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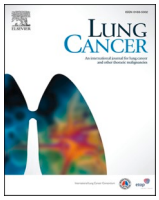

Diagnostic yield and safety of navigation bronchoscopy: A systematic review and meta-analysis

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ABSTRACT

Background: Navigation bronchoscopy has seen rapid development in the past decade in terms of new navigation techniques and multi-modality approaches utilizing different techniques and tools. This systematic review analyses the diagnostic yield and safety of navigation bronchoscopy for the diagnosis of peripheral pulmonary nodules suspected of lung cancer.

Methods: An extensive search was performed in Embase, Medline and Cochrane CENTRAL in May 2022. Eligible studies used cone-beam CT-guided navigation (CBCT), electromagnetic navigation (EMN), robotic navigation (RB) or virtual bronchoscopy (VB) as the primary navigation technique. Primary outcomes were diagnostic yield and adverse events. Quality of studies was assessed using QUADAS-2. Random effects *meta*-analysis was performed, with subgroup analyses for different navigation techniques, newer versus older techniques, nodule size, publication year, and strictness of diagnostic yield definition. Explorative analyses of subgroups reported by studies was performed for nodule size and bronchus sign.

Results: A total of 95 studies (n = 10,381 patients; n = 10,682 nodules) were included. The majority (n = 63; 66.3%) had high risk of bias or applicability concerns in at least one QUADAS-2 domain. Summary diagnostic yield was 70.9% (95%-CI 68.4%-73.2%). Overall pneumothorax rate was 2.5%. Newer navigation techniques using advanced imaging and/or robotics (CBCT, RB, tomosynthesis guided EMN; n = 24 studies) had a statistically significant higher diagnostic yield compared to longer established techniques (EMN, VB; n = 82 studies): 77.5% (95%-CI 74.7%-80.1%) vs 68.8% (95%-CI 65.9%-71.6%) ($p < 0.001$). Explorative subgroup analyses showed that larger nodule size and bronchus sign presence were associated with a statistically significant higher diagnostic yield. Other subgroup analyses showed no significant differences.

Conclusion: Navigation bronchoscopy is a safe procedure, with the potential for high diagnostic yield, in particular using newer techniques such as RB, CBCT and tomosynthesis-guided EMN. Studies showed a large amount of heterogeneity, making comparisons difficult. Standardized definitions for outcomes with relevant clinical context will improve future comparability.

Abbreviations: 95%-CI, 95% confidence interval; 95%-PI, 95% prediction interval; AF, augmented fluoroscopy; CBCT, cone beam computed tomography; CT-fl, computed tomography fluoroscopy; CBCT-NB, cone beam computed tomography guided navigation bronchoscopy; EMN, electromagnetic navigation; fEMN, tomosynthesis guided electromagnetic navigation; Fl, fluoroscopy; GGO, ground glass opacity; GS, guide sheath; IQR, interquartile range; NR, not reported; Pr, prospective; PS, Part solid; RB, robot assisted bronchoscopy; rEBUS, radial endobronchial ultrasound; Re, retrospective; S, solid; SD, standard deviation; SEM, standard error of the mean; TB, Thin bronchoscope; UTB, ultrathin bronchoscope; VB, virtual bronchoscopy.

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1. Introduction

Peripheral pulmonary nodules are a common finding and often present a diagnostic challenge. The increased resolution of CT, the increased use of CT for a variety of indications (for both pulmonary and non-pulmonary disease), and the implementation of CT screening programs have led to an increase in their incidence [1]. When these pulmonary nodules are suspected to be malignant, as determined by prediction models utilizing patient and nodule characteristics, image-guided minimally invasive biopsy is indicated [2].

Navigation bronchoscopy is a frequently performed method to sample peripheral pulmonary nodules. Conventionally, it conveyed fluoroscopy-guided transbronchial biopsy by a standard flexible bronchoscope, with a limited diagnostic yield of around 37% [3]. To improve diagnostic yield, new technologies were developed. Electromagnetic navigation (EMN) and virtual bronchoscopy (VB) were primarily aimed at optimizing navigation. Ultrathin bronchoscopy (UTB) was often utilized in combination with VB and facilitated the navigation process but also offered direct visualization. Radial endobronchial ultrasound (rEBUS) did not offer any additional navigation possibilities but could confirm correct positioning. In a *meta*-analysis, Wang-Memoli et al. already showed in 2012 that these techniques were able to obtain a navigation success of 95% and a diagnostic yield of 70% [4], illustrating that with navigation assistance considerable improvements in diagnostic yield could be achieved, but there was still a discrepancy between reaching the target and obtaining a diagnosis.

Newer technologies integrating advanced imaging support have aimed to reduce this gap. Pre-existing techniques such as cone-beam CT are now being applied for navigation bronchoscopy (CBCT-NB) and can be used as a navigation technique but also gives precise positioning confirmation [5]. The implementation of tomosynthesis techniques in EMN aims at reducing CT to body divergence resulting in more accurate sampling (fEMN) [6]. Robot-assisted bronchoscopy (RB), aims at further optimizing navigation accuracy, positioning, and tissue sampling [7]. The combined use of these techniques might further increase diagnostic yield [5].

There is a growing body of literature on these different techniques, with unfortunately a large amount of heterogeneity in the definitions used for outcomes such as diagnostic yield. This makes it difficult to compare results across studies, especially because it is not always clearly reported which definition researchers applied. A recent study has increased interest in creating more uniform definitions to improve the comparability of different studies [8].

Given the development of new technologies and their increased combined use in the last decade, it is important to assess if diagnostic yield for pulmonary nodule evaluation has improved while applying the newly proposed definitions for reporting this outcome. This systematic review evaluates the diagnostic yield and safety of navigation bronchoscopy in the diagnostic work-up of patients with peripheral pulmonary nodules suspected of lung cancer.

2. Methods

2.1. Search strategy and study selection

Using the search strategies in supplemental Table S1, we searched Embase, Medline, and Cochrane Central Register of Controlled Trials (CENTRAL) for primary diagnostic studies published from inception to the 6th of May 2022. Subsequently, two researchers independently assessed titles and abstracts of all retrieved records for potential relevance and disagreements were discussed. Full texts of potentially eligible studies were independently assessed for final inclusion by both researchers. Again, discrepancies were discussed until a consensus was reached. Additionally, previously published systematic reviews were checked for missed studies, which were included for further assessment if found (n = 14) [9–11]. We included primary studies that evaluated the diagnostic accuracy or diagnostic yield of EMN, VB, CBCT, or RB as the primary navigation tool in patients with peripheral pulmonary nodules suspected of lung cancer. We excluded studies focusing on other navigation techniques as the sole tool under investigation, such as (augmented) fluoroscopy (AF), UTB,and rEBUS. These tools assist in the navigation process but are not a strict navigation technique itself. However, we included studies performed in a multi-modality setting, where a combination of navigation techniques (e.g., CBCT with EMN or VB with UTB) was used. We excluded studies with average or median pulmonary nodule sizes larger than 3 cm (limiting lesion size to T1 tumors[12]), or studies explicitly reporting that lesions could be reached with traditional bronchoscopy. We also excluded studies with tumor marking as research aim (e.g. marking of a nodule with a radiopaque marker with the aim to assist in surgery), studies in languages other than English, or studies including <10 study participants.

2.2. Data extraction

For every included study, one researcher extracted the following data, which was checked by a second researcher: type of data collection (prospective versus retrospective), number of patients and lesions included, size of pulmonary nodules, navigation technique, additional navigation tools used, sampling tools used, if a structured sampling strategy was described, bronchus sign, nodule location, diagnostic yield, and adverse events. If a study compared two different navigation techniques (e.g. VB vs EMN), data from the subgroups were extracted separately. If a study compared aspects of a procedure (e.g. VB with guide sheath vs. VB with UTB) data were extracted separately. In cases where a study had more than one study arm, but only one of those arms fulfilled the inclusion criteria, only this study arm was included.

2.3. Study quality assessment

Two researchers independently used the QUADAS-2 tool [13] to assess risk of bias and applicability concerns of included studies. Disagreements were solved through discussion. No applicability concerns were expected for the 'reference standard' domain and were considered not applicable for all studies. If a subcategory of patients was excluded or exclusively included from the study, risk of bias and applicability concerns for the 'patient selection' domain were considered high. If insufficient information was provided on patient selection, risk of bias for this domain was considered unclear. In the 'flow and timing' domain, a separate signaling question was added for the adverse events outcome. This domain was considered at low risk of bias if structural monitoring and reporting of adverse events were described. However, if this was only described on indication, this domain was considered at high risk of bias. Risk of bias in the 'flow and timing' domain for diagnostic yield was considered high if follow-up duration was not described or was < 1 year.

2.4. Outcomes

The primary outcome parameter was diagnostic yield, defined as the number of nodules in which the procedure was diagnostic (either malignant or non-malignant), relative to the total number of attempted navigation procedures. If studies excluded patients (e.g. loss to follow-up), these were manually added to the total number of included nodules, and diagnostic yield was recalculated. A variety of definitions for diagnostic yield with differing strictness are used in the medical

literature on navigation bronchoscopy, and included studies were categorized based on the three categories recently proposed by Vachani et al. [8]:

(1) Strict: diagnosis can only be made at the moment of the procedure. Diagnostic outcomes are malignant or specific benign diagnoses (e.g., granulomatous inflammation). All other findings are categorized as non-diagnostic.
(2) Intermediate: as strict definition, but also non-specific benign outcomes (e.g. non-specific inflammation) are considered diagnostic if confirmed benign with follow-up.
(3) Liberal: as intermediate, but also nondiagnostic samples (e.g., alveolar tissue and blood) are considered diagnostic if confirmed benign with follow-up.

The definition was classified as not reported (fourth category) if insufficient explanation was given on how diagnostic yield was calculated or if mandatory follow-up to confirm non-specific benign outcomes was not specified and could not be deduced from the study report.

2.5. Data analysis

Meta-analysis was performed using a random effects model. Diagnostic yield was transformed using a logit transformation, then pooled and transformed back. The results were aggregated in a forest plot with 95% confidence intervals (95%-CI), using the Hartung-Knapp-Sidik-Jonkman correction. A 95% prediction interval (95%-PI) was calculated for the summary diagnostic yield. The 95%-PI provides a 95% probability of what the diagnostic yield of a new (future) study will be and is therefore a measure to assess the variability across included studies. A generalized mixed linear model was used to perform subgroup analyses. Subgroup analyses were performed following two strategies.

1) Subgroup analysis was performed by dividing all included studies based on the following criteria: different navigation techniques (EMN vs. VB vs. RB vs. CBCT), longer established and more recent techniques (EMN and VB vs. CBCT, RB, and fEMN), strictness of definition of diagnostic yield (strict vs. intermediate vs. liberal vs. not reported), median/mean nodule size (<20 mm vs. $\geq$ 20 mm), and year of publication (before 2012 vs. after 2012, to provide a comparison with a previous *meta*-analysis by Wang-Memoli et al. [4]). For all EMN studies, an additional subgroup analysis was performed (no additional navigation tools vs. additional navigation tools vs. fEMN).
2) Additional explorative analyses were performed for studies that specifically reported on diagnostic yield for subgroups based on nodule size $<$ 20 mm vs. $\geq$ 20 mm or bronchus sign presence (negative vs. positive). These subgroups of individual studies were separately pooled, and the overall summary results were compared. In this analysis, only studies that reported results for both the subgroups (i.e. both for patients with nodules $<$ 20 mm and $\geq$ 20 mm, or both for patients with a negative bronchus sign and a positive bronchus sign) were included, while studies that only reported results for a single subgroup (e.g. only for patients with nodules $<$ 20 mm, or with a negative bronchus sign) were excluded.

3. Results

3.1. Study selection

The literature search retrieved 3,297 papers, of which 2,361 remained after deduplication. After screening titles and abstracts, 274 papers remained for full-text assessment, of which 95 fulfilled the inclusion criteria. Fig. 1 shows the study selection process in detail.

3.2. Study characteristics

A total of 95 studies were included, from which data of 10,381 patients with a total of 10,682 lesions were extracted. Fifty studies (52.6%) reported to have collected data prospectively. Eleven studies had two study arms included separately. The median sample size was 61 patients (IQR 35–111) with 61 lesions (IQR 35–109). In 82 study arms (77.4%) additional navigation tools such as rEBUS, fluoroscopy, and (ultra)thin bronchoscopes were used. Thirty studies (or study arms) versus 70 studies (or study arms) had median/mean nodule sizes of $<$ 20 mm and $\geq$ 20 mm, respectively. Only categorical data on nodule size was presented in 6 studies. The median percentage of lesions with bronchus sign per study was 66.9% (range 0%-100%, IQR 51.1%-81.5%), with 44 studies (study arms) not reporting on bronchus sign. The median percentage of nodules located in the upper lobes per study was 57% (IQR 50.0%-62.4%), with 13 studies not reporting on lesion location. Median percentage of a solid nodule aspect was per study 79.3% (range 0%-100%, IQR 70.0%-89.2%) with 57 study(arms) not reporting on the lesion aspect. Most studies reported how samples were collected (e.g. brush and forceps were used), but only 43 studies reported a structured sampling strategy. A multimodality sampling strategy was employed in 31 of these studies and a single modality sampling strategy in 12 studies. Individual study characteristics are presented in Table 1.

3.3. Quality assessment

A detailed QUADAS-2 assessment for individual studies is presented in supplemental Table S2. A high risk of bias or applicability concerns in at least one domain was present in 63 studies (66.3%). Most risk of bias was found in the 'flow and timing' for diagnostic yield (n = 47, 49.5%). Risk of bias for the 'flow and timing' domain for adverse events was unclear in the majority of studies (n = 65, 68.4%), because monitoring and registration of adverse events was seldomly described in a systematic manner. Six studies (6.3%) had a low risk of bias in all domains, and an additional 12 studies (12.6%) had a low risk of bias in all domains aside from the 'flow & timing' domain for adverse events.

3.4. Diagnostic yield

Summary diagnostic yield after *meta*-analysis was 70.9% (95%-CI 68.4%-73.2% and 95%-PI 48.1–86.5%) (Fig. 2, Table 2). Summary results for subgroup analyses are reported in Table 2, with detailed results in supplemental Figs. S1–S5. Subgroup analysis based on navigation technique showed that diagnostic yield appears highest when CBCT is utilized (as sole primary navigation technique or in combination with other navigation techniques such as RB, EMN or VB): 77.3% (95%-CI 72.8–81.3% and 95%-PI 66.3%-85.5%). However, no statistically significant difference between navigation techniques was found (Fig. 2). When distinguishing recently developed navigation techniques (CBCT, RB and fEMN) and longer established navigation techniques (EMN and VB), a statistically significant difference was observed with a diagnostic yield of 77.5 (95%-CI 74.7–80.1% and 95%-PI 69.5%-83.9%) compared to 68.8% (95%-CI 65.9%-71.6% and 95%-PI 45.5%-85.4%), respectively ($p < 0.001$) (supplemental Fig. S1).

Subgroup analyses for strictness of definition of diagnostic yield, median nodule size and publication year (before and after 2012) did not show significant differences (Table 2 and supplemental Figs. S2–S4), and this also applied to further subgroup analysis of EMN studies (supplemental Fig. S5). However, the explorative analyses of the pooled

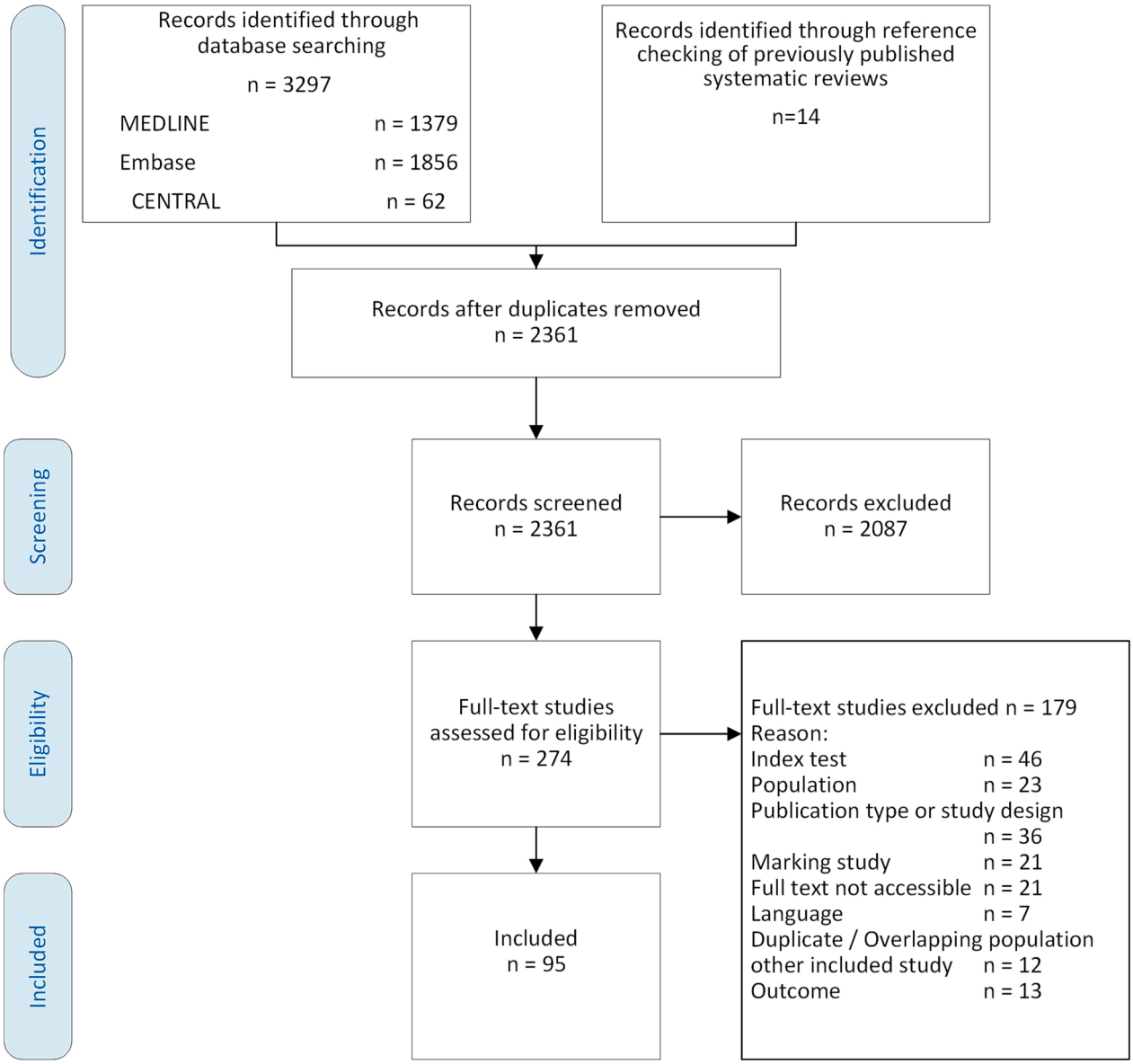

Fig. 1. Flowchart describing the study selection process.

Table 1
Study characteristics.

Author + year	Guidance technique	Additional navigation tools	Study design	Size of lesion (mm)	Bronchus sign (%)	Upper lobe (%)	Solid lesion (%)
Casal 2018 [14]	CBCT	Fl, rE, UTB	Pr	21; 11–30 (median; range)	60%	60%	65%
Hohenforst-Schmidt 2014 [15]	CBCT	Fl	Pr	NR	NR	NR	NR
Lin 2022 [16]	CBCT	Fl, rE	Re	24; 6–62 (median; range)	82.6%	55.6%	76.5%
Verhoeven 2021 [17]	CBCT	Fl, GS, rE	Pr	13; 5–65 (median; range)	61%	61%	NR
Yu 2021 [18]	CBCT	Fl, GS, rE	Re	28; 10–69 (median; range)	75.5%	5.8%	86.8%
Bowling 2017 [19]	CBCT + EMN	Fl	Re	23.5 (mean)	0%	57.1%	85.7%
Kheir 2021 [20]	CBCT + EMN	Fl, rE	Re	16; 12.6–25.5 (median; IQR)	45.2%	67.7%	61.3%
Pritchett 2018 [21]	CBCT + EMN	AF	Re	16; 7–55 (median; range)	39%	71%	NR
Sobieszczyk 2018 [22]	CBCT + EMN	Fl, rE	Re	21 ± 10 (mean ± SD)	NR	68.2%	NR
Verhoeven 2021 [17]	CBCT + EMN	Fl, GS, rE	Pr	13; 5–65 (median; range)	61%	61%	NR
Katsis 2021 [23]	CBCT + fEMN	AF, rE	Pr	12.8 ± 3.8 (mean ± SD)	17.2%	62%	NR

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Table 1 (*continued*)

Author + year	Guidance technique	Additional navigation tools	Study design	Size of lesion (mm)	Bronchus sign (%)	Upper lobe (%)	Solid lesion (%)
Benn 2021 [24]	CBCT + RB	CBCT	Pr	21.9 ± 11.6 (mean ± SD)	54%	66%	70%
Reisenauer 2022 [25]	CBCT + RB	Fl, rE	Pr	17.5 ± 6.8 (median ± SD)	40%	60%	76.7%
Ali 2019 [26]	CBCT + VB	Fl	Pr	20; 9–30 (median; range)	100%	50%	70%
Kawakita 2021 [27]	CBCT + VB	Fl	Re	21; 17 – 24 (median; IQR)	100%	49.3%	69.6%
Aftab 2022 [28]	EMN	None	Re	24.5 (mean)	52%	60%	NR
Al-Jaghbeer 2016 [29]	EMN	Fl	Re	26 (mean)	60%	59.2%	94%
Andersen 2020 [30]	EMN	None	Pr	21 ± 11 (mean ± SD)	37.6%	64.2%	100%
Belanger 2019 [31]	EMN	None	Re	20; 15–29 (median; IQR)	63.4%	62.4%	89.2%
Bellinger 2021 [32]	EMN	Fl, rE	Re	24.2 ± 12.1 (mean ± SD)	93%	48.9%	56.1%
Bhatt 2018 [33]	EMN	rE	Re	22 ± 9 (mean ± SD)	NR	58%	86.7%
Bowling 2015 [34]	EMN	Fl	Re	NR	NR	NR	NR
Chee 2013 [35]	EMN	rE	Pr	22 ± 10 (mean ± SD)	20.0%	74%	NR
Cheng 2019 [36]	EMN	Fl, rE	Re	26; 20–37 (median; IQR)	84%	26.3%	86%
Eberhardt 2007 [37]	EMN	None	Pr	24 ± 8 (mean ± SD)	NR	56.5%	NR
Eberhardt 2007 [38]	EMN	rE	Pr	24 ± 5 (mean ± SD)	NR	57%	NR
Eberhardt 2007 [38]	EMN	None	Pr	28.9 ± 8 (mean ± SD)	NR	51%	NR
Eberhardt 2010 [39]	EMN	rE	Pr	23.3 ± 4.4 (mean ± SD)	NR	60%	NR
Flenaugh 2016 [40]	EMN	rE	Re	22.1 ± 9.8 (mean ± SD)	NR	49.3%	NR
Folch 2022[b] [41,42]	EMN	CBCT, Fl, rE	Pr	20; 14–29 (median IQR)	50.8%	58.1%	93.8%
Garwood 2016 [43]	EMN	rE	Re	22.7 ± 16.0 (mean ± SD)	NR	58.7%	NR
Gildea 2006 [44]	EMN	None	Pr	22.8 ± 12.6 (mean ± SD)	NR	62.5%	NR
Gu 2017 [45]	EMN	Fl, GS	Re	19 ± 6.2 (mean ± SD)	100%	68%	NR
Jensen 2012 [46]	EMN	None	Re	26 ± 14 (mean ± SD)	NR	64.1%	NR
Kheir 2021 [20]	EMN	Fl, rE	Re	21.5; 16–27 (median; IQR)	41.9%	64.5%	58.1%
Lamprecht 2012 [47]	EMN	None	Pr	27.1 ± 1.3 (mean ± SD)	NR	50.9%	NR
Loo 2014 [48]	EMN	None	Re	26; 3–80 (mean; range)	NR	NR	NR
Ma 2020 [49]	EMN	GS, rE	Re	20.9 ± 9.6 (mean ± SD)	26.9%	NR	NR
Mahajan 2011 [50]	EMN	Fl	Re	20 ± 13 (mean ± SD)	NR	57.8%	NR
Makris 2007 [51]	EMN	None	Pr	23.5 ± 1.5 (mean ± SEM)	NR	NR	NR
Mukherjee 2017 [52]	EMN	Fl	Re	18 ± 10 (mean ± SD)	NR	54.9%	NR
Odronic 2014 [53]	EMN	rE	Re	27; 7 – 71 (mean; range)	NR	63.2%	NR
Oh 2021 [54]	EMN	None	Pr	25.2 ± 7.8 (mean ± SD)	66.7%	56.7%	73.3%
Oh 2021 [55]	EMN	None	Re	27.9 ± 13.7 (mean ± SD)	71%	49%	55%
Ost 2016 [56]	EMN	Fl, rE	Pr	NR	NR	58.7%	95.4%
Patrucco 2018 [57]	EMN	Fl	Re	24.6 ± 10.1 (mean ± SD)	61%	80%	91%
Patrucco 2021 [58]	EMN	None	Re	28.9 ± 14.3 (mean ± SD)	28.2%	77.8%	79.6%
Pearlstein 2012 [59]	EMN	None	Re	28; 8–100 (median; range)	NR	NR	NR
Sato 2018[a] [60]	EMN	None	Re	15.3 ± 5.5 (mean ± SD)	NR	45.7%	NR
Seijo 2010 [61]	EMN	None	Pr	25; 15–35 (median; IQR)	74%	61%	NR
Steinfort 2016 [62]	EMN	rE	Pr	22.8 ± 12.4 (mean ± SD)	23.2%	NR	NR
Stenger 2020 [63]	EMN	None	Re	15.5 ± 4 (mean ± SD)	NR	67.9%	NR
Sun 2017 [64]	EMN	Fl, rE	Pr	21.1 ± 5.3 (mean ± SD)	100%	50%	NR
Taton 2018 [65]	EMN	Fl, rE	Pr	16 ± 3 (mean ± SD)	34.3%	46.9%	96.9%
Toennesen 2021 [66]	EMN	Fl, rE	Pr	25; 2–74 (median; range)	77.2%	62.3%	NR
Wang 2021 [67]	EMN	rE	Re	23.3 ± 10.1 (mean ± SD)	NR	59.5%	62.2%
Wilson 2007 [68]	EMN	Fl	Re	21 ± 14 (mean ± SD)	NR	50.4%	NR
Yutaka 2022 [69]	EMN	Fl, rE	Re	19.4 ± 9 (mean ± SD)	58%	47%	NR
Avasarala 2022 [70]	fEMN	Fl, rE	Pr	20.1; 12–30.3 (median; IQR)	36%	47%	80%
Dunn 2022 [71]	fEMN	Fl, rE	Re	20; 8–40 (median; range)	NR	69.2%	NR
Katsis 2021 [72]	fEMN	AF, rE	Re	19 ± 11 (mean ± SD)	24%	53.2%	89.3%
Agrawal 2022 [73]	RB	Fl, rE	Re	24; 13–30 (median; IQR)	75%	54.8%	57.3%
Chaddha 2019 [74]	RB	rE	Re	25.0 ± 15 (mean ± SD)	63.5%	51.5%	74.9%
Chen 2021 [75]	RB	Fl, rE	Pr	23.2 ± 10.8 (mean ± SD)	59.3%	57.4%	NR
Ekeke 2022 [76]	RB	None	Re	NR	84%	64%	NR
Fielding 2019 [77]	RB	Fl, rE	Pr	14.8 ± 4.5 (mean ± SD)	58.6%	68.9%	79.3%
Kalchiem-Dekel 2022 [78]	RB	Fl, rE	Pr	18; 13–27 (median; IQR)	62.9%	59.1%	73%
Asahina 2005 [79]	VB	Fl, GS, rE	Pr	18.9 ± 6.5 (mean ± SD)	NR	60%	NR
Asano 2006 [80]	VB	Fl, UTB, CT	Pr	18.5; 6–30 (median; range)	NR	55.2%	NR
Asano 2008 [81]	VB	Fl, GS, rE, UTB	Pr	21; 10–53.3 (median)	NR	65.7%	NR
Asano 2013 [82]	VB	Fl, UTB	Pr	17.5; 7.5 – 29.0 (median; range)	NR	51.5%	NR
Bae 2020 [83]	VB	GS, rE	Pr	28.43 ± 18.20 (mean ± SD)	6%	54%	75%
Bo 2019 [84]	VB	GS, rE	Pr	21.8 ± 4.8 (mean ± SD)	NR	52.2%	NR
Diez-Ferrer 2019 [85]	VB	Fl	Pr	23 ± 13 (mean ± SD)	67%	NR	NR
Eberhardt 2010 [86]	VB	UTB	Pr	28 ± 7 (mean ± SD)	NR	NR	NR
Fukusumi 2016 [87]	VB	rE, GS	Pr	20.2 (mean)	NR	49.9%	NR
Haidong 2017 [88]	VB	Fl, rE, GS	Re	24 ± 13 (mean ± SD)	NR	45.8%	NR
Ikezawa 2017 [89]	VB	Fl, GS, rE	Re	23 ± 8 (mean ± SD)	76%	66.9%	0%
Ishida 2011 [90]	VB	rE	Pr	18; 9.5–30.0 (median; range)	NR	55.9%	NR
Iwano 2011 [91]	VB	Fl	Re	27.5; 12–58 (median; range)	NR	65.5%	71.3%
Kato 2018 [92]	VB	CT-Fl	Pr	13.3 ± 3.9 (mean ± SD)	100%	NR	NR
Kawakita 2021 [27]	VB	CT-Fl	Re	19; 15 – 23.5 (median; IQR)	100%	51.6%	76.3%

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Table 1 (*continued*)

Author + year	Guidance technique	Additional navigation tools	Study design	Size of lesion (mm)	Bronchus sign (%)	Upper lobe (%)	Solid lesion (%)
Li 2020 [93]	VB	GS, rE	Pr	24; 7–68 (median; range)	75.2%	60.5%	NR
Maekura 2017 [94]	VB	GS, Fl, rE	Pr	22; 10–29 (median; range)	NR	64.4%	NR
Matsumoto 2017 [95]	VB	rE, GS	Re	NR	NR	45.5%	72.7%
Miyoshi 2018 [96]	VB	Fl	Re	NR	71.4%	64.3%	91.1%
Nakai 2017 [97]	VB	Fl, GS, rE	Re	17.9 ± 5.3 (mean ± SD)	80%	48.6%	0%
Nakai 2017 [97]	VB	Fl, GS, rE	Re	19.6 ± 5.8 (mean ± SD)	82.1%	46.2%	0%
Oki 2015 [98]	VB	Fl, rE, UTB	Pr	19; 8.8–30.0 (median; range)	77%	45%	77%
Oki 2015 [98]	VB	Fl, rE, GS, TB	Pr	19.4; 7–30 (median; range)	82%	58%	81%
Oki 2019 [99]	VB	Fl, rE, UTB	Pr	19.1; 7.4–29.9 (median; range)	74.3%	54.2%	85.5%
Oki 2019 [99]	VB	Fl, rE, TB	Pr	18.9; 7.7–30 (median; range)	73.4%	48%	83.6%
Oki 2021 [100]	VB	Fl, TB, GS	Pr	20; 6.7–30 (median; range)	80%	53.3%	86.7%
Oki 2021 [100]	VB	Fl, rE, UTB	Pr	19; 6.9–30 (median; range)	87%	54.7%	85.9%
Oshige 2011 [101]	VB	rE, GS	Pr	28.4 ± 2.2 (mean ± SD)	NR	40.4%	NR
Shinagawa 2007 [102]	VB	CT-Fl, UTB	Re	13.6 (mean)	48%	49%	NR
Sun 2022 [103]	VB	rE, Fl	Pr	24 ± 11.3 (mean ± SD)	56.1%	56.2%	NR
Tachihara 2017 [104]	VB	rE	Pr	19; 12–30 (median; range)	100%	NR	100%
Tachihara 2017 [104]	VB	rE, Fl	Pr	22; 15–30 (median; range)	100%	NR	100%
Tamiya 2013 [105]	VB	Fl, GS, rE	Pr	22; 10–30 (median; range)	NR	50%	53%
Wong 2014 [106]	VB	rE	Unclear	28.8 ± 9.3 (mean ± SD)	NR	NR	NR
Xu 2019 [107]	VB	rE	Pr	27 ± 2 (mean ± SD)	NR	38.2%	NR
Yutaka 2021 [69]	VB	Fl, rE	Re	27.6 ± 8.9 (mean ± SD)	70%	46%	NR
Zhang 2020 [108]	VB	rE	Re	20.3 ± 4.8 (mean ± SD)	NR	25%	NR
Zheng 2021 [109]	VB	UTB	Pr	26.3 ± 11.4 (mean ± SD)	100%	53.4%	95%
Zheng 2021 [109]	VB	Fl, UTB	Pr	29.0 ± 11.3 (mean ± SD)	100%	63.3%	97%

AF = augmented fluoroscopy; CBCT = cone beam computed tomography; CT-fl = computed tomography fluoroscopy; EMN = electromagnetic navigation; fEMN = tomosynthesis guided electromagnetic navigation; Fl = fluoroscopy; GGO = ground glass opacity; GS = guide sheath; IQR = interquartile range; NR = not reported; Pr = prospective; PS = Part solid; RB = robot assisted bronchoscopy; rE = rEBUS; Re = retrospective; S = solid; SD = standard deviation; SEM = standard error of the mean; TB = Thin bronchoscope; UTB = ultrathin bronchoscope; VB = virtual bronchoscopy. a: no additional guidance aside from three cases where fluoroscopy was used. b CBCT was used as an additional navigation tool in 77/1388 cases. Guide sheaths were not counted as additional navigation tools for EMN studies, because EMN always utilizes a guide sheath with a locatable guide as part of its navigation.

subgroups for individual nodule size and bronchus sign did show significant differences. Sixty studies reported subgroup analysis for individual nodule size < 20 and ≥ 20 mm, resulting in a summary diagnostic yield of 67.4% (95%-CI 63.1%-71.5% and 95%-PI 43.9%-83.9%) versus 79.4% (95%-CI 76.0%-82.4% and 95%-PI 46.6%-94.8%), respectively. Furthermore, 36 studies reported subgroup analysis for bronchus sign positive or negative lesions, resulting in a summary diagnostic yield of 73.7% (95%-CI 69.4%-77.6% and 95%-PI 50.8%-88.3%) versus 54.1% (95%-CI 48.5%-59.6% and 95%-PI 25.2–80.3%), respectively.

To illustrate the clinical correlation of the different definitions for diagnostic yield, a hypothetical diagnostic patient pathway is shown in Fig. 3. When a patient is diagnosed based on the navigation procedure without follow-up, the summary diagnostic yield is 68.6% (95%-CI 61.7%-74.8%) for patients with nodules < 20 mm and 66.7% (95%-CI 56.8%-75.3%) for nodules ≥ 20 mm. This is based solely on studies with a strict definition for diagnostic yield as it does not incorporate follow-up. The diagnostic yield after follow-up is 72.1% (95%-CI 66.1%-77.5%) and 69.7% (95%-CI 65.4%-73.7%) for nodules < 20 mm and ≥ 20 mm, respectively, based on both studies with a strict and intermediate definition of diagnostic yield. These studies require representative plausible samples for both malignant and benign lesions, which need to be confirmed by follow-up in case of non-specific outcomes. The outcomes from all studies with a liberal definition for diagnostic yield or from those who did not report a definition cannot be extrapolated to real life practice and were therefore excluded from this hypothetical diagnostic patient flow.

3.5. Adverse events

Adverse event analyses were performed on a per procedure analysis. Five studies (including 519 patients) did not report if adverse events occurred and were excluded from analyses. Table 3 specifies adverse events among the remaining 90 studies (including 9862 patients). Overall adverse event rate was 5.6% (n = 547 patients), with pneumothorax occurring in 2.5% (n = 246 patients) and pneumothorax requiring intervention occurring in 1.2% (n = 115 patients). Bleeding was reported in 2.1% of all cases (n = 205 patients), however, the clinical significance of the bleeding was reported only sporadically. There was one reported case of procedure related death. Other reported adverse events were pneumonia/infection in 0.2% (n = 17), respiratory insufficiency/hypoxemia in 0.3% (n = 31), arrythmia in 0.02% (n = 2), minor complaints (e.g. nausea, headache) in 0.4% (n = 37), and other in 0.1% (n = 8).

4. Discussion

This systematic review shows that the pooled diagnostic yield of all included navigation bronchoscopy studies is approximately 71%. In the subgroup analysis comparing more recently developed navigation techniques using advanced imaging and/or robotic support (CBCT, RB and, fEMN) against longer-established navigation techniques using EMN and VB, a statistically significant higher diagnostic yield for the newer techniques was found ($p < 0.001$). Additionally, explorative analyses performed on studies that reported diagnostic yield for individual

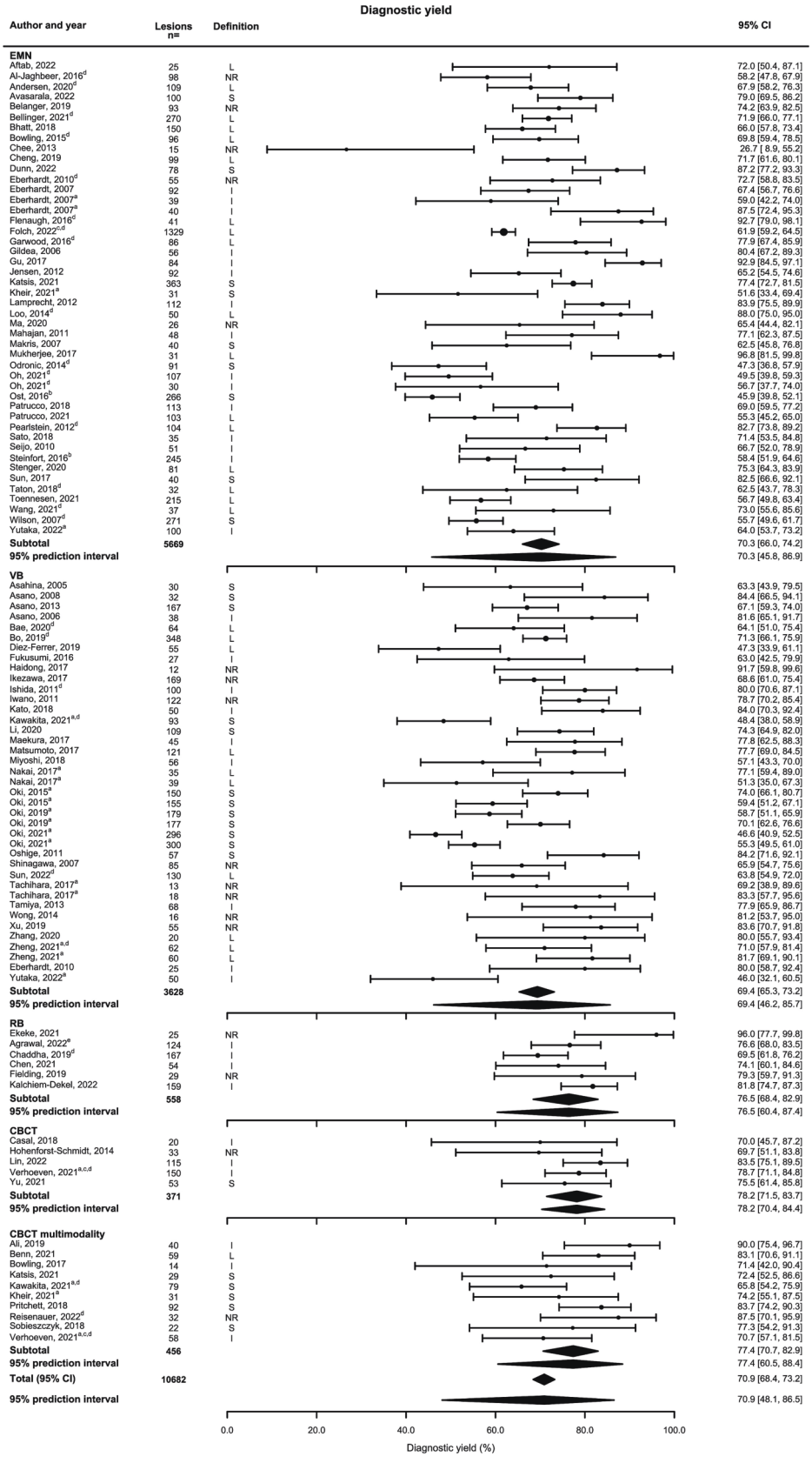

Fig. 2. Summary diagnostic yield divided by different navigation techniques. 95% CI = 95% confidence interval; CBCT = Cone beam CT guided navigation bronchoscopy; EMN = electromagnetic navigation; RB = Robot assisted bronchoscopy; VB = virtual bronchoscopy. a: study with two arms presented separately; b: studies with a case mix of EMN and VB procedures. The two navigation modalities could not be differentiated and were presented in the EMN subgroup. c: studies that included patients with multiple sampled nodules per patient but with per patient analysis which could not be analyzed as a per nodule analysis. d: diagnostic yield differs from the primary results reported by primary study. Rationale for different outcomes can be found in supplemental Table S3. e. 39 patients were also included in the study by Chaddha et al. [74].

Table 2
Summary of subgroup analyses.

	Number of studies or study arms (nodules)	Summary diagnostic yield (95%-CI)	p-value
Overall	**95 (n = 10682)**	**70.9% (68.4–73.2)**	
Navigation technique (1)			**P = 0.091**
EMN	46 (n = 5669)	70.3 (66.0–74.2)	
VB	39 (n = 3628)	69.4 (65.3–73.2)	
RB	6 (n = 558)	76.5 (68.4–82.9)	
CBCT	5 (n = 371)	78.2 (71.5–83.7)	
CBCT multimodality	10 (n = 456)	77.4 (70.7–82.9)	
Navigation technique (2)			**P < 0.001**
Recent	24 (n = 1926)	77.5 (74.7–80.1)	
Longer established	82 (n = 8756)	68.8 (65.9–71.6)	
Strictness of definition of diagnostic yield			**P = 0.255**
Strict	27(n = 3331)	67.6 (62.0–72.7)	
Intermediate	34 (n = 2604)	72.9 (68.7–76.8)	
Liberal	28 (n = 3851)	70.7 (66.1–74.9)	
Not reported	17 (n = 896)	72.4 (65.5–78.3)	
Median nodule size (1)			**P = 0.506**
< 20 mm	30 (n = 2843)	72.1 (67.2–76.6)	
≥ 20 mm	76 (n = 7839)	70.4 (67.5–73.2)	
Publication year			**P = 0.254**
Before 2012	20 (n = 1489)	73.9 (69.0–78.3)	
After 2012	86 (n = 9193)	70.2 (67.3–72.9)	
Additional navigation tools in EMN			**P = 0.154**
No additional tools	20 (n = 1508)	64.0 (61.8–73.1)	
Additional tools	21 (n = 3109)	70.9 (63.5–77.4)	
Tomosynthesis guided EMN	3 (n = 541)	79.5 (65.4–88.8)	
Explorative subgroup analyses			
Individual nodule size (2)			
< 20 mm	60 (n = 3499)	67.4 (63.1–71.5)	P < 0.001
≥ 20 mm	60 (n = 3744)	79.4 (76.0–82.4)	
Bronchus sign			
Positive	36 (n = 3302)	73.7 (69.4–77.6)	P < 0.001
Negative	36 (n = 1826)	54.1 (48.5–59.6)	

95%-CI = 95% confidence interval; CBCT = Cone beam CT guided navigation bronchoscopy; EMN = electromagnetic navigation; RB = Robot assisted bronchoscopy; VB = virtual bronchoscopy.

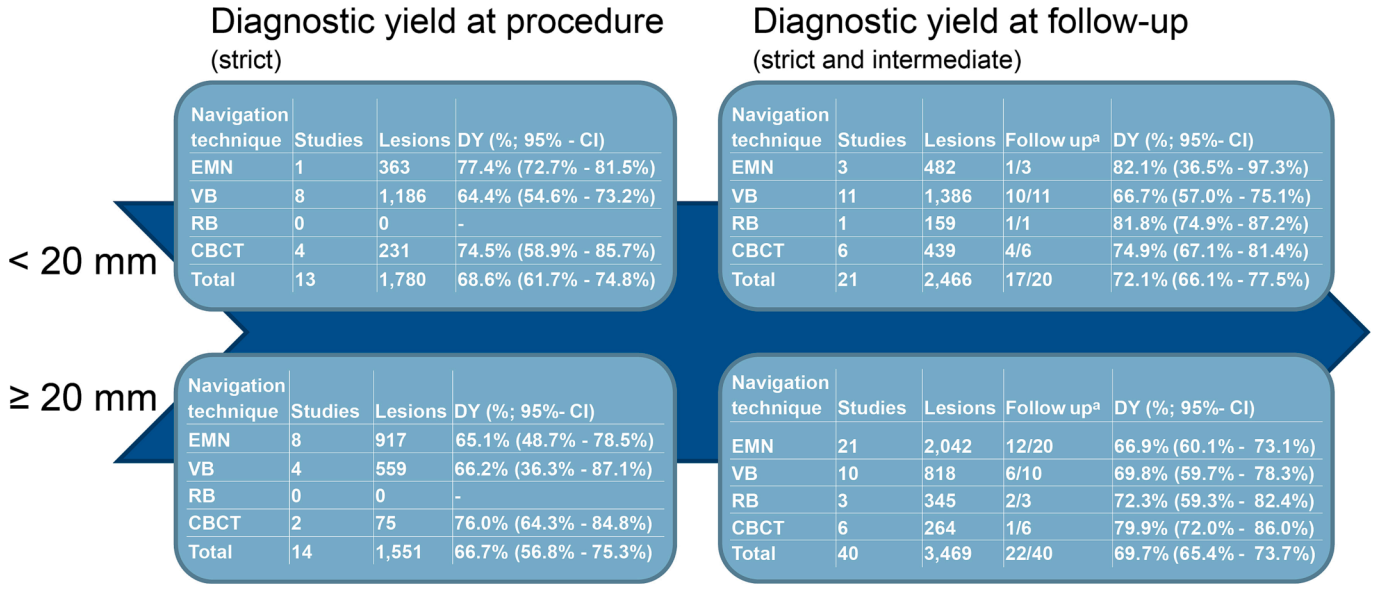

Fig. 3. Hypothetical diagnostic workup for patient with a peripheral pulmonary nodule. EMN = electromagnetic navigation; VB = virtual bronchoscopy; RB = Robot assisted bronchoscopy CBCT = Cone beam CT guided navigation bronchoscopy; 95%-CI = 95% confidence interval; DY = diagnostic yield. a = (adequate) follow up is defined as >1 year follow-up, or definitive diagnostic confirmation by follow up procedure (e.g., TTNB, surgery), or a study with a strict definition for diagnostic yield, eliminating the need for follow up.

variables showed a statistically significant higher diagnostic yield for subgroups with a positive bronchus sign and subgroups with individual nodules ≥ 20 mm. Navigation bronchoscopy has an excellent safety profile with an overall adverse event rate of 5.6%, most of which were minor (i.e. intra-procedural bleeding).

The findings in our systematic review are comparable to several

Table 3
Adverse events.

	Total patients	All adverse events	All pneumothorax (including intervention)	Pneumothorax requiring intervention	Bleeding
Overall	9862	547 (5.6%)	246 (2.5%)	115 (1.2%)	205 (2.1%)
EMN	5204	328 (6.3%)	175 (3.4%)	89 (1.7%)	99 (1.9%)
VB	3330	157 (4.8%)	43 (1.3%)	11 (0.3%)	94 (2.9%)
RB	528	30 (5.7%)	14 (2.7%)	8 (1.5%)	4 (0.8%)
CBCT (including multimodality)	800	32 (4.0%)	14 (1.8%)	7 (0.9%)	8 (1.0%)

EMN = electromagnetic navigation; VB = virtual bronchoscopy; RB = Robot-assisted bronchoscopy CBCT = Cone-beam CT-guided navigation bronchoscopy.

systematic reviews published in recent years. Most recently Nadig et al. [110] reported a similar summary diagnostic yield of 69.4%, although applying different study selection criteria than we did. Despite the comparable overall results, our systematic review performed different subgroup analyses, and categorized and evaluated studies by newly proposed definitions of diagnostic yield [8] to underline the importance of their uniformity. We furthermore propose a workflow that helps interpret the clinical value of different navigation bronchoscopy techniques during the diagnostic phase and follow-up in case of non-conclusive initial findings (Fig. 3).

In the subgroup analyses, we compared more recently developed navigation techniques utilizing advanced imaging and/or robotics with longer-established ones. The diagnostic yield seems to improve with newer technologies based on this analysis. However, we also found that there is significant heterogeneity in study criteria, reflected by the large overall 95% prediction interval of 48.1%-86.6%. This heterogeneity limits the comparability of technologies and studies over time. We hypothesize this might also explain the outcome that our diagnostic yield has not changed more considerably with the advent of improved technology when compared to the *meta*-analysis by Wang-Memoli et al. as published in 2012 [4].

The reported diagnostic yield estimates vary greatly across studies, ranging from 26.7% to 97%. There are multiple potential explanations for this variability: heterogeneity in study methodology (e.g. risk of bias), operator experience (e.g. learning curve analyses [17,66]), test characteristics or patient characteristics (e.g. nodule size ranging from 12.8 mm to 29 mm mean/median size, or bronchus sign presence ranging from 0% to 100%). The impact of patient/nodule characteristics is highlighted by the results of our explorative subgroup analyses. We found that larger nodules and bronchus sign presence resulted in a significantly higher diagnostic yield. When looking at the entire group of included studies, however, this difference is averaged out.

Previous studies have shown that the employed sampling strategy may also impact diagnostic yield [112,113]. For example, Gildea et al. [111] reported that by adding biopsy forceps or an aspiration needle to the sampling strategy, sensitivity improved by 9.3% and 5.8% respectively. Although almost all studies described some form of sampling strategy, a clear presentation of results per sampling tool/strategy or a structured sampling strategy was rarely presented, precluding further subgroup analysis of this parameter. The same applied to other factors that may influence diagnostic yield, such as the type of lesion or pretest probability of malignancy. Such incomplete reporting makes it very difficult to evaluate and compare study results.

In a hypothetical cohort, Vachani et al. recently illustrated that diagnostic yield may vary by 13%–22% depending on whether a strict versus a liberal definition was used [8]. We assessed how diagnostic yield was defined and calculated across primary studies, and applied the proposed categorization by Vachani et al.. This remains subject to discussion as especially older studies have not been designed with these definitions in mind. In our analysis, a considerable number of studies (n = 20) provided insufficient information on how diagnostic yield was calculated to allow categorization. This does not mean that these studies were not diligent in obtaining objective diagnoses, only that we could not reproduce how these diagnoses were made for non-malignant findings. Moreover, follow-up duration to determine true benign findings is another point of attention as it is heterogeneously reported. The optimal follow-up duration is not well established, but shorter follow-up will increase the risk of missing slow-growing malignancies. All previously mentioned factors highlight the need for a standardized and objective description of the outcomes of navigation bronchoscopy. Improved adherence to reporting guidelines such as STARD 2015 for diagnostic accuracy studies [112] is likely to improve this situation.

This systematic review showed a good safety profile for navigation bronchoscopy, but the QUADAS-2 assessment also showed that the risk of bias for the reporting of adverse events could not be determined adequately in 79% of included studies. Adverse events are most likely reported truthfully, but the methodological assessment shows that structured reporting of adverse events according to a predetermined protocol is uncommon. Similar to how diagnostic yield is defined, structured reporting of adverse events will most likely lead to better comparability between research.

4.1. Clinical implications

This systematic review illustrates that the navigation bronchoscopy field has become an important area of research with a multitude of technological options. Real-life practice resembles the large variability described in this systematic review. The peripheral nodule patient population is heterogeneous in nature and not every patient requires the same approach. Multimodality approaches to navigation bronchoscopy have become standard practice, with 75/95 studies in this systematic review employing such an approach. The use of multiple different navigation techniques and tools will most likely increase the possibility of obtaining a diagnosis. However, not every hospital has access to the same resources, both in access to technology and in financial assets. A recent decision analytical cost-effectiveness study [113] showed that diagnostic yield is the most important factor in determining the cost-effectiveness of a navigation bronchoscopy modality. This implies that the more recently developed navigation techniques can be cost-effective, even while being initially more expensive to acquire or implement. Also important, however, will be an optimal preprocedural patient selection. By selecting the correct patients for the employed navigation technique, a high diagnostic yield can be obtained. This will result in the most cost-effective manner of diagnosis. One of the challenges going forward will be to determine which patient in what hospital setting will benefit the most from which navigation approach.

Regardless of how the navigation bronchoscopy research field will develop in coming years, standardized and clearly described definitions for outcomes and on how to report adverse events will be indispensable for more accurate comparisons between studies and technologies. Ideally, from a patient perspective, the strict and intermediate definitions of diagnostic yield will become more widely employed as these definitions can be correlated to daily practice.

5. Conclusion

This systematic review and *meta*-analysis shows that navigation bronchoscopy is a safe procedure with the potential for a high diagnostic yield. Our analysis shows that more recently developed navigation techniques using advanced imaging and robotics are more accurate in

comparison to longer-established techniques, within the context of a highly heterogeneous population with a multitude of variables that can also affect diagnostic yield. High heterogeneity between studies in terms of patient and nodule characteristics limits extensive sensitivity analyses, but bronchus sign and nodule size appear to significantly impact the diagnostic yield. The standardized definitions for diagnostic yield as used in our systematic review can be utilized to improve comparability between future studies in this field and may result in a better clinical correlation of the outcomes and better comparison of the performance of different technologies.

Declaration of Competing Interests

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CRediT authorship contribution statement

Stephan E.P. Kops: Methodology, Validation, Formal analysis, Investigation, Data curation, Visualization, Writing – original draft. **Pauline Heus:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing. **Daniël A. Korevaar:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing. **Johanna A.A. Damen:** Methodology, Validation, Formal analysis, Data curation, Writing – review & editing. **Demy L. Idema:** Investigation, Data curation, Validation. **Roel L.J. Verhoeven:** Conceptualization, Validation, Writing – review & editing. **Jouke T. Annema:** Conceptualization, Writing – review & editing. **Lotty Hooft:** Conceptualization, Writing – review & editing. **Erik H.F.M. van der Heijden:** Conceptualization, Validation, Writing – review & editing.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

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