.76	90.0	None	Brush, forceps	Standard	22 Bleed, 7 PNX	NE
7	Sanchez -Font 2014 [29]	RCT	PLL not visible on routine bronchoscopy	50	0.78	90.0	GS, Flu	Brush, forceps	Standard	9 Bleed	Histology by alternative means or clinical/radiologic surveillance (6 mo)

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Table 2. Continued

No.	Author/ year	Study design	Selection criteria	No. of lesions	Diagnostic yield	Prevalence of malignancy (%)	Additional guidance	Biopsy method	Bronchoscope	Complications	Reference/ Comparison test
8	Asano 2015 [30]	Retrospective	PLL ≤ 30 mm	194	0.74	NE	GS, Flu, VBN	Brush, forceps	Thin	1 PNX (1 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance (24 mo)
9	Boonsarng-suk 2015 [31]	Prospective	PLL with feeding bronchi, but not visible on routine bronchoscopy	112	0.80	67.9	GS, Flu	Brush, forceps	Standard	1 PNA	Histology by alternative means or clinical/radiologic surveillance
10	Chan 2015 [32]	Retrospective	Exclusion: PLL < 1 cm, endobronchial lesions, airway narrowing, pure GGO, absence of CT bronchus sign, presence of a submucosal lesion	120	0.69	63.3	GS, Flu	Forceps	Standard	7 Bleed, 1 PNX	Histology by alternative means or clinical/radiologic surveillance (12 mo)
11	Guvenc 2015 [33]	Retrospective	Exclusion: bronchopneu-monia, solid lesions < 10 mm, glass opacity (pure or part-solid less than 50%) lesions, solid lesions < 15 mm touching the visceral pleura	760	0.62	73.0	None	Forceps	Standard	9 PNX (1 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance (6 mo)
12	Minezawa 2015 [34]	Retrospective	PLL ≤ 30 mm	149	0.73	73.8	GS	Brush, forceps	Thin	1 Delirium, 4 PNA, 5 PNX (5 requiring chest tube)	Clinical/radiologic surveillance (12 mo)

(Continued to the next page)

Table 2. Continued

No.	Author/ year	Study design	Selection criteria	No. of lesions	Diagnostic yield	Prevalence of malignancy (%)	Additional guidance	Biopsy method	Bronchoscope	Complications	Reference/ Comparison test
13	Oki 2015 [35]	RCT	PLL ≤ 30 mm	305	0.67	76.1	GS, Flu, VBN	Forceps	Thin, ultrathin	2 Bleed, 1 PNA, 8 PNX (3 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance (12 mo)
14	Jacomelli 2016 [36]	Retrospective	Pulmonary nodule or mass (non-diagnostic by routine bronchoscopy) Exclusion: PLL with endobronchial lesions or lost to follow-up	51	0.67	NE	Flu	Brush, forceps, needle	Standard	5 Bleed, 2 PNX (2 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance (6 mo)
15	Kunimasa 2016 [37]	Retrospective	NE	88	0.82	97.7	GS, Flu	Brush, forceps	Thin	NE	Histology by alternative means or clinical/radiologic surveillance
16	Steinfort 2016 [38]	Prospective	NE	245	0.58	82.4	ENB, GS, Flu, VBN	Brush, forceps	Thin	NE	Histology by alternative means or clinical/radiologic surveillance (12 mo)
17	Wang 2016 [39]	Prospective	PLL in the outer 1/3 pulmonary field, invisible under routine bronchoscopy	54	0.82	87.0	GS, Flu	Brush, forceps	Thin	1 Bleed	Histology by alternative means or clinical/radiologic surveillance
18	Asano 2017 [40]	RCT	PLL > 30 mm Exclusion: endobronchial lesion, GGO lesion	129	0.81	93.8	GS, Flu, VBN	Brush, forceps	Thin	2 Bleed, 1 hyperventi-lation, 1 PNA	Histology by alternative means or clinical/radiologic surveillance (24 mo)
19	Huang 2017 [41]	Retrospective	PLL ≥ 8 mm, not visible on routine bronchoscopy	2,144	0.72	77.9	None	Brush, forceps	Thin	10 Bleed, 38 PNX	Histology by alternative means or clinical/radiologic surveillance

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Table 2. Continued

No.	Author/ year	Study design	Selection criteria	No. of lesions	Diagnostic yield	Prevalence of malignancy (%)	Additional guidance	Biopsy method	Bronchoscope	Complications	Reference/ Comparison test
20	Eom 2018 [42]	Retrospective	NE	200	0.73	77.5	GS, Flu	Brush, forceps	Thin,	1 PNA, 2 PNX	NE
21	Good 2018 [43]	Retrospective	NE	68	0.56	75.0	GS	Brush, forceps, needle	NE	1 Dislodgement of GS, 3 PNX	Histology by alternative means or clinical/radiologic surveillance (12 mo)
22	Tanner 2018 [44]	RCT	PLL 15-50 mm	112	0.49	75.0	GS, Flu	Brush, forceps	Standard, thin	NE	Histology by alternative means or clinical/radiologic surveillance (12 mo)
23	Zhang 2018 [45]	Retrospective	Exclusion: Bronchial lesions on routine bronchoscopy, EBUS-GS TBB, malignant lesions without postoperative pathology, follow-up loss, or final diagnosis unknown	328	0.55	58.8	None	Brush, forceps	Thin	13 Bleed, 3 chest pain	Histology by alternative means or clinical/radiologic surveillance
24	Bo 2019 [46]	RCT	PLL with a high likelihood of malignancy, 8-30 mm	670	0.73	51.3	GS, VBN	Forceps	Thin	7 Bleed, 12 PNX (4 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance (24 mo)
25	Kho 2019 [47]	Retrospective	Exclusion: endobronchial lesion, incomplete clinical data, not visualized by RP-EBUS	114	0.68	NE	GS, Flu	Forceps, cryoprobe	NE	24 Bleed, 1 PNX	Histology by alternative means or clinical/radiologic surveillance

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Table 2. Continued

No.	Author/ year	Study design	Selection criteria	No. of lesions	Diagnostic yield	Prevalence of malignancy (%)	Additional guidance	Biopsy method	Bronchoscope	Complications	Reference/ Comparison test
26	Oki 2019 [22]	RCT	PLL ≤ 30 mm	356	0.64	79.2	GS, Flu, VBN	Forceps, needle	Thin, ultrathin	3 Bleed, 1 myocardial infarction, 1 nausea, 4 PNX (1 requiring chest tube), 1 vomiting	Histology by alternative means or clinical/radiologic surveillance (12 mo)
27	Xu 2019 [48]	RCT	PLL 8-30 mm	115	0.84	65.2	VBN	Forceps	Thin	1 Bleed, 1 PNX	Histology by alternative means or clinical/radiologic surveillance (6 mo)
28	Zhu 2019 [49]	Retrospective	NE	239	0.78	52.3	GS	Forceps	NE	21 Bleed, 2 chest pain, 18 fever, 2 PNA, 1 PNX,	Histology by alternative means or clinical/radiologic surveillance
29	Boonsarng-suk 2020 [50]	Prospective	PLL with feeding bronchi Exclusion: PLL < 10 mm, no feeding bronchi	90	0.82	77.8	GS, Flu	Brush, forceps	Thin	NE	Histology by alternative means or clinical/radiologic surveillance
30	Samarana-yake 2020 [51]	RCT	Exclusion: PLL < 15 mm, lack of bronchus sign, less than 180-degree view of the lesion on ultrasound, previous RP-EBUS TBB within 2 wk	54	0.78	81.5	GS, Flu	Brush, forceps	NE	7 Bleed	Histology by alternative means or clinical/radiologic surveillance
31	Goel 2021 [52]	Retrospective	NE	126	0.79	50.0	None	Cryoprobe	Standard	126 Bleed, 4 respiratory failure not requiring escalation of care	NE

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Table 2. Continued

No.	Author/ year	Study design	Selection criteria	No. of lesions	Diagnostic yield	Prevalence of malignancy (%)	Additional guidance	Biopsy method	Bronchoscope	Complications	Reference/ Comparison test
32	Hong 2021 [53]	Retrospective	NE	607	0.76	61.4	GS	Brush, forceps	Thin	12 PNX (3 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance (12 mo)
33	Jiang 2021 [54]	Prospective	PLL 10-50 mm, solid or part-solid nodule, bronchus sign pulmonary nodule Exclusion: endobronchial lesion, atelectasis, or obstructive pneumonia	59	0.70	NE	GS, Flu, VBN	Brush, cryoprobe, forceps	Standard	8 Bleed, 2 PNX (1 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance (6 mo)
34	Zheng 2021 [55]	RCT	PLL with the presence of the bronchus sign Exclusion: pure GGO, endobronchial lesion	120	0.78	83.3	Flu, VBN	Brush, forceps	Ultrathin	None	Histology by alternative means or clinical/radiologic surveillance (12 mo)
35	Ito 2022 [56]	RCT	PLL with no endobronchial lesion	1,634	0.70	84.8	GS, Flu, VBN	Brush, forceps, needle	NE	NE	Histology by alternative means or clinical/radiologic surveillance (24 mo)
36	Kim 2023 [57]	Retrospective	PLL ≤ 30 mm	110	0.79	83.6	GS, Flu, VBN	Brush, cryoprobe, forceps, needle	Standard, thin, ultrathin	9 Bleed, 1 PNA, 1 PNX	Histology by alternative means or clinical/radiologic surveillance (12 mo)
37	Lee 2022 [58]	Retrospective	NE	954	0.75	NE	GS, Flu	Brush, forceps	Thin	3 Bleed, 5 PNA, 2 PNX	NE
38	Liu 2022 [59]	RCT	PLL ≤ 30 mm, with the bronchial sign Exclusion: endobronchial lesion	138	0.74	69.6	GS, VBN	Forceps, cryoprobe	Standard	133 Bleed, 5 PNX	Histology by alternative means or clinical/radiologic surveillance (6 mo)

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Table 2. Continued

No.	Author/ year	Study design	Selection criteria	No. of lesions	Diagnostic yield	Prevalence of malignancy (%)	Additional guidance	Biopsy method	Bronchoscope	Complications	Reference/ Comparison test
39	Oki 2022 [60]	RCT	PLL ≤ 30 mm	596	0.64	78.5	GS, Flu, VBN	Brush, cryoprobe, forceps, needle	Thin, ultrathin	1 Arrhythmia, 4 bleed (1 significant bleeding), 1 broken GS, 7 PNA, 8 PNX (4 requiring chest tube), 2 transient hypoxemia	Histology by alternative means or clinical/radiologic surveillance (12 mo)
40	Tanaka 2022 [61]	Prospective	PLL < 30 mm, located beyond the subsegmental bronchi	50	0.94	94.0	Flu, VBN	Cryoprobe	Thin	46 Bleed, 1 PNA, 1 PNX (1 requiring chest tube)	Histology by alternative means or clinical/radiologic surveillance
41	Zheng 2023 [62]	RCT	PLL ≥ 8 mm Exclusion: absence of the bronchus sign, pure GGO, endobronchial lesion	426	0.84	80.8	GS, Flu, VBN	Forceps, needle	Thin	7 Bleed	Histology by alternative means or clinical/radiologic surveillance (12 mo)

CT, computed tomography; EBUS-GS, endbronchial ultrasound guide sheath; ENB, electromagnetic navigation bronchoscopy; Flu, fluoroscopy; GGO, ground glass opacity; GS, guide sheath; NE, not evaluable; PLL, peripheral lung lesion; PNA, pneumonia; PNX, pneumothorax; RCT, randomized controlled trial; RP-EBUS, radial probe endobronchial ultrasound; TBB, transbronchial biopsy; VBN, virtual bronchoscopic navigation.

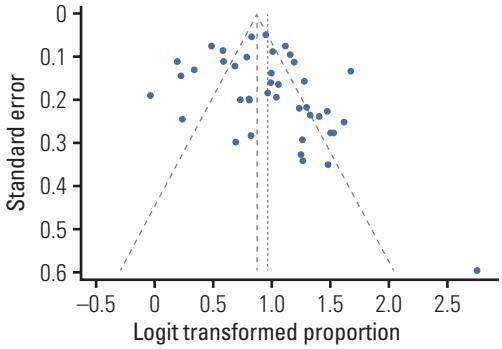


Fig. 2. Funnel plot of publication bias.

hilum in 11 studies (peripheral vs. non-peripheral: RR, 0.90; 95% CI, 0.84 to 0.96) (S3D Fig.) [22,30,35,37,40,45,55,56,60-62].

4. Test performance based on technologies

Regarding frequently used adjunctive modalities (Table 4), Flu+GS was the most commonly used combination during TBB using RP-EBUS (13 studies) [25,29-32,37,39,42,44,47,50,51,58], followed by Flu+GS+VBN (10 studies) [22,24,30,35,40,54,56,57,60,62], GS only (seven studies) [26,27,34,43,46,49,53], and no adjunctive modalities (six studies) [23,28,33,41,45,52]. The pooled diagnostic yields of adjunctive modalities were 0.73 (95% CI, 0.67 to 0.79) for Flu+GS+VBN, 0.73 (95% CI, 0.67 to 0.78) for Flu+GS, 0.72 (95% CI, 0.68 to 0.76) for GS only, and 0.70 (95% CI, 0.62 to 0.76) for no adjunctive modalities (p=0.903) (S4 Fig.). Regarding a single adjunctive modality, the pooled diagnostic yield was higher without statistical significance for GS (0.72; 95% CI, 0.69 to 0.75) compared with non-GS (0.70; 95% CI, 0.62 to 0.78) (p=0.658), VBN (0.74; 95% CI, 0.69 to 0.79) compared with non-VBN (0.71; 95% CI, 0.68 to 0.74) (p=0.356), but not for Flu (0.73; 95% CI, 0.69 to 0.77) compared with non-Flu (0.73; 95% CI, 0.69 to 0.76) (p=0.929) (S5A-S5D Fig.). Regarding bronchoscope type, the pooled diagnostic yields of thin (22 studies) [22,24,30,34,35,37-42,44-46,48,50,53,57,58,60-62], standard (12 studies) [23,27-29,32,33,36,44,50,52,54,59], and ultrathin (four studies) [22,35,55,57] bronchoscopes were 0.73 (95% CI, 0.68 to 0.78), 0.71 (95% CI, 0.66 to 0.75), and 0.73 (95% CI, 0.69 to 0.77), respectively (p=0.715) (S6 Fig.). Regarding the biopsy method, the pooled diagnostic yield of cryobiopsy (six studies) [47,52,54,57,59,61] was 0.78 (95% CI, 0.70 to 0.85) (one study, not evaluable due to insufficient data) [60].

5. Complication rates

Complication rates were 6.8% (726 out of 10,700 lesions) across 34 studies [22,23,26-36,39-43,45-49,51-55,57-62], whereas seven studies [24,25,37,38,44,50,56] did not report complication rates (Table 2). Among 34 studies, no complication was noted in one study [55]. The most common complication was bleeding, with a pooled rate of 4.5% (482 out of 10,700). The pooled rate of pneumothorax was 1.4% (148 out of 10,700), whereas that of chest tube insertion was 0.3% (33 out of 10,700). The pooled infection rate (including pneumonia) was 0.4% (45 out of 10,700). There were two cases of life-threatening complications without death (one myocardial infarction and one severe bleeding). No death was reported in any study.

Discussion

To our knowledge, this is the first updated meta-analysis investigating the performance of RP-EBUS for diagnosing PLLs, including 13,133 PLLs from recent publications in 10 years. Our study showed the overall diagnostic yield of RP-EBUS as 0.72. Moreover, subgroup analysis showed that lesion size, histologic diagnosis, RP-EBUS findings, CT bronchus sign, lesion character, and distance from the hilum were associated with the performance of TBB using RP-EBUS. Lastly, our study showed a good safety profile during TBB using RP-EBUS, where the overall complication rate was 6.8% (bleeding, 4.5%; pneumothorax, 1.4%).

RP-EBUS finding was previously reported as an important factor for the diagnostic yield, which correlates with our study results. Tay et al. [25] reported that visualized PLLs on RP-EBUS were associated with significantly higher diagnostic yield than invisible PLLs on RP-EBUS (0.66 vs. 0.20; p=0.001). Among visualized PLLs on RP-EBUS, Ali et al. [63] reported significantly higher diagnostic yield in within oriented lesions compared to that of adjacently oriented lesions on RP-EBUS (0.79 vs. 0.52; $p < 0.001$). In line with this, the presence of CT bronchus sign was also known to be associated with the diagnostic yield, which correlates with our study finding. The same group also reported significantly higher diagnostic yield in PLLs with bronchus sign compared to that of PLLs without bronchus sign on CT (0.77 vs. 0.52, p=0.008) [63]. This might be attributed to the fact that the presence of CT bronchus sign is significantly associated with the visualization of the lesion on RP-EBUS (odds ratio [OR], 31.1; $p < 0.001$) and within the orientation of RP-EBUS to the lesion (OR, 44.8; $p < 0.001$) [27]. Therefore, TBB with RP-EBUS is highly recommended in within oriented or CT bronchus sign present PLLs.

Our study also showed that smaller size (≤ 2 cm), benign, and peripheral location were associated with significantly lower diagnostic yield during TBB using RP-EBUS. A previous meta-analysis showed that the diagnostic yield of PLLs ≤ 2 cm and > 2 cm were 0.61 and 0.76, respectively ($p < 0.001$) [63]. This might be attributed to lower visualization of PLLs

Study	Events	Total	Weight (%)	IV, random (95% CI)
Fuso 2013	343	447	2.8	0.767 (0.725-0.806)
Tamiya 2013	53	68	2.0	0.779 (0.662-0.871)
Tay 2013	109	196	2.7	0.556 (0.484-0.627)
Chen 2014	321	467	2.9	0.687 (0.643-0.729)
Evison 2014	81	117	2.4	0.692 (0.600-0.774)
Kuo 2014	198	271	2.7	0.731 (0.674-0.783)
Sánchez-Font 2014	39	50	1.7	0.780 (0.640-0.885)
Asano 2015	144	194	2.6	0.742 (0.675-0.802)
Boonsarngsuk 2015	90	112	2.2	0.804 (0.718-0.873)
Chan 2015	83	120	2.4	0.692 (0.601-0.773)
Guvenc 2015	471	760	2.9	0.620 (0.584-0.654)
Minezawa 2015	108	149	2.5	0.725 (0.646-0.795)
Oki 2015	203	305	2.8	0.666 (0.610-0.718)
Jacomelli 2016	34	51	1.9	0.667 (0.521-0.792)
Kunimasa 2016	72	88	2.0	0.818 (0.722-0.892)
Steinfort 2016	143	245	2.8	0.584 (0.519-0.646)
Wang 2016	44	54	1.7	0.815 (0.686-0.907)
Asano 2017	105	129	2.3	0.814 (0.736-0.877)
Huang 2017	1,547	2,144	3.0	0.722 (0.702-0.740)
Eom 2018	146	200	2.6	0.730 (0.663-0.790)
Good 2018	38	68	2.2	0.559 (0.433-0.679)
Tanner 2018	55	112	2.5	0.491 (0.395-0.587)
Zhang 2018	180	328	2.8	0.549 (0.493-0.604)
Bo 2019	491	670	2.9	0.733 (0.698-0.766)
Kho 2019	77	114	2.4	0.675 (0.581-0.760)
Oki 2019	229	356	2.8	0.643 (0.591-0.693)
Xu 2019	96	115	2.2	0.835 (0.754-0.897)
Zhu 2019	187	239	2.6	0.782 (0.725-0.833)
Boonsarngsuk 2020	74	90	2.0	0.822 (0.727-0.895)
Samaranayake 2020	42	54	1.8	0.778 (0.644-0.880)
Goel 2021	99	126	2.3	0.786 (0.704-0.854)
Hong 2021	462	607	2.9	0.761 (0.725-0.795)
Jiang 2021	41	59	2.0	0.695 (0.561-0.808)
Zheng 2021	93	120	2.3	0.775 (0.690-0.846)
Ito 2022	1,138	1,634	3.0	0.696 (0.674-0.719)
Kim 2023	87	110	2.2	0.791 (0.703-0.863)
Lee 2022	719	954	2.9	0.754 (0.725-0.781)
Liu 2022	102	138	2.4	0.739 (0.658-0.810)
Oki 2022	383	596	2.9	0.643 (0.603-0.681)
Tanaka 2022	47	50	0.9	0.940 (0.835-0.987)
Zheng 2023	359	426	2.7	0.843 (0.805-0.876)
Total (95% CI)		13,133	100	0.724 (0.697-0.750)

Heterogeneity: Tau^2=0.1510; Chi^2=293.38, df=40 ($p < 0.01$); I^2=86%

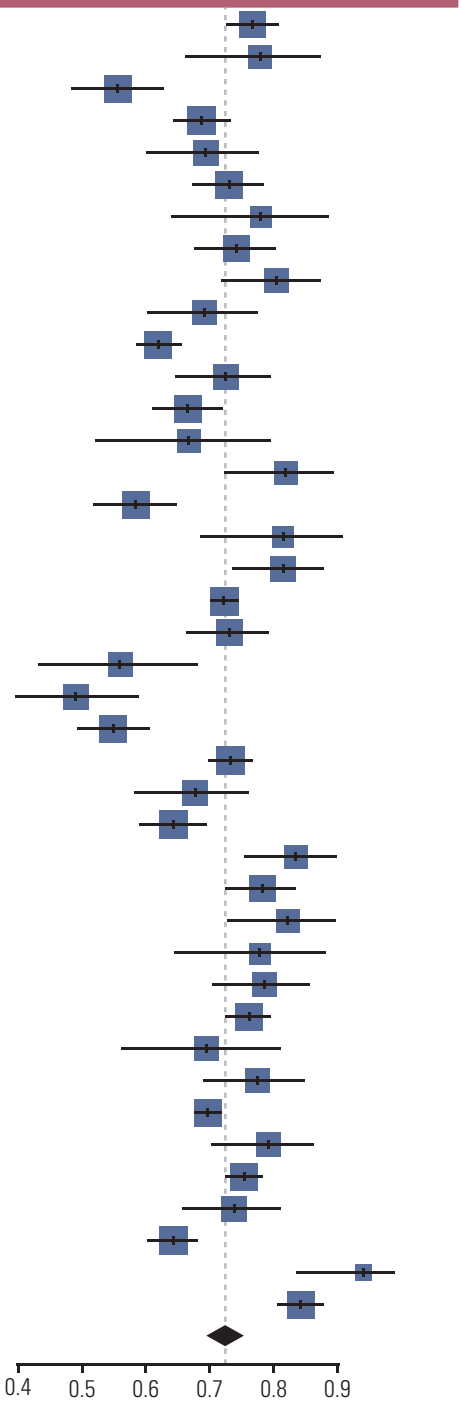


Fig. 3. Overall diagnostic yield of radial probe endobronchial ultrasound. CI, confidence interval; IV, inverse variance [22-62].

Table 3. Stratified meta-analysis for clinical factors

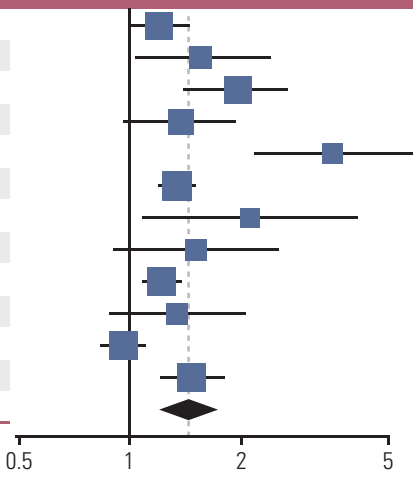
Variable	No. of studies	No. of lesions	Pooled diagnostic yield (95% CI)	Risk ratio (95% CI)	Heterogeneity			Overall effect	
					χ^2	I^2 (%)	p-value	z	p-value
RP-EBUS findings (1 vs. 2, 1 vs. 3, 2 vs. 3)	12			1.45 (1.23-1.72)	47.3	77	< 0.001	4.37	< 0.001
	5			4.20 (1.89–9.32)	16.23	75	0.003	3.52	< 0.001
	5			2.59 (1.32-5.01)	12.60	68	0.013	2.75	0.006
Within (1)	12	2,225	0.83 (0.80-0.86)						
Adjacent to (2)	12	670	0.57 (0.46-0.67)						
Invisible (3)	5	243	0.18 (0.06-0.43)						
Lesion characters (1 vs. 2, 1 vs. 3, 2 vs. 3)	7			1.15 (1.03-1.28)	11.04	46	0.087	2.59	0.010
	3			1.40 (0.93-2.11)	3.26	39	0.196	1.559	0.112
	2			1.39 (0.87-2.22)	0.67	0	0.414	1.39	0.166
Solid (1)	8	2,894	0.73 (0.65-0.79)						
Part-solid (2)	7	597	0.58 (0.53-0.62)						
GGO (3)	3	46	0.52 (0.33-0.70)						
Lesion size (mm)				0.78 (0.73-0.83)	51.3	61	< 0.001	–7.49	< 0.001
≤ 20	21	2,380	0.58 (0.52-0.63)						
> 20	21	5,392	0.77 (0.73-0.80)						
Histologic diagnosis				1.30 (1.12-1.52)	473.4	94	< 0.001	3.33	< 0.001
Malignancy	30	7,644	0.76 (0.72-0.79)						
Benign	30	2,320	0.57 (0.48-0.66)						
Bronchus sign				1.68 (1.32-2.14)	236.2	94	< 0.001	4.24	< 0.001
Present	14	4,556	0.77 (0.72-0.82)						
Absent	14	1,231	0.44 (0.33-0.56)						
Distance from hilum				0.90 (0.84-0.96)	17.8	44	0.058	–3.38	< 0.001
Peripheral	11	2,518	0.69 (0.61-0.76)						
Central and/or intermediate	11	1,360	0.76 (0.71-0.80)						

CI, confidence interval; GGO, ground glass opacity; RP-EBUS, radial probe endobronchial ultrasound.

A

Study	Within		Adjacent		Weight (%)	Risk ratio
	Events	Total	Events	Total		MH, random (95% CI)
Kuo 2014	145	188	53	83	10.5	1.208 (1.009-1.445)
Boonsarngsuk 2015	80	92	10	18	6.8	1.565 (1.028-2.384)
Steinfort 2016	117	144	23	55	8.3	1.943 (1.409-2.680)
Eom 2018	130	162	14	24	7.9	1.376 (0.973-1.946)
Zhang 2018	110	136	13	57	6.0	3.546 (2.185-5.757)
Bo 2019	336	387	118	183	11.3	1.346 (1.201-1.510)
Kho 2019	68	96	6	18	4.1	2.125 (1.092-4.135)
Goel 2021	92	113	7	13	5.7	1.512 (0.907-2.520)
Hong 2021	380	425	82	112	11.3	1.221 (1.087-1.372)
Zheng 2021	84	104	9	15	6.8	1.346 (0.881-2.056)
Tanaka 2022	24	26	23	24	11.0	0.963 (0.838-1.107)
Zheng 2023	315	352	41	68	10.3	1.484 (1.220-1.806)
Total (95% CI)	1,881	2,225	399	670	100	1.453 (1.229-1.718)

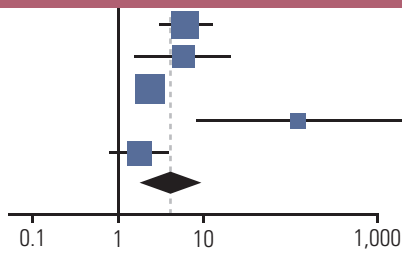
Heterogeneity: Tau^2=0.0612; Chi^2=47.28, df=11 ($p < 0.001$); I^2=77%
Test for overall effect Z=4.37 ($p < 0.001$)



B

Study	Within		Invisible		Weight (%)	Risk ratio
	Events	Total	Events	Total		MH, random (95% CI)
Steinfort 2016	117	144	7	53	24.5	6.152 (3.071-12.321)
Eom 2018	130	162	2	14	16.9	5.617 (1.553-20.312)
Bo 2019	336	387	37	100	29.1	2.347 (1.812-3.039)
Hong 2021	380	425	0	70	6.5	126.088 (7.963-1,996.469)
Zheng 2023	315	352	3	6	23.0	1.790 (0.803-3.987)
Total (95% CI)	1,278	1,470	49	243	100	4.195 (1.888-9.323)

Heterogeneity: Tau^2=0.5533; Chi^2=16.23, df=4 (p=0.003); I^2=75%
Test for overall effect Z=3.52 ($p < 0.001$)



C

Study	Adjacent		Invisible		Weight (%)	Risk ratio
	Events	Total	Events	Total		MH, random (95% CI)
Steinfort 2016	23	55	7	53	24.2	3.166 (1.485-6.752)
Eom 2018	14	24	2	14	14.9	4.083 (1.083-15.392)
Bo 2019	118	183	37	100	32.8	1.743 (1.321-2.300)
Hong 2021	82	112	0	70	5.1	103.400 (6.517-1,640.593)
Zheng 2023	41	68	3	6	23.0	1.206 (0.529-2.746)
Total (95% CI)	278	442	49	243	100	2.588 (1.316-5.091)

Heterogeneity: Tau^2=0.3428; Chi^2=12.60, df=4 (p=0.013); I^2=68%
Test for overall effect Z=2.75 (p=0.006)

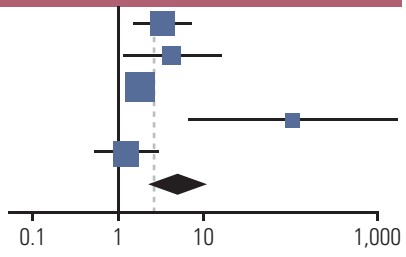


Fig. 4. Diagnostic yield of radial probe endobronchial ultrasound based on sonographic findings [28,31,38,42,45-47,52,53,55,61,62]. (A) Within vs. adjacent to. (B) Within vs. invisible. (C) Adjacent to vs. invisible. CI, confidence interval.

Table 4. Stratified meta-analysis for technologies

	No. of studies	No. of lesions	Pooled diagnostic yield (95% CI)	Heterogeneity			Overall effect	
				χ^2	I^2 (%)	p-value	χ^2	p-value
Combined adjunctive modalities				247.53	86	< 0.001	0.57	0.903
Flu+GS	13	2,194	0.73 (0.67-0.78)					
Flu+GS+VBN	10	3,274	0.73 (0.67-0.79)					
GS	7	1,799	0.72 (0.68-0.76)					
None	6	4,076	0.70 (0.62-0.76)					
Single adjunctive modality								
GS				380.46	89	< 0.001	0.20	0.658
Yes	31	8,196	0.72 (0.69-0.75)					
No	12	4,693	0.70 (0.62-0.78)					
Flu				377.65	89	< 0.001	0.01	0.929
Yes	26	6,215	0.73 (0.69-0.77)					
No	17	6,674	0.73 (0.69-0.76)					
VBN				381.04	89	< 0.001	0.85	0.356
Yes	16	4,724	0.74 (0.69-0.79)					
No	27	8,165	0.71 (0.68-0.74)					
Bronchoscopes				383.28	90	< 0.001	0.67	0.715
Standard	12	2,363	0.71 (0.66-0.75)	66.69	84	< 0.001		
Thin	22	7,648	0.73 (0.68-0.78)	310.39	93	< 0.001		
Ultrathin	4	462	0.73 (0.69-0.77)	2.06	0	0.559		
Biopsy method								
Cryobiopsy	6	419	0.78 (0.70-0.85)	14.69	66	0.012		

CI, confidence interval; Flu, fluoroscopy; GS, guide sheath; VBN, virtual bronchoscopic navigation.

≤ 2 cm compared to PLLs > 2 cm on RP-EBUS (0.49 vs. 0.90, p < 0.001) [64]. Furthermore, the previous meta-analysis also showed that the diagnostic yields of malignant PLLs and benign PLLs were 0.72 and 0.60, respectively (p=0.018) [63]. This might be associated with a higher visualization rate in malignant PLLs compared to benign PLLs on RP-EBUS (0.85 vs. 0.66, p=0.025), which could be attributed to distinct features of bronchial invasion and airway distortion in malignant PLLs compared to ill-defined borders with subtle changes in benign PLLs, such as inflammation [25,32]. Lastly, Huang et al. [64] showed that the diagnostic yield of peripheral and central PLLs were 0.50 and 0.94, respectively (p < 0.001), which might be attributed to differences in accessibility regarding RP-EBUS scanning and sampling. Therefore, to improve the diagnostic yield in PLLs with the above factors, our study highlights the need for newer technologies in the field of bronchoscopic TBB.

Regarding subgroup analysis of the frequently used adjunctive modalities, our study showed that the diagnostic yield of RP-EBUS with GS (0.72) was slightly higher than that of RP-EBUS alone (0.70), as well as that of the GS group (0.72) compared with that of the non-GS group (0.70). GS enables accurate, repeated sampling at the same lesion after fixation at PLLs, and also prevents excessive bleeding by wedging GS after TBB [6]. In a recent study by Oki et al. [60], GS showed significantly higher diagnostic yield compared to non-GS (0.55 vs. 0.74, p=0.033), where interaction was especially evident based on lobar locations for GS (upper, 0.63 vs. lower, 0.46; p=0.004) and non-GS (upper, 0.43 vs. others, 0.50; p=0.197) (p-interaction=0.003). However, due to the small diameter of GS (SG-200C; Olympus; external diameter, 1.95 mm) for thin bronchoscopes, the use of biopsy tools for larger samples such as standard forceps (1.8 or 1.9 mm) is limited. This can be overcome by additional TBB by the non-GS method following the GS method, which is beneficial, especially in part-solid or GGO nodules [37,50]. Furthermore, there is a technical issue such as kinking of GS, which interrupts the introduction of biopsy tools, which can be overcome by parallel alignment of the bronchoscope to GS and advancement of the bronchoscope to PLLs as close as possible [42].

For the diagnosis of PLLs, transthoracic needle aspiration/biopsy (TTNA/B) is another alternative method that shows a high diagnostic yield (> 90%) [4]. However, it is associated with a higher risk of complications, especially pneumothorax (any pneumothorax, 15%; pneumothorax requiring a chest tube, 6.6%) [4]. Therefore, TTNA/B could be recommended for PLLs, especially those with pleural contact, but should be

performed with caution considering the high complication rates, especially in patients with chronic obstructive pulmonary disease, pleural effusion, and interstitial lung disease [4]. The diagnostic yield of TBB with RP-EBUS may be relatively low, but recent advances in the field of bronchoscopy have improved it. Ultrathin bronchoscopy showed improved RP-EBUS positioning for PLLs, as well as an improved diagnostic yield of PLLs, even in peripheral locations from the hilum and upper lobes with an acute angle [15]. In a recent meta-analysis by Folch et al. [65] on ENB, RP-EBUS combined with ENB showed a pooled sensitivity of 0.80 (95% CI, 0.74 to 0.83) in PLLs suspected of lung cancer, which was higher than that with ENB alone (0.72; 95% CI, 0.66 to 0.76). Cryobiopsy is characterized by large tissue samples with good quality, which is associated with improved diagnostic yield, even in PLLs ≤ 2 cm and adjacent to findings on RP-EBUS [66,67]. Thus, TBB could be a reasonable modality in patients, especially those with a positive bronchus sign and a high risk of complications during TTNA/B.

Although our study includes recent publications from the past 10 years, we reported the diagnostic yield of PLLs as 0.72, which does not appear to be significantly different from the 0.71 reported in the subgroup analysis of RP-EBUS in a previous meta-analysis [7]. Possible explanations are as follows. First, our study included a higher proportion of studies with a low risk of bias (n=16/41, 0.39) compared to the previous meta-analysis (n=5/19 [one study not reported], 0.26) [7]. Studies with a lower risk of bias are known to be associated with a significantly lower diagnostic yield compared to those with a high risk of bias (0.66 vs. 0.71, p=0.018) [68]. Thus, the diagnostic yield in the previous meta-analysis might have been overestimated, thereby hampering the accurate evaluation of the diagnostic yield of RP-EBUS between the recent and past publications. Second, the included studies evaluating new modalities, such as cryobiopsy (seven studies), ENB (one study), and ultrathin bronchoscope (five studies), were relatively limited in number. A relatively small number of included studies on these factors might have led to the underestimation of the accurate diagnostic yield of PLLs.

Our study has some limitations. First, the quality of the included studies was inconsistent, which might be attributed to different designs, patient selection, and reference standards, including the radiological follow-up period. This might have led to heterogeneity in the diagnostic yield among the included studies. Second, the number of studies on GGO of lesion character was also relatively low, which could hamper accurate evaluation of overall diagnostic yield and RR compared with other variables of lesion character. Third, our study excluded articles not available in English, systematic reviews, and conference abstracts due to the possibility of low study quality. However, this could have an influence on publication bias. Fourth, our study could not collect data on the grade of bleeding due to the heterogeneity of the included studies, which limited analysis of clinically meaningful bleeding.

In conclusion, our study showed that TBB with RP-EBUS is an accurate diagnostic tool for diagnosing PLLs with good safety profiles, especially in PLLs with within orientation on RP-EBUS or the CT bronchus sign.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

An ethics statement is not applicable because this study is based exclusively on the published literature.

Author Contributions

Conceived and designed the analysis: Eom JS.
Collected the data: Kim SH, Chung HS, Kim I, Eom JS.
Contributed data or analysis tools: Kim SH, Kim J, Kim MH, Lee MK, Kim I, Eom JS.
Performed the analysis: Kim SH, Kim J, Kim MH, Lee MK, Kim I, Eom JS.
Wrote the paper: Kim SH, Eom JS.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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