Original Article

Efficacy and safety of cone-beam computed tomography-guided bronchoscopy for peripheral pulmonary lesions: a systematic review and meta-analysis

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Background: Cone-beam computed tomography (CBCT)-guided bronchoscopy is increasingly utilized for diagnosing peripheral pulmonary lesions (PPLs). We carried out the meta-analysis for assessing the efficacy and safety of CBCT-guided bronchoscopy for PPLs.

Methods: An extensive search in several databases was conducted to identify relevant articles. We evaluated the quality of studies with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. The pooled diagnostic yield (DY) and adverse event rate with the 95% confidence interval (CI) were computed. Subgroup analyses were performed according to additional use of navigation, use of radial endobronchial ultrasound (rEBUS), use of fixed or mobile CBCT, whether computed tomography (CT) spin was performed before biopsy to affirm tool-in-lesion, use of rapid onsite cytologic examination (ROSE), strictness of the definition of DY, and study design. Further analysis was performed to explore the association between odds of diagnosis with CBCT guided bronchoscopy and PPLs characteristics (>20 *vs.* ≤20 mm, non-upper lobe *vs.* upper lobe, with bronchus sign *vs.* without bronchus sign, and solid *vs.* non-solid) as well as sampling methods (forceps *vs.* fine needle aspiration, forceps *vs.* cryoprobe sampling). The pooled odds ratio (OR) and 95% CI were calculated. The significance level was set at 0.05. All analyses were performed by using meta package in R version 4.3.2.

Results: We included 23 studies involving 1,769 patients and 1,863 PPLs in the meta-analysis. The overall pooled DY of CBCT-guided bronchoscopy was 80.2% (95% CI: 76.0–84.1%). Subgroup analysis showed that the DY was highest when CBCT was used with robotic-assisted navigation bronchoscopy (pooled DY 87.5%; 95% CI: 81.5–92.4%), the DY was 78.9% (95% CI: 70.8–85.9%) when CBCT was used alone without other navigation techniques. Lesion size >20 mm, presence of bronchus sign and solid lesions were associated with significant increase in the odds of diagnosis with CBCT-guided bronchoscopy. Pooled adverse event rate was 2.3% (95% CI: 1.2–3.6%).

Conclusions: CBCT-guided bronchoscopy is a safe technique with high DY in diagnosing PPLs.

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Introduction

The detection rate of pulmonary lesions has risen significantly due to the ubiquitous utilization of low-dose computed tomography (CT) for lung cancer screening in recent years. The overall five-year survival rate for lung cancer is approximately 20% after being diagnosed (1,2). Early detection and diagnosis of malignant pulmonary lesions is crucial (3). The sensitivity of conventional transbronchial biopsy or transbronchial needle aspiration (TBNA) is 14–63% in diagnosing malignant lesions (4). CT-guided transthoracic biopsy or needle aspiration possesses high diagnostic yield (DY) (88–93%) but high adverse events rate (pneumothorax 16.8–25.9%) (5). Guided bronchoscopy has been increasingly used for the diagnosis of peripheral pulmonary lesions (PPLs) over the past decade. A meta-analysis showed that the DY for virtual bronchoscopy (VB) and electromagnetic navigation bronchoscopy (ENB) was 69.4% and 70.3%, respectively (6). Recently, cone-beam computed tomography (CBCT) have been utilized in the navigation of PPLs. CBCT provides comprehensive three-dimensional intra-procedural imaging and can be employed to affirm tool-in-lesion before biopsy, potentially influencing all stages of diagnostic bronchoscopy: navigation, verification and tissue obtaining (7).

The DY of CBCT-guided bronchoscopy was ranging from 45% to 93% (8-30). Nadig *et al.* reported that DY of lesions >20 mm [78.7%, 95% confidence interval (CI): 76.2–81.3%] was higher than that of lesions ≤20 mm (58.7%, 95% CI: 55.1–62.3%), and the DY of lesions with bronchus sign (78.6%, 95% CI: 75.2–82.0%) was higher than that of lesions without bronchus sign (51.2%, 95% CI: 45.0–57.4%) in guided bronchoscopy (31). Whether lesions >20 mm and bronchus sign can be used as predictors of successful CBCT-guided bronchoscopy was still not known. Therefore, we conducted a meta-analysis to assess the efficacy and safety of CBCT-guided bronchoscopy for PPL and tried to identify factors that predict higher DY of CBCT-guided bronchoscopy. We present this article in accordance with the PRISMA-DTA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1224/rc).

Highlight box

Key findings

- Cone-beam computed tomography (CBCT) guided bronchoscopy for peripheral pulmonary lesions (PPLs) is a safe technique with high diagnostic yield (DY), especially used with robotic-assisted navigation bronchoscopy (RAB). Lesion size >20 mm, presence of bronchus sign, and solid lesions may serve as predictors for higher DY in CBCT-guided bronchoscopy.

What is known and what is new?

- The DY of CBCT-guided bronchoscopy for PPLs was ranging from 45% to 93%. Previous study reported that DY of lesions >20 mm was higher than that of lesions ≤20 mm, and the DY of lesions with bronchus sign was higher than that of lesions without bronchus sign in guided bronchoscopy.
- Our meta-analysis showed that the overall pooled DY of CBCT-guided bronchoscopy was 80.2% [95% confidence internal (CI): 76.0–84.1%]. Subgroup analysis showed that the DY was highest when CBCT was used with RAB (pooled DY 87.5%; 95% CI: 81.5–92.4%). Lesion size >20 mm, presence of bronchus sign and solid lesions were associated with significant increase in the odds of diagnosis with CBCT-guided bronchoscopy. Pooled adverse event rate was 2.3% (95% CI: 1.2–3.6%).

What is the implication, and what should change now?

- CBCT-guided bronchoscopy is effective and safe in the diagnosis of PPLs. Lesion size >20 mm, presence of bronchus sign, and solid lesions may serve as predictors for higher DY in CBCT-guided bronchoscopy. However, more clinical studies are needed in the future to confirm or correct our results.

Methods

Search strategy

We searched PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chongqing VIP Information (VIP), and China Biology Medicine disc (CBM) databases to identify relevant articles (last search updated in April 2024). The

following terms were used in searching: (pulmonary lesions or pulmonary nodules or pulmonary neoplasms or lung lesions or lung carcinoma) and (bronchoscopy or bronchoscopes) and (C-arm cone-beam CT or cone-beam computed tomography or CBCT) and (diagnosis or diagnose or diagnostic). The search was not limited in terms of publication date or language. The references of the retrieved articles and reviews were manually examined in order to discover additional relevant publications.

Inclusion and exclusion criteria

We included studies which assessed diagnostic accuracy or DY of CBCT-guided bronchoscopy in patients with PPLs. If any of the following circumstances were present, studies would be excluded: abstracts or reviews; meta or editorial materials; case reports or studies with participants less than 10; animal studies; not relevant to bronchoscopy or CBCT or included central pulmonary lesions. We also excluded studies aimed at marking PPLs to assist in surgery. For overlapping studies, only studies with larger sample size or more complete data were involved.

Data extraction

Two researchers extracted the data and checked the accuracy of all data at a second review independently. Disagreements were discussed by both researchers and a consensus was reached on all the data. The following information was collected for each included study: type of study design, additional use of navigation, use of radial endobronchial ultrasound (rEBUS, which is not strict navigation techniques) (32), fixed or mobile CBCT, sampling methods, use of rapid onsite cytologic examination (ROSE), CT spin before biopsy to affirm tool-in-lesion, number of patients and lesions, lesion size, bronchus sign, location, lesion density, DY, and adverse events.

Quality assessment

Two investigators evaluated the quality of included literatures independently by means of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (33). Disagreements were resolved by discussion with a third researcher. We assessed 7 items in total, including 4 risks of bias (patient selection, index test, reference standard, flow and timing), as well as 3 applicability concerns (patient selection, index test, reference standard). Each item is classified as "low risk", "high risk" or "unclear risk".

Outcomes

DY was the primary outcome parameter. There were three commonly used definitions of DY in articles. All the three definitions consider that a bronchoscopic procedure being positive for malignancy is a true positive (TP). (I) Strict: only the procedures that have a specific benign (SPB) diagnosis (e.g., infection, granuloma) at the index are regarded as true negative (TN). DY is (TP + SPB) divided by the total number of procedures; (II) intermediate: nonspecific benign (NSB) outcomes (e.g., inflammation) are classified as TNs if confirmed to be benign in follow-up, which is termed NSBTN. DY is (TP + SPB + NSBTN) divided by the total number of procedures; (III) liberal: DY calculation allows for the addition of follow-up data for all cases which are negative for malignancy at index bronchoscopy (6,34).

Statistical analysis

The pooled DY and adverse event rate were estimated with 95% CI. The heterogeneity among studies was evaluated by Cochran's Q test and the inconsistency index (I^2). $P<0.1$ and $I^2>50\%$ indicates substantial heterogeneity in studies (35). We used random effects model to estimate pooled data when heterogeneity existed. Subgroup analyses were conducted according to additional use of navigation or rEBUS, fixed or mobile CBCT, use of ROSE, CT spin before biopsy to affirm tool-in-lesion, strictness of the definition of DY, and study design. Further analysis was performed to explore the association between odds of diagnosis with CBCT guided bronchoscopy and PPLs characteristics (>20 *vs.* ≤20 mm, non-upper lobe *vs.* upper lobe, with bronchus sign *vs.* without bronchus sign, and solid *vs.* non-solid) as well as sampling methods [forceps *vs.* fine needle aspiration (FNA), forceps *vs.* cryoprobe sampling]. The pooled odds ratio (OR) and 95% CI were calculated. The significance level was set at 0.05. All analyses were performed by using meta package in R version 4.3.2.

Results

Literature search

There were 684 records retrieved initially, and 448 related studies remained after deduplications removed. After

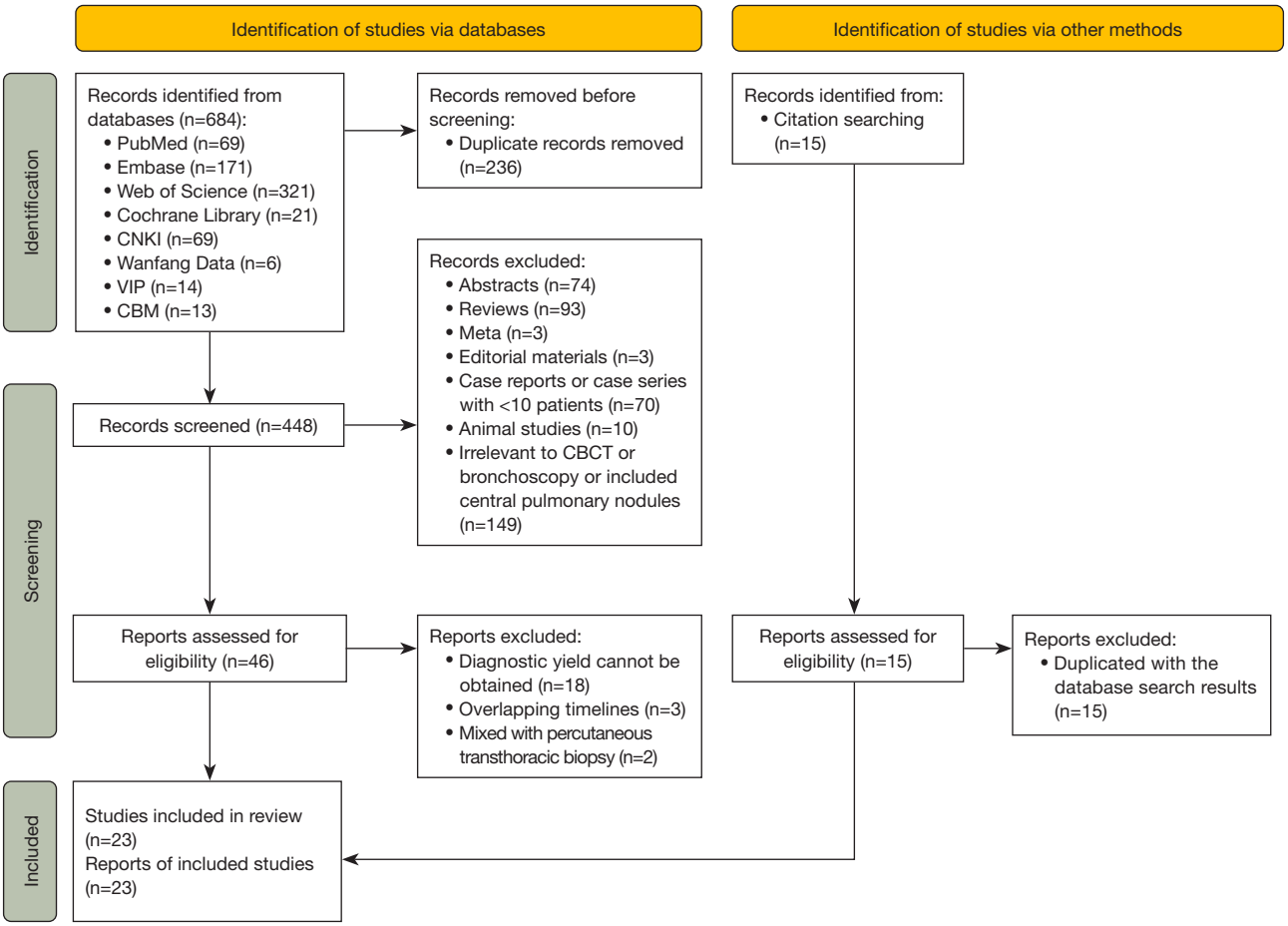

Figure 1 Flow diagram of included/excluded studies. CBCT, cone beam computed tomography; CBM, China Biology Medicine disc; CNKI, China National Knowledge Infrastructure; VIP, Chongqing VIP Information.

screening step by step, 23 studies were finally included (8-30). *Figure 1* presents the selection process.

Study characteristics

There were 1,769 patients with 1,863 PPLs from 23 studies included in the study. Ten studies (43.5%) were prospective and 13 studies (56.5%) were retrospective. Ten studies (43.5%) used CBCT as the sole navigation technology, 5 studies (21.7%) used CBCT and ENB, 4 studies (17.4%) used CBCT and VB, 3 studies (13.0%) used CBCT and robotic-assisted navigation bronchoscopy (RAB), and 1 study (4.3%) used CBCT and novel endobronchial augmented fluoroscopic navigation system (NEAFNS). Nineteen studies (82.6%) used fixed CBCT, and four studies (17.4%) used mobile CBCT. rEBUS was used in 13 studies (56.5%). Nine studies (39.1%) used strict definition of DY, 7 studies (30.4%) used intermediate definition, 5 studies (21.7%) used liberal definition, and 2 studies (8.7%) did not report the definition of DY. Except for one study that did not mention lesion size, the average/median lesion size in all other studies was less than 3 centimeters. Nine studies compared DY between lesions ≤20 and >20 mm. Six studies compared DY between upper and non-upper lobe lesions. Five studies compared DY between lesions with and without bronchus sign. Five studies compared DY between solid lesions and non-solid lesions. Four studies compared DY between forceps and FNA. Four studies compared DY between forceps and cryoprobe sampling. ROSE was utilized in thirteen studies (56.5%). Nine studies (39.1%) did not mention whether ROSE was used. In one study, 54.4% of patients underwent ROSE evaluation. Thirteen studies (56.5%) performed CT spin before biopsy to affirm tool-in-lesion. In four studies

(17.4%), only a subset of patients underwent CT spin before biopsy. Six studies (26.1%) did not mention whether CT spin was performed before biopsy to affirm tool-in-lesion. Detailed characteristics of individual study are showed in *Table 1*.

Quality assessment

We used QUADAS-2 tool to assess the risk of bias. Most studies had a high or indistinct risk of bias in the patient selection, index test, and reference standard domains. The majority (78.3%) exhibited a high risk of bias or applicability concerns in at least one domain. None of the studies possessed a low risk of bias in all domains. The failure to use an appropriate reference standard and different definitions of "navigational success" may have contributed to these results. *Table 2* presents QUADAS-2 assessment for each study.

Diagnostic performance

The overall DY of CBCT-guided bronchoscopy for PPLs was 80.2% (95% CI: 76.0–84.1%, I^2=75.0%, *Figure 2*). Random effects model was adopted to compute the pooled DY due to significant heterogeneity. And subgroup analyses were conducted according to additional use of navigation, use of fixed or mobile CBCT, use of rEBUS, use of ROSE, CT spin before biopsy to affirm tool-in-lesion, strictness of the definition of DY, and study design. The summary of the subgroup analyses is shown in *Table 3*. Subgroup analysis based on additional navigation techniques showed that DY was highest when CBCT was used with RAB (pooled DY 87.5%; 95% CI: 81.5–92.4%), whereas DY was 78.9% (95% CI: 70.8–85.9%) when CBCT was used alone. The pooled DY was 79.0% (95% CI: 73.5–84.0%) when CBCT was used with longer established navigation (ENB and VB). Only one study used CBCT with NEAFNS, the DY was 77.2%. Subgroup analysis based on the use of fixed or mobile CBCT showed that the DY of fixed CBCT-guided bronchoscopy was 81.2% (95% CI: 77.8–84.3%), while the DY of mobile CBCT-guided bronchoscopy was 76.7% (95% CI: 54.1–93.3%). Subgroup analysis was also conducted according to whether rEBUS was used. The pooled DY was 80.9% (95% CI: 77.1–84.4%) when CBCT was used with rEBUS, and the pooled DY was 79.8% (95% CI: 70.5–87.7%) when CBCT was not used with rEBUS. Subgroup analysis according to definition of DY indicated that the pooled DY was 78.9% (95% CI: 72.9–84.3%) in studies using strict definition. For studies using intermediate definition, the pooled DY was 81.3% (95% CI: 76.8–85.4%), while the pooled DY was 78.2% (95% CI: 62.2–90.7%) in studies using liberal definition. Two studies did not report the definition of DY, the pooled DY was 89.0% (95% CI: 78.1–96.5%). Subgroup analysis according to study design indicated that the pooled DY was 80.6% (95% CI: 76.5–84.4%) in retrospective studies, while the pooled DY was 80.3% (95% CI: 71.3–87.9%) in prospective studies. Subgroup analysis was conducted according to whether ROSE was used. The pooled DY was 82.3% (95% CI: 78.5–85.9%) when ROSE was used, and the pooled DY was 76.3% (95% CI: 66.5–84.8%) when ROSE was not mentioned in the article. In one study, 54.4% of patients underwent ROSE evaluation, the DY was 83.3%. Subgroup analysis based on whether CT spin was performed to affirm tool-in-lesion before biopsy showed that the pooled DY was 83.1% (95% CI: 78.6–87.2%) when CT spin was performed. The pooled DY was 80.8% (95% CI: 73.6–87.0%) when a subset of patients underwent CT spin before biopsy, and the pooled DY was 73.4% (95% CI: 62.1–83.3%) when it was not mentioned in the article.

As shown in *Table 4*, nine studies compared DY between lesions ≤20 mm and lesions >20 mm. Lesions >20 mm was associated with significant increase in the odds of diagnosis compared with lesions ≤20 mm (OR =3.01, P<0.001). Six studies compared the DY between upper and non-upper lobe lesions. No significant difference was observed in the odds of diagnosis between upper lode lesions and non-upper lobe lesions (OR =1.39, P=0.13). Five studies compared DY between lesions with and without bronchus sign. Lesions with bronchus sign was associated with significant increase in the odds of diagnosis compared with lesions without bronchus sign (OR =3.43, P=0.03). Five studies compared DY between solid lesions and non-solid lesions. Solid lesions were associated with significant increase in the odds of diagnosis compared with non-solid lesions (OR =2.28, P<0.001). Four studies compared DY between forceps and FNA. No significant difference was observed in the odds of diagnosis between forceps and FNA (OR =1.00, P=0.99). Four studies compared DY between forceps and cryoprobe sampling. No significant difference was observed in the odds of diagnosis between forceps and cryoprobe sampling (OR =0.94, P=0.85).

Safety analysis

Twelve studies reported pneumothorax (n=19 patients),

Table 1 Study characteristics

Study (first author, year)	Design	Total patients (No.)	Navigation	Use of rEBUS	Sampling methods	CT spin before biopsy[†]	Use of ROSE	Number of lesions	Lesion size (mm)	Bronchus sign (%)	Upper lobe (%)	Solid lesion (%)	Adverse events (No.)
Ali, 2019 (8)	Pro	40	CBCT + VB	No	Forceps	Yes	NR	40	20; 9–30 (median; range)	100.0	50.0	70.0	1
Benn, 2021 (9)	Pro	52	CBCT + RAB	No	Forceps (76%), TBNA	Yes	NR	59	21.9±11.6 (mean ± SD)	45.8	66.1	69.5	2
Bhadra, 2024a (10)	Retro	200	CBCT	Yes	Forceps, FNA, Cryo	Yes	Yes	222	17.3 (median)	71.2	62.2	NR	4
Bhadra, 2024b (11)	Retro	100	CBCT	Yes	NR	Yes	Yes	106	23.5±13.6 (mean ± SD)	67.9	NR	NR	2
Bowling, 2017 (12)	Retro	14	CBCT + ENB	No	Forceps, FNA	Yes (50%)	Yes	14	23.5 (mean)	0	57.1	85.7	1
Casal, 2018 (13)	Pro	20	CBCT	Yes	Forceps (65%), TBNA (85%)	Yes	Yes	20	21; 11–30 (median; range)	60.0	60.0	65.0	1
Emre, 2016 (14)	Pro	60	CBCT	No	NR	NR	NR	60	NR	NR	68.3	NR	0
Kawakita, 2021 (15)	Retro	79	CBCT + VB	No	Forceps	Yes	NR	79	21.0; 17.0–24.0 (median; IQR)	100.0	49.4	69.6	2
Kawakita, 2023 (16)	Pro	20	CBCT + VB	Yes	Forceps	Yes	NR	20	24.8; 10.0–46.0 (mean; range)	100.0	50.0	80.0	1
Kheir, 2021 (17)	Retro	31	CBCT + ENB	Yes	Forceps, FNA	Yes	NR	31	16.0; 12.6–25.5 (median; IQR)	45.2	67.7	61.3	2
Lin, 2022 (18)	Retro	115	CBCT	Yes	Forceps	Yes (partially)	Yes	115	24.0; 6.0–62.0 (mean; range)	82.6	55.7	76.5	9
Lin, 2024 (19)	Retro	198	CBCT	Yes	Forceps, Cryo	Yes (48%)	Yes	198	24.7; 8.3–65.3 (mean; range)	72.2	55.6	88.9	14
Liu, 2022 (20)	Pro	31	CBCT	Yes	Forceps	Yes	NR	31	24.8±13.9 (mean ± SD)	NR	NR	80.6	0
Meng, 2023 (21)	Retro	50	CBCT + RAB	No	Forceps, FNA, Cryo	Yes	Yes	52	21.0; 14.4–29.6 (median; IQR)	42.3	65.4	63.5	3
Pritchett, 2018 (22)	Retro	75	CBCT + ENB	No	Forceps, FNA	NR	Yes	92	16.0; 7.0–55.0 (median; range)	38.7	71.0	NR	3
Pritchett, 2021 (23)	Pro	53	CBCT + NEAFNS	No	Forceps, FNA	NR	Yes	57	18.0; 7.0–48.0 (median; range)	50.0	73.7	NR	0
Pritchett, 2024 (24)	Pro	52	CBCT	No	Forceps (60%), FNA (51%)	Yes (partially)	Yes	58	19.0; 7.0–48.0 (median; range)	42.4	57.6	NR	0
Reisenauer, 2022 (25)	Pro	30	CBCT + RAB	No	NR	Yes	Yes	30	17.5±6.8 (median ± SD)	40.0	60.0	76.7	0

Table 1 (*continued*)

Table 1 (*continued*)

Study (first author, year)	Design	Total patients (No.)	Navigation	Use of rEBUS	Sampling methods	CT spin before biopsy†	Use of ROSE	Number of lesions	Lesion size (mm)	Bronchus sign (%)	Upper lobe (%)	Solid lesion (%)	Adverse events (No.)
Reisenauer, 2022 (25)	Pro	30	CBCT + RAB	No	NR	Yes	Yes	30	17.5±6.8 (median ± SD)	40.0	60.0	76.7	0
Salahuddin, 2023 (26)	Retro	51	CBCT	Yes	Forceps (57%), TBNA (94%)	NR	Yes	51	26.0±13.0 (mean ± SD)	76.5	74.5	72.5	1
Sobieszczyk, 2018 (27)	Retro	22	CBCT + ENB	Yes	Forceps, FNA	NR	NR	22	21.0±9.8 (mean ± SD)	NR	68.2	NR	0
Verhoeven, 2021 (28)	Pro	195	CBCT + ENB	Yes	Forceps (89%), TBNA (73%), Cryo (40%)	NR	Yes	225	15; 5–65 (median; range)	64.4	61.8	77.8	NR
Yu, 2021 (29)	Retro	53	CBCT	Yes	Forceps	Yes	NR	53	28; 10–69 (median; range)	75.5	54.7	86.8	2
Zhang, 2024 (30)	Retro	228	CBCT + VB	Yes	NR	Yes	Yes (54.4%)	228	21.0; 15.5–29.0 (median; range)	87.7	49.1	61.4	4

†, CT spin performed to affirm tool-in-lesion before biopsy. CBCT, cone beam computed tomography; Cryo, cryoprobe sampling; CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; FNA, fine needle aspiration; IQR, interquartile range; NEAFNS, novel endobronchial augmented fluoroscopic navigation system; NR, not reported; Pro, prospective; RAB, robotic-assisted navigation bronchoscopy; rEBUS, radial endobronchial ultrasound; Retro, retrospective; ROSE, rapid onsite cytologic examination; SD, standard deviation; TBNA, transbronchial needle aspiration; VB, virtual bronchoscopy.

six studies reported bleeding (n=18 patients), three studies reported respiratory failure or hypoxia (n=3 patients), one study reported pneumomediastinum (n=1 patient), two studies reported fever (n=9 patients), one study reported broken scope (n=2 patients). No adverse events occurred in 6 studies. One study did not report whether adverse events occurred. The overall adverse event rate was 2.3% (95% CI: 1.2–3.6%, I^2=34.2%). The adverse event rate for fixed CBCT-guided bronchoscopy was 2.8% (95% CI: 1.6–4.3%, I^2=33.5%), whereas the adverse event rate for mobile CBCT-guided bronchoscopy was 0.2% (95% CI: 0.0–2.1%, I^2=0.0%).

Discussion

We performed the meta-analysis to assess the efficacy and safety of CBCT-guided bronchoscopy for PPLs. To our knowledge, this is the largest meta-analysis on this topic to date. The pooled DY of all included CBCT-guided bronchoscopy studies was 80.2%. Pooled adverse event rate was 2.3%.

In our meta-analysis, when CBCT-guided bronchoscopy was used alone, the pooled DY was 78.9%, which was comparable to the pooled DY of 78.2% reported by Kops *et al.* (6). In the study by Kops *et al.*, only five studies evaluated the efficacy of CBCT-guided bronchoscopy when used alone, whereas we included ten studies. Although they evaluated the DY of CBCT multimodality, however, the DY of CBCT used with different navigation was not provided. Our subgroup analysis showed that the pooled DY was higher when CBCT used with RAB (87.5%), whereas the pooled DY of CBCT combined with longer established navigation (VB and ENB) was 79.0%. ENB and VB are guided by preoperative CT images. In the operation, changes in lung volume or atelectasis may result in lower DY. Some platforms of RAB have incorporated a system to address CT to body divergence by incorporating a target-location-updating function utilizing digital tomography (36). We performed subgroup analysis based on the use of fixed or mobile CBCT, which, to our knowledge, is the first subgroup analysis based on the use of fixed or mobile CBCT. The result showed that the DY of fixed CBCT-guided bronchoscopy was 81.2% (95% CI: 77.8–84.3%), which was higher than that of mobile CBCT-guided bronchoscopy (76.7%, 95% CI: 54.1–93.3%). Mobile CBCT provides lower image quality and requires more time for image acquisition compared to fixed CBCT, which may explain this result. However, fixed CBCT is

Table 2 The QUADAS-2 assessment of all studies

Study (first author, year)	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ali, 2019 (8)	High	Low	Low	High	High	Low	Low
Benn, 2021 (9)	Low	Low	Low	High	Low	Low	Low
Bhadra, 2024a (10)	Low	Unclear	Low	High	Low	Low	Unclear
Bhadra, 2024b (11)	High	Low	Low	Low	High	Low	Low
Bowling, 2017 (12)	High	Low	Low	High	Low	Low	Low
Casal, 2018 (13)	Unclear	Low	Unclear	High	Low	Low	Low
Emre, 2016 (14)	Low	Unclear	Unclear	High	Low	Low	Low
Kawakita, 2021 (15)	High	Low	Low	Low	High	Low	Low
Kawakita, 2023 (16)	High	Low	Low	Low	High	Low	Low
Kheir, 2021 (17)	High	Unclear	Low	Low	Low	Unclear	Unclear
Lin, 2022 (18)	High	Low	Low	High	Low	Low	Low
Lin, 2024 (19)	Unclear	Unclear	Low	Low	Low	Low	Low
Liu, 2022 (20)	High	Unclear	Low	High	High	Low	Low
Meng, 2023 (21)	Low	Unclear	Low	Low	Low	Low	Low
Pritchett, 2018 (22)	High	Low	Low	High	Low	Low	Low
Pritchett, 2021 (23)	Unclear	Low	Unclear	High	Low	Low	Low
Pritchett, 2024 (24)	Low	Unclear	Low	Low	Low	Low	Low
Reisenauer, 2022 (25)	Low	Low	Low	High	Low	Low	Low
Salahuddin, 2023 (26)	Unclear	Low	Low	Low	Low	Low	Low
Sobieszczyk, 2018 (27)	High	Low	Low	High	Low	Low	Low
Verhoeven, 2021 (28)	Low	Low	Low	High	Low	Low	Low
Yu, 2021 (29)	Unclear	Low	Low	Low	Low	Low	Low
Zhang, 2024 (30)	Unclear	Unclear	Low	High	Low	Low	Low

QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2.

usually mounted on the floor or ceiling of interventional radiology or hybrid operating rooms, making them inaccessible to most bronchoscopists. Our subgroup analysis based on the use of rEBUS showed that the combined DY was similar regardless of whether rEBUS was used or not. rEBUS is not real-time guidance and is not considered as strict navigation technique in many articles (6,32). The radial probe must be removed from the bronchoscope before biopsy, the forceps may enter a bronchus other than the one initially identified (37). CBCT offers comprehensive three-dimensional intra-procedural imaging and can be utilized to confirm tool-in-lesion, potentially having an impact on all phases of diagnostic bronchoscopy: navigation, verification, and tissue acquisition (7). Similar DY was observed in prospective (80.3%, 95% CI: 71.3–87.9%) and retrospective (80.6%, 95% CI: 76.5–84.4%) subgroups. In a hypothetical cohort generated by Vachani *et al.*, DYs could have a variation of 13% to 22% depending on whether strict and liberal definitions were adopted (34). In our subgroup analysis, the DY of liberal group was 78.2% which was similar to the DY of strict group and intermediate group (78.9% and 81.3%). Similar to the study by Kops *et al.* (6), the DY did not vary greatly between strict, intermediate and liberal definitions. In addition to the difference in follow-

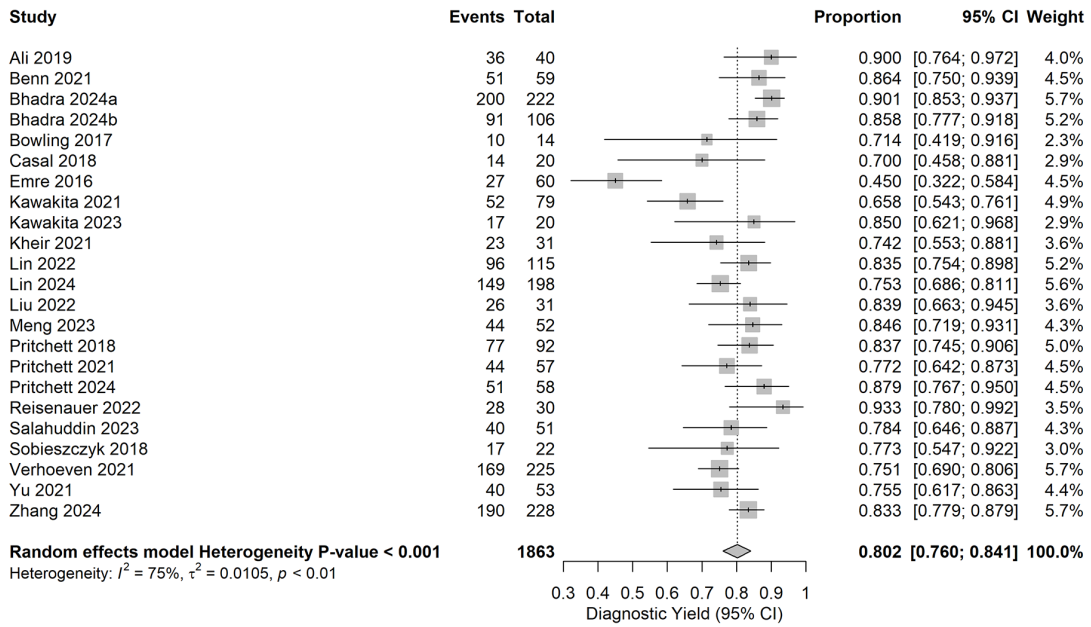

Figure 2 Forest plot of diagnostic yield of CBCT-guided bronchoscopy in PPLs. CBCT, cone beam computed tomography; CI, confidence interval; PPLs, peripheral pulmonary lesions.

up duration mentioned by Kops *et al.*, other confounding factors such as the combination of different navigation systems, characteristics of pulmonary lesions, whether ROSE was used, and operator experience may affect the DY. Recently, the official research statement of American Thoracic Society/American College of Chest Physicians recommended strict definition of DY (38). However, old studies have not taken these definitions into account. More future studies following this statement will be helpful in obtaining more accurate and standardized data.

Different characteristics of lesions can also affect the DY of CBCT-guided bronchoscopy. Consistent to the study by Nadig *et al.* (31), lesion size >20 mm and presence of bronchus sign were associated with significant increase in the odds of diagnosis (P<0.05). Besides, we conducted meta-analysis based on lesion density (solid *vs.* non-solid) and location (upper lobe *vs.* non-upper lobe) of nodules. Our results showed that solid lesions were associated with significant increase in the odds of diagnosis (P<0.05), while the odd of diagnosis was not significantly different between upper lobe and non-upper lobe lesions (P=0.13). Lesion size >20 mm, presence of bronchus sign, and solid lesions could serve as predictors for higher DY in CBCT-guided bronchoscopy. In addition, we evaluated sampling tools, confirmation of tool-in-lesion before biopsy, and ROSE. There was no significant difference in the odds of diagnosis between forceps and FNA (P=0.99), or between forceps and cryoprobe sampling (P=0.85). Since limited studies provide complete data, further studies are required to confirm or correct the result. When CT spin was performed before biopsy to confirm tool-in-lesion, the pooled DY (83.1%, 95% CI: 78.6–87.2%) was higher than that (73.4%, 95% CI: 62.1–83.3%) when it was not mentioned in the article. Similarly, when ROSE was used, the pooled DY (82.3%, 95% CI: 78.5–85.9%) was higher than that (76.3%, 95% CI: 66.5–84.8%) when ROSE was not mentioned in the article.

CBCT-guided bronchoscopy was a safe navigation technique, the adverse event rate was only 2.3% in all studies. It may be an excellent navigation option for patients with PPLs. Nevertheless, there are still certain limitations in our meta-analysis which should be considered. First, more clinical studies are needed in the future, especially those using strict definition of DY. Second, most studies had a high or unclear risk of bias in patient selection, index test, and reference standard domains. Third, operator experience may also affect the results. Most studies did not provide sufficient information on procedure time and radiation exposure, which was not analyzed in the meta-analysis. Finally, this meta-analysis only included published studies, and potential publication bias may affect the results.

Table 3 Summary of subgroup analyses for all studies

Subgroup	Number of studies	Number of lesions	Summary diagnostic yield (95% CI) (%)	P value
Navigation techniques				0.12[†]
CBCT	10	914	78.9 (70.8–85.9)	<0.001[‡]
CBCT + longer established navigation (ENB and VB)	9	751	79.0 (73.5–84.0)	0.02[‡]
CBCT + RAB	3	141	87.5 (81.5–92.4)	0.44[‡]
CBCT + NEAFNS	1	57	77.2 (65.5–87.1)	NA[‡]
rEBUS				0.81[†]
Yes	13	1,322	80.9 (77.1–84.4)	<0.001[‡]
No	10	541	79.8 (70.5–87.7)	<0.001[‡]
Definition of diagnostic yield				0.40[†]
Strict	9	801	78.9 (72.9–84.3)	<0.001[‡]
Intermediate	7	667	81.3 (76.8–85.4)	0.11[‡]
Liberal	5	334	78.2 (62.2–90.7)	<0.001[‡]
Not reported	2	61	89.0 (78.1–96.5)	0.23[‡]
Study design				0.94[†]
Prospective	10	600	80.3 (71.3–87.9)	<0.001[‡]
Retrospective	13	1,263	80.6 (76.5–84.4)	<0.001[‡]
CBCT systems				0.66[†]
Fixed	19	1,691	81.2 (77.8–84.3)	<0.001[‡]
Mobile	4	172	76.7 (54.1–93.3)	<0.001[‡]
ROSE				0.38[†]
Yes (100%)	13	1,240	82.3 (78.5–85.9)	<0.001[‡]
Yes (partially)	1	228	83.3 (78.2–87.8)	NA[‡]
NR	9	395	76.3 (66.5–84.8)	<0.001[‡]
CT spin before biopsy[§]				0.22[†]
Yes (100%)	13	971	83.1 (78.6–87.2)	<0.001[‡]
Yes (partially)	4	385	80.8 (73.6–87.0)	0.08[‡]
NR	6	507	73.4 (62.1–83.3)	<0.001[‡]

[†], P values for heterogeneity between groups; [‡], P values for intragroup heterogeneity; [§], CT spin performed to affirm tool-in-lesion before biopsy. 95% CI, 95% confidence interval; CBCT, cone beam computed tomography; ENB, electromagnetic navigation bronchoscopy; NA, not available; NEAFNS, novel endobronchial augmented fluoroscopic navigation system; NR, not reported; RAB, robotic-assisted navigation bronchoscopy; rEBUS, radial endobronchial ultrasound; ROSE, rapid onsite cytologic examination; VB, virtual bronchoscopy; CT, computed tomography.

Conclusions

This meta-analysis indicates that CBCT-guided bronchoscopy is a safe procedure with high DY, especially used with RAB. Lesion size >20 mm, presence of bronchus sign, and solid lesions are associated with significant increase in the odds of diagnosis, which may serve as predictors for higher DY in CBCT-guided bronchoscopy. More clinical studies, especially those using strict definition of DY, are needed in the future to confirm or correct our results.

Table 4 Summary of comparisons of lesions with different characteristics

Comparison	Number of studies	OR	95% CI	P value[†]	I^2
Size					
>20 *vs.* ≤20 mm	9	3.01	2.05–4.44	<0.001	0.0%
Lobes					
Non-upper *vs.* upper	6	1.39	0.91–2.12	0.13	11.6%
Bronchus sign					
Positive *vs.* negative	5	3.43	1.12–10.45	0.03	78.1%
Density					
Solid *vs.* non-solid	5	2.28	1.43–3.65	<0.001	38.7%
Sampling methods					
Forceps *vs.* FNA	4	1.00	0.37–2.70	0.99	89.6%
Forceps *vs.* Cryo	4	0.94	0.48–1.82	0.85	79.5%

[†], P values for test of association. CI, confidence interval; Cryo, cryoprobe sampling; FNA, fine needle aspiration; OR, odds ratio.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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