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Diagnostic Yield and Safety of Electromagnetic Navigation Bronchoscopy for Lung Nodules: A Systematic Review and Meta-Analysis

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Key Words
Electromagnetic navigation bronchoscopy · Peripheral lung lesions · Solitary pulmonary nodule

Abstract
Background: Electromagnetic navigation bronchoscopy (ENB) is an emerging endoscopic technique for the diagnosis of peripheral lung lesions. A thorough analysis of ENB's yield and safety is required for comparison to other sampling modalities. ***Objectives:*** To describe ENB's yield and safety profile. ***Methods:*** The MEDLINE and EMBASE databases were systematically searched for studies reporting ENB's yield for peripheral lung lesions. Two independent investigators extracted data and rated each study on a scale of methodological quality. Clearly defined performance outcomes were reconstructed and meta-analyzed. Subgroup analysis and meta-regression were used to identify possible sources of study heterogeneity. ***Results:*** A total of 15 trials were included (1,033 lung nodules). A positive and definitive diagnosis was obtained after 64.9% of all ENB procedures (95% CI 59.2–70.3). Overall diagnostic accuracy was 73.9% (95% CI 68.0–79.2). Sensitivity to detect cancer was 71.1% (95% CI 64.6–76.8), with a negative predictive value of 52.1% (95% CI 43.5–60.6). Pneumothorax occurred in 3.1% of patients, requiring chest tube drainage in 1.6% of these cases. Original trials identified 6 variables associated with higher ENB yields: nodule location in the upper or middle lobes, nodule size, lower registration error, presence of a bronchus sign on CT imaging, combined use of an ultrasonic radial probe, and catheter suctioning as a sampling technique. Heterogeneity exploration revealed that studies using general anesthesia or rapid on-site cytological evaluation reported better yields. ***Conclusions:*** ENB is effective and particularly safe. Prospective studies are needed to clarify the role of several variables conditioning the yield of this technique.

Introduction

The need to establish an optimal diagnostic approach to a newly discovered lung nodule is becoming increasingly important because of the escalating use of CT scanning in cardiopulmonary disease, and the advent of CT screening for lung cancer in high-risk populations. Competing diagnostic options include CT follow-up for low-risk nodules, minimally invasive procedures and surgical resection of highly suspicious lesions in operable patients [1]. For nodules with an intermediate risk of malignancy,

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a minimally invasive alternative to surgery is ideal for the initial diagnostic approach, in order to limit morbidity and mortality associated with invasive procedures. Because the diagnostic yield of conventional fiberoptic bronchoscopy for peripheral lung nodules is low, ranging from 14 to 62% [2], a guided endoscopic approach may be the best choice in selected cases. Electromagnetic navigation bronchoscopy (ENB) is an emerging option for guided bronchoscopy.

ENB employs a 3-dimensional reconstruction of CT-scan data and sensor location technology in order to guide a steerable endoscopic probe to peripheral lung lesions [3]. ENB consists of three key elements: dedicated software which converts CT-scan images into a multiplanar virtual bronchoscopy reconstruction of the patient's airways, a steerable locatable guide which facilitates navigation within the endobronchial tree, and an electromagnetic board generating a magnetic field surrounding the patient's chest. The exact position of the location sensor is depicted on the multiplanar CT images, which are superimposed on the real anatomy of the patient by matching the virtual and actual bronchoscopic views. Once the targeted nodule has been reached, it can be sampled either through an extended working channel left in place (Super Dimension System) or alternatively using locatable instruments (SPiN Drive System).

The best nonsurgical approach for sampling a peripheral lung nodule is still debated and relies mostly on local idiosyncrasies and personal expertise [1]. Ideally, a well-informed choice should be based on a thorough comparison of the diagnostic yield and safety profile of each available approach. Several studies have investigated the diagnostic yield of ENB [4]. However, conclusions drawn from published data are limited by sample size, alternative definitions of diagnostic yield and major heterogeneity of settings. We performed a systematic review and meta-analysis in order to assess more accurately the diagnostic yield and safety of ENB in the diagnosis of peripheral lung nodules and explore the variables influencing the yield.

Materials and Methods

Data Sources

A literature search was performed in order to identify all published studies reporting diagnostic yields of ENB for peripheral lung nodules. MEDLINE and EMBASE databases were searched in March 2012 using a predefined search strategy detailed in the online data supplement. Reference lists of retrieved papers were independently hand-searched by two investigators for additional articles.

Study Selection and Data Extraction

Two investigators (G.G. and J.A.P.) performed independently and in duplicate the complete selection process and data extraction using a standardized form. Discordance was resolved by consensus. Predefined criteria for inclusion were: any trial enrolling at least 10 patients and reporting diagnostic yield of ENB for peripheral lung nodules or masses, without any restriction. Trials reporting assessment of a combination of mediastinal and lung lesions were only included if data on lung nodules could be extracted separately, if necessary by contacting the authors. The quality of included studies was further assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool [5]. This 14-item checklist was specifically developed to assess the methodological quality of diagnostic accuracy studies included in systematic reviews.

Because studies of diagnostic accuracy are known to report heterogeneous and incomplete outcomes [6], we extracted the actual results of ENB in order to reconstruct well-defined outcomes. We classified ENB results as positive (either malignant or benign), intermediate (histological diagnosis needing confirmation such as chronic inflammation, organizing pneumonia or atypical cells without sufficient features to ascertain malignancy) or indeterminate (e.g. normal lung tissue or reported as inconclusive). For each of these categories, we extracted the final diagnoses confirmed by surgery, further biopsies or extended follow-up, when necessary by contacting the authors for additional information (online suppl. table E1; see www.karger.com/doi/10.1159/000355710 for all online suppl. material). From these data, we reconstructed 7 outcomes assessing ENB's navigation success, diagnostic yield and ability to identify malignancy. These performance outcomes are defined in table 1 and cover all outcomes reported in included studies. Finally, we reviewed the assessment of variables conditioning ENB yields in original trials and extracted each related analyzed parameter.

Statistical Analysis

The aforementioned outcomes were pooled by using the inverse-variance method with random effects on the logit-transformed proportions [7]. Sensitivity analyses were conducted to check the robustness of the results and the presence of between-study heterogeneity was assessed by using the indicator I^2 [8]. Potential heterogeneity factors were analyzed by meta-regressions or the Cochran Q test on the between-strata heterogeneity. Prespecified analyzed factors were classified in study-level characteristics and patient-level characteristics, which are at higher risk for ecological bias. Only significant associations were reported. Publication bias was explored by using the Egger test and the trim and fill method [9]. Additional details on statistical analysis are provided in the online data supplement.

Results

Study Selection

The bibliographic search yielded 174 studies. Following review of the abstracts, 18 papers were selected for full text review (fig. 1). Of these, 3 were excluded because they enrolled less than 10 patients [10–12]. At the end of the selection process, 15 studies were included [3, 13–26].

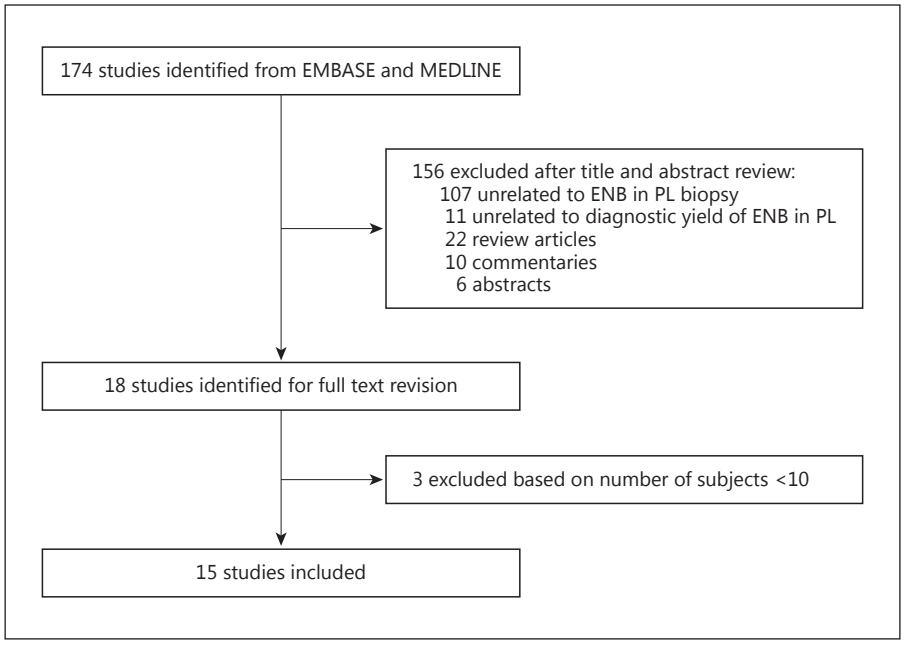

Fig. 1. Flow diagram. PL = Pulmonary lesion.

Table 1. Reconstructed performance outcomes of ENB: definitions

	Numerator	Denominator
Technical feasibility		
Navigation success	Nodules successfully reached by ENB on multiplanar views	Targeted nodules
Diagnosis		
Diagnostic yield	Malignancies[1] and benign diagnoses[1]	Targeted nodules
Diagnostic accuracy	Malignancies[1] and benign diagnoses[1] and intermediate results[1] confirmed correct	Sampled nodules with known final diagnosis[2]
Malignancy status		
Sensitivity for malignancy	Malignancies[1]	Final number of malignancies after further testing[2]
Accuracy for malignancy	Malignancies[1] and nonmalignant results[1] confirmed benign[3]	Sampled nodules with known final diagnosis[2]
Negative predictive value	Final number of true benign diagnoses after further testing[2]	Nonmalignant ENB results (including indeterminate)
Negative predictive value of intermediate benign results	Final number of true benign diagnoses after further testing[2]	Intermediate benign results[1]

[1] As results of ENB. [2] Not reported if the number of missing final diagnoses is >5%. [3] Benign definitive diagnoses after ENB + suspicion of benign diagnoses confirmed benign + indeterminate results revealing as benign after further testing.

Study Description

Main study characteristics are depicted in tables 2 and 3 and in the online data supplement (online suppl. tables E2 and E3). A total of 1,033 lung nodules or masses in 971 patients (37.6% females, mean age 64.2 years) were included. The median number of nodules per study was 50 (range 13–271), with a median diameter of 25 mm and a median distance to the pleural surface of 11 mm. Thirty-eight percent of nodules were located in the lower lobes. The median study prevalence of malignancy was 77.5% (range

Table 2. Main characteristics of selected studies (participants/nodules)

Study (first author)	Patient selection	Participants, n (% female)	Mean age, years	Lung lesions, n	Prevalence of lung cancer	Mean diameter, mm
Becker, 2005 [3]	PPL beyond the field of FB, regardless of lesion size	30 (23)	65	30	83%	39.8
Hautmann, 2005 [13]	PPL beyond the field of FB	16 (38)	63.7	16	ND	ND
Gildea, 2006 [14]	Referral for PPL beyond the field of FB	49 (40)	67.9	56	74%	22.8
Schwarz, 2006 [15]	PPL beyond the field of FB, regardless of lesion size	13	ND	13	92%	33.5
Makris, 2007 [16]	PPL beyond the field of FB, suggestive of malignancy, after nondiagnostic or impracticable FB, TTNA and MLN-TBNA, high-risk surgery	40 (25)	60	40	85%	23.5
Eberhardt, 2007 [17]	PPL beyond the field of FB	89 (44)	67	93	76%	24
Eberhardt, 2007 [18]	PPL beyond the field of FB	39 (49)	55	39	74%	28
Eberhardt, 2007 [18] EBUS	PPL beyond the field of FB	40 (38)	51	40	78%	24
Wilson, 2007 [19]	PPL beyond the field of FB	222 (51)	63.1	271	57%[1]	21
Bertoletti, 2009 [20]	PET-positive PPL beyond the field of FB, high-risk surgery	54 (13)	67	54	78%	31.2
Eberhardt, 2009 [21]	Referral for small PPL suggestive of malignancy	54 (26)	65.1	55	89%	23.3
Lamprecht, 2009 [22]	PPL beyond the field of FB and/or too small to be visible on fluoroscopy	13 (23)	64.2	13	69%	30
Seijo, 2010 [23]	PPL, straightforward surgery or TTNA deemed suboptimal	51 (27)	62	51	72%	25
Mahajan, 2011 [24]	PPL beyond the field of FB, high-risk surgery	48	ND	49	57%	20
Lamprecht, 2012 [26]	PPL beyond the field of FB	112 (33)	66.7	112	85%	27.1
Pearlstein, 2012 [25]	PPL suggestive of malignancy based on CT and PET scan, unsuitable for TTNA, high-risk surgery, no other available biopsy site	101 (39)	69	101	81%	28

FB = Flexible bronchoscopy; MLN-TBNA = mediastinal lymph node transbronchial needle aspiration; ND = no data available; PPL = peripheral pulmonary lesion; TTNA = transthoracic needle aspiration.

[1] High incidence of histoplasmosis in the study population (Ind., USA); 33% unknown final diagnoses.

See table E3 in the online data supplement for further details.

56.5–92.3%) and the overall pooled prevalence was 76.5% (95% CI 70.2–81.8). All studies used the SuperDimension® ENB system, except for one trial which used a commercially unavailable system named Aurora, which lacks a steerable probe [13]. ENB settings were highly variable. Several studies relied on additional techniques or strategies to enhance performance, such as fluoroscopy, endobronchial ultrasound (EBUS) radial probe, rapid on-site cytological evaluation (ROSE) and general anesthesia (table 3). In 1 study comparing three different endoscopic techniques (ENB alone, ENB with radial EBUS and radial EBUS alone), the 2 subgroups using ENB and ENB + EBUS were analyzed separately [18]. All trials used biopsy forceps and obtained an average of 3–6 samples, except for 1 in which 9 biopsy attempts were systematically performed [16]. Some studies incorporated other sampling techniques such as brushing, needle aspiration, catheter suction, limited lavage through the extended working channel or traditional bronchoalveolar lavage (table 3). Discordance between the virtual bronchoscopic landmarks and the actual anatomic reference points (e.g. the main carina and lobar carinas) was evaluated by the average fiducial target registration error (AFTRE). Median AFTRE was 4.6 mm (range 3.6–6.6 mm), with an overall pooled AFTRE of 5.1 mm. The mean duration of the entire ENB procedure ranged from 25.7 to 70 min with a median of 46 min. With the exception of 2 trials, definitive diagnosis or malignancy status were known for the vast majority of lung lesions (98.8% overall). Diagnostic certainty was achieved by surgical resection, alternative biopsy techniques or extended follow-up. In the studies by Hautmann et al. [13] and Wilson and Bartlett [19], only 63 and 67%, respectively, of definitive diagnoses were known, thus precluding the determination of most outcomes.

The methodological quality of the studies included in this meta-analysis was poor, as determined by the low overall QUADAS scores (table 3). No study compared ENB to surgery as a gold standard. Thus, QUADAS scores

Table 3. Main characteristics of selected studies (methods, intervention)

Study (first author)	QUADAS scores	Type of sedation	Additional technique	AFTRE, mm	Mean distance between tip of sensor and center of nodule, mm	Sampling technique	Mean exam duration, min
Becker, 2005 [3]	3	GA	fluoroscopy, radial probe EBUS	6.2	8.4	forceps, brush, curette	ND
Hautmann, 2005 [13]	3	CS	fluoroscopy[3]	ND	ND	forceps	ND
Gildea, 2006 [14]	3	CS	fluoroscopy	6.6	9	forceps, brush, BAL, needle	51
Schwarz, 2006 [15]	3	CS	fluoroscopy	5.7	ND	forceps, brush	46
Eberhardt, 2007 [17]	3	GA/CS	0	4.6	9	forceps, brush, BAL[5], needle	26.9
Eberhardt, 2007 [18]	3	GA/CS	0	ND	ND	forceps	ND
Eberhardt, 2007 [18] EBUS	3	GA/CS	radial-probe EBUS	ND	ND	forceps	ND
Makris, 2007 [16]	4	GA	0	4	8.7	forceps[4]	ND
Wilson, 2007 [19]	3	CS	fluoroscopy, ROSE	5	8	forceps, needle	ND
Bertoletti, 2009 [20]	3	CS[1]	0	4.7	10	forceps, brush	29.5
Eberhardt, 2009 [21]	3	GA	0[2]	3.6	9	forceps, suction[6]	25.7
Lamprecht, 2009 [22]	3	GA	ROSE	3.8	8.4	forceps, brush, needle	60
Seijo, 2010 [23]	3	CS	ROSE	4	8	forceps, needle	56
Mahajan, 2011 [24]	3	CS	fluoroscopy	ND	ND	forceps, brush, BAL	ND
Lamprecht, 2012 [26]	4	GA	ROSE	ND	ND	forceps, brush, needle	45.2
Pearlstein, 2012 [25]	3	GA	ROSE	4	7.4	forceps, brush, needle	70

BAL = Bronchoalveolar lavage; CS = conscious sedation; GA = general anesthesia; ND = no data available.
[1] 50%/50% Nitrous oxide/oxygen mixture.
[2] EBUS performed, but without additional navigation if peripheral pulmonary lesion not seen on ultrasound.
[3] Commercially unavailable ENB system, without any steerable catheter.
[4] Nine attempts for biopsies, instead of mostly 3–5 in other studies.
[5] Through extended working channel.
[6] Suction of the nodule through a dedicated catheter, with back and forth moves.
See table E4 in online data supplement for further details.

were only assessable in 6 of the 14 domains. Selection criteria were rarely clear enough to allow reproducibility, especially regarding the choice of diagnostic procedure and, in particular, why ENB rather than another diagnostic technique or surgical resection was performed. In all publications, it was unclear if the study subjects were representative of the patients who would undergo ENB-sampling in real-world practice, making it impossible to account for selection bias.

Performance Outcomes

In the study by Lamprecht et al. [26], successful navigation toward targeted lung lesions ranged from 90.2 [26] to 100%, with the definition of navigation success being particularly restrictive, i.e. the distance from the tip of the locatable guide to the center of the lesion ≤10 mm, irrespective of the nodule's size. Navigation failures in most studies were attributed to airway distortion or poor patient tolerance despite sedation. Meta-analysis of all studies demonstrated an accessibility rate of 97.4% (95% CI 95.4–98.5) (online fig. E1). Diagnostic yield ranged from 55.7% [19] to 87.5% [18] and the pooled diagnostic yield was 64.9% (95% CI 59.2–70.3) (fig. 2). Diagnostic accuracy was analyzable in 14 trials and reached 73.9% (95% CI 68.0–79.2), ranging from 59.0% [18] to 93.1% [26] (fig. 3).

Fourteen studies were suitable for evaluation of outcomes regarding malignancy status. The overall sensitivity of ENB to detect cancer was 71.1% (95% CI 64.6–76.8),

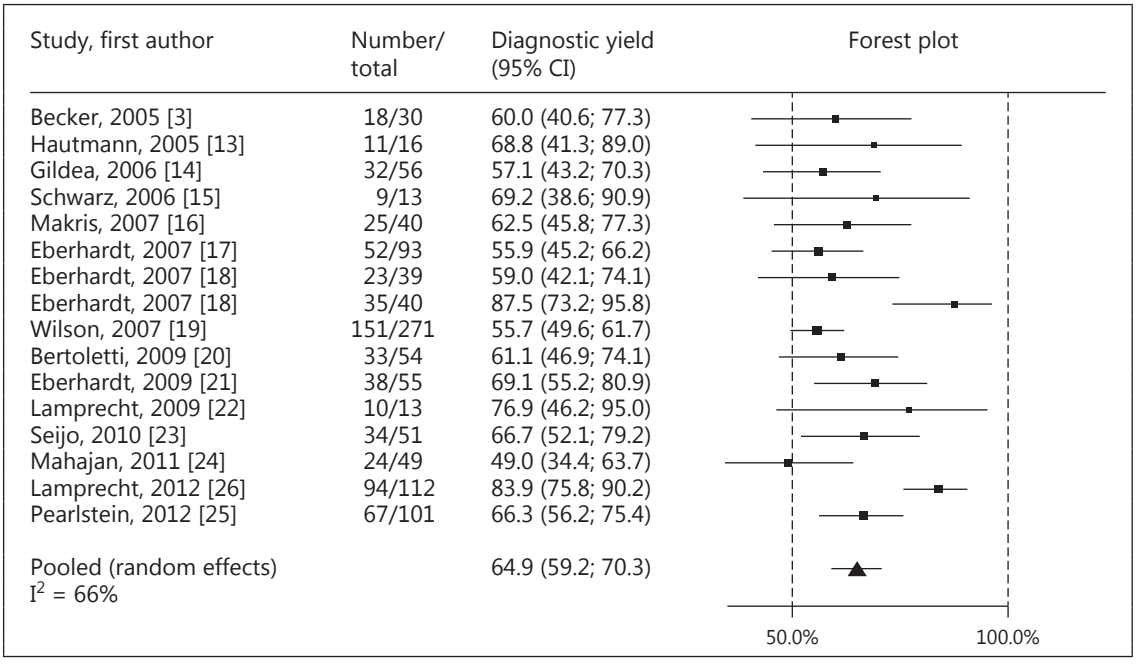

Fig. 2. Diagnostic yield of ENB.

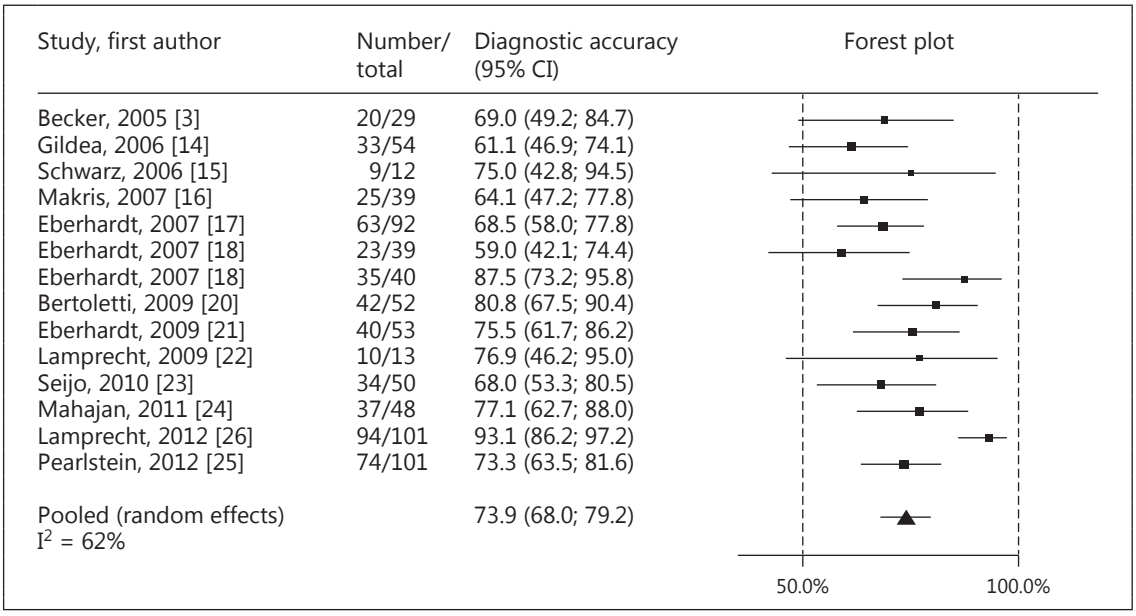

Fig. 3. Diagnostic accuracy of ENB.

ranging from 55.2 to 90.3% [18] (fig. 4). The accuracy to determine the correct malignancy status ranged from 66.7% [16] to 98.0% [26], leading to a pooled accuracy for malignancy of 78.6% (95% CI 72.8–83.4) (fig. 5). The negative predictive value of ENB for cancer was 52.1% (95% CI 43.5–60.6, range 25.0–89.5%; online suppl. fig. E2). Eight studies took into account the fact that some carcinomas may be surrounded by a rim of chronic inflammation and specifically reported outcomes of intermediate benign cases after ENB, i.e. histologically benign abnormalities not

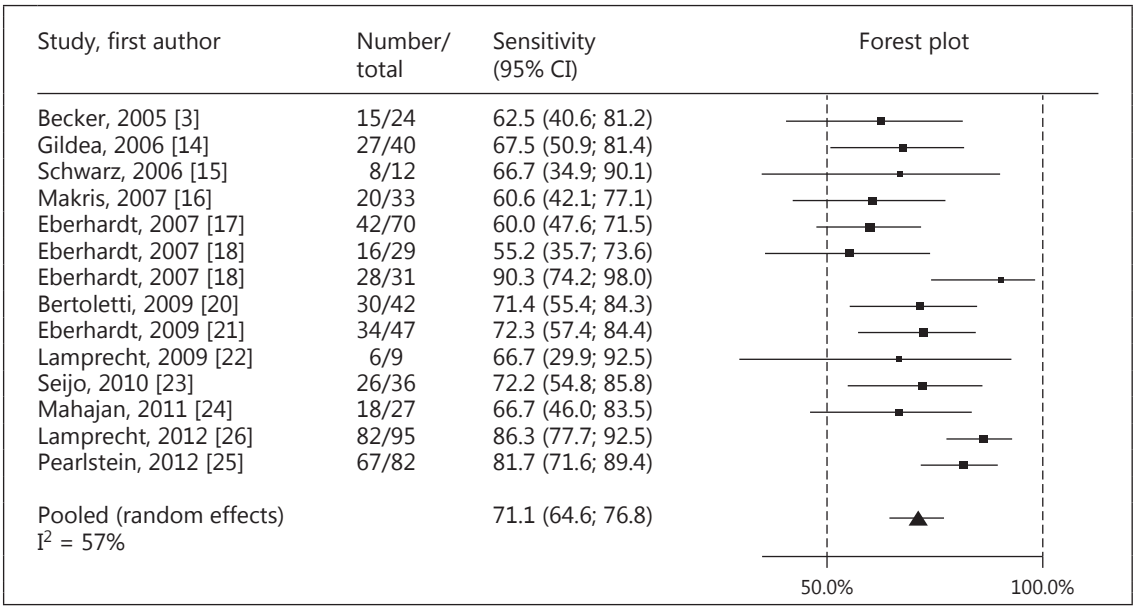

Fig. 4. ENB's sensitivity for malignancy.

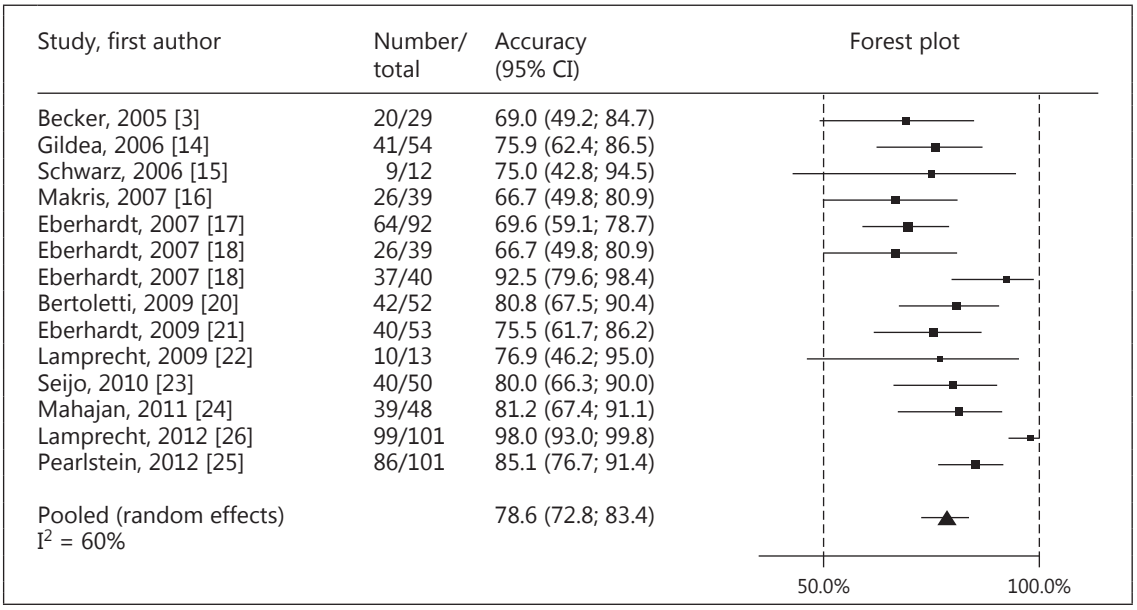

Fig. 5. ENB's accuracy for malignancy.

sufficient to rule out cancer including chronic or granulomatous inflammation [3, 14, 17, 20, 21, 24, 25]. Eight out of 53 nodules with intermediate benign results following ENB were eventually diagnosed with malignancy. Therefore, the overall negative predictive value of ENB for these intermediate cases was 78.5% (95% CI 53.1–92.1).

No significant reporting bias was identified, except for the rate of successful navigation. After correction for a potential publication bias, this outcome was only slightly decreased (96.0 vs. 97.4%). Moreover, this potential publication bias was exclusively dependent on a single study

Table 4. Systematic review: predicting factors of ENB's yield

Analyzed variables (number of studies)
Nodule characteristics
Location of the nodule (10)
Size of the nodule (10)
Etiology of the nodule (4)
Distance to visceral pleura (2)
Bronchus sign (1)
Uptake on PET-CT (1)
Patient characteristics
Predicted FEV_1 (1)
Procedure characteristics
AFTRE (6)
Navigation error[1] (4)
Type of sedation (2)
Nodule visualization with radial-probe EBUS (2)
Sampling technique (1)
Number of biopsies obtained (1)
Total procedure time (1)
Navigation time (1)
Learning curve (2)
Reported significant predicting factors in univariate analysis
Location in lower lobe [18]
Size of the nodule [23]
Bronchus sign [23]
AFTRE [16]
Nodule visualization with radial-probe EBUS [18, 21]
Catheter suction technique versus forceps biopsies [21]
Reported significant predicting factors in multivariate analysis
Bronchus sign [23]

[1] Distance between the tip of the sensor and the center of the nodule.

Table 5. Study level characteristics associated with significant modification of ENB's performance

		Studies, n	Pooled outcome (95% CI)	p values
			diagnostic yield	
General anesthesia	yes	9	69.2% (60.6–76.7)	0.02
	no	7	57.5% (53.2–61.8)	
			sensitivity for malignancy	
ROSE	yes	4	80.2% (72.1–86.4)	0.006
	no	10	66.3% (60.3–71.8)	
			diagnostic yield	
Fluoroscopy	yes	6	56.3% (51.5–60.9)	0.006
	no	10	68.8% (61.3–75.4)	

[26], which differed from the others in an exceptionally restrictive definition of navigation success.

Variables Influencing the Performance of ENB

Systematic review of all 15 original trials identified 16 variables analyzed for their postulated influence on ENB's diagnostic yield (table 4). Univariate analyses identified 6 statistically significant variables. Location of the lower lobe correlated with decreased yields in 1 trial [18], whereas greater nodule size [23], presence of a bronchus sign [23], lower registration error (AFTRE) [16], nodule visualization with an EBUS radial probe [18, 21] and catheter suction technique [21] were associated with increased yields. Multivariate analysis was only performed by Seijo et al. [23], who identified the bronchus sign as the key variable conditioning ENB yields [OR 7.6 (95% CI 1.8–31.7), 79% positive diagnoses with bronchus sign vs. 31% without] [23]. Most studies found a trend toward a greater yield for larger nodules, but only 1 found a statistically significant association, which disappeared on multivariate analysis [23].

In our meta-analysis, the between-study heterogeneity allowed analysis of parameters associated with variations of performance outcomes. The assessed study-level characteristics included study design (retrospective vs. prospective), conflict of interest, type of sedation (general anesthesia vs. conscious sedation), combined use of fluoroscopy, EBUS or ROSE, type of sampling tools and year of publication. The use of general anesthesia was associated with better diagnostic yields (69.2 vs. 57.5% in studies with conscious sedation, $p = 0.02$), while sensitivity for cancer was better in trials using ROSE (80.2 vs. 66.3%, $p = 0.006$; table 5). However, the number of trials using this technique (i.e. 4) was limited, precluding definitive conclusions. Surprisingly, studies combining fluoroscopy with ENB to confirm navigation success reported lower diagnostic yields (56.3 vs. 69.2% without fluoroscopy, $p = 0.006$). This association remained statistically significant after omitting the study responsible for the largest heterogeneity in this outcome [19].

Factors of between-study heterogeneity were also explored among patient-level characteristics of studies, including mean age and gender of included patients, nodule location (% in upper lobes) and mean diameter, distance from the nodule to the visceral pleura, prevalence of malignancy, mean AFTRE scores and distance from the tip of the location sensor to the center of the nodule. A higher malignancy prevalence was associated with a lower negative predictive value for cancer ($p = 0.02$), as commonly described, but also with better diagnostic yields ($p = 0.02$)

(online suppl. table E4). In addition, more recent studies reported significantly higher sensitivity, accuracy and negative predictive value for malignancy. All these associations showed robustness on sensitivity analyses ($p < 0.1$). We also found an inverse correlation between the location of the upper lobe and sensitivity and accuracy for malignancy as well as negative predictive value. However, these three associations were highly dependent on a single study [26], as shown by sensitivity analyses.

Safety

ENB sampling of peripheral nodules caused 32 pneumothoraces in 1,033 procedures (3.1%, 95% CI 2.1–4.3), but only 17 patients required chest tube drainage (1.6%, 95% CI 1.0–2.6). Minor or moderate bleeding was reported in 9 cases (0.9%, 95% CI 0.4–1.6), none of them requiring specific treatment. Additional complications included one self-limited hematoma and one episode of hypercapnic respiratory failure attributed to sedation.

Discussion

The results of our review and meta-analysis indicate that successful navigation to peripheral lung nodules with ENB is universal (97.4%), but that a definitive diagnosis can only be obtained in 64.9% of cases. Overall diagnostic accuracy is 73.9%, while the sensitivity to detect cancer is 71.1%. Malignancy cannot be excluded with ENB, as the negative predictive value for cancer is only 52.1%. Even when the samples obtained show chronic inflammation or granulomatous inflammation, the negative predictive value of ENB remains suboptimal (78.5%). This finding may be accounted for by the occasional presence of a rim of chronic inflammatory changes surrounding malignant tissue. The accuracy of ENB to distinguish malignant from nonmalignant conditions is 78.6%. This last outcome is frequently reported in trials assessing the performance of any sampling technique, but tends to overestimate the yield of the procedure. Indeed, any nonmalignant result is considered as an accurate outcome when the final diagnosis is benign, even if the sampling was suboptimal or inconclusive.

The discrepancy between navigation success and diagnostic yield can be attributed to at least two factors. First, the relationship between the airways and the lesion plays a major role. When the nodule is extrabronchial and located tangentially to the airway, the sampling tool will tend to follow the trajectory of the bronchus and miss the nodule, even if the locatable guide has reached its immediate vicinity. This limitation concerns all variants of guided bronchoscopy, and may be resolved with newer curved catheter designs. Secondly, ENB data is based on a virtual spatial reconstruction, and may therefore be misleading in some cases. The actual position of the locatable guide may differ significantly from the virtual location. Thus, a mismatch between the virtual and actual location of the electromagnetic guide can decrease the diagnostic yield of ENB, despite what appears to be a successful navigation.

This meta-analysis includes several studies reporting preliminary experience with ENB. One might expect better yields in trials performed after overcoming of the learning curve in the future and thanks to the ongoing optimization of the ENB system. This notwithstanding, the performance of ENB is inferior to the gold standard, i.e. surgical resection. Transthoracic CT-guided needle biopsy may have a higher yield than ENB in certain patient populations, as its published diagnostic yield ranges from 59 to 96%, with a median value of 79% [27]. However, lung nodules included in these studies tend to be larger than those included in our analysis. Furthermore, the definition of diagnostic yield is often heterogeneous and includes more favorable outcomes such as diagnostic accuracy or malignancy status accuracy. Thus, the relative performance of ENB compared to CT-guided biopsy requires examination in future studies. It should be noted that ENB enjoys a far more favorable safety profile. Pneumothorax after CT-guided transthoracic biopsy is quite common, occurring in as many as 15–43% of patients (median 26.5%), with 4–18% of patients requiring chest tube drainage (median 5%) [27]. The rate of hemoptysis ranges between 3 and 12% [28–32]. By contrast, the pneumothorax rate following ENB was 3.1% in our analysis, with only 1.6% of patients requiring chest tube drainage. Minor or moderate bleeding occurred in 0.9% of patients. Therefore, ENB can be considered an attractive alternative to transthoracic needle sampling in nonoperable patients at a higher risk of pneumothorax. Particular attention should thus be paid to reported risk factors for pneumothorax during transthoracic needle biopsy, including emphysema, older age, nodule depth, small size or proximity to the fissures, a lateral pleural puncture site, a small angle of entry between the needle and the pleura and greater coaxial needle size [28, 32–35].

Direct comparison of ENB with conventional or alternative guided endoscopic techniques is limited to a single trial assessing the yield of ENB compared to nodule localization using EBUS radial probes or a combination of

both [18]. This randomized study was included in our meta-analysis and reported yields of 59, 69 and 87.5% for the three arms, respectively. The yield differences were only statistically significant between the combined procedure and either procedure alone. A recent meta-analysis of EBUS radial probes for peripheral lung cancer reported a sensitivity for the detection of cancer of 73% (95% CI 0.70–0.76) [36], which is similar to the sensitivity of 71.1% (95% CI 64.6–76.8) of ENB in our analysis. Wang Memoli et al. [4] reported similar yields with ultrathin bronchoscopy, radial endobronchial ultrasound and virtual bronchoscopy, with comparable safety profiles. Naturally, conclusions in terms of diagnostic performance cannot be drawn until further head-to-head comparisons are available. Nevertheless, ENB compares favorably with conventional bronchoscopic techniques in real-life practice. The steerable locatable guide, for example, can be a significant advantage, extending the reach of conventional bronchoscopy to small peripheral nodules where other guided techniques fail. Furthermore, while some endoscopists use fluoroscopy routinely in combination with bronchoscopy, small nodules can be either difficult or impossible to locate with fluoroscopy, even in expert hands. In such cases, ENB offers an unquestionable advantage over conventional bronchoscopy akin to instrument-flying of a plane when no horizon is visible. Unfortunately, ENB is relatively expensive, time-consuming and requires a lot of resources. It mandates adequate preprocedure planning with a recent adequate CT scan. Peripheral navigation using a radial EBUS probe does not require such planning, can be improvised at a moment's notice and is cheaper, since radial probes are reusable. Furthermore, real-time visualization of the lesion prior to obtaining diagnostic samples may be considered superior to virtual imaging. Therefore, it is unlikely that standalone ENB will surpass other guided bronchoscopic techniques. It may very well find itself a niche, depending on regional or personal expertise, financial concerns and the availability of other technologies. As mentioned earlier, combined approaches may be the best alternative if costs can be contained.

Because the current performance of ENB leaves room for improvement, factors contributing to increase diagnostic yields are under continued investigation. As shown by our systematic review, original trials identified 6 predicting factors of ENB's yield: nodule location in the upper or middle lobes, greater nodule size, lower AFTRE scores (meaning better radiographic-anatomic alignment), the presence of a bronchus sign on CT imaging, visualization of the nodule with an EBUS radial probe before sampling and the use of the catheter suction technique. Multivariate analysis was only performed in 1 trial and identified the bronchus sign as the only predicting factor of ENB's yield. In our meta-analysis, we observed that studies using ENB in combination with general anesthesia or ROSE had significantly better yields, which was strongly expected but not yet proven. In fact, the effect of ROSE on ENB's performance was not assessed in original trials, whereas the influence of general anesthesia was only analyzed in two trials, without sufficient power to reach a statistically significant conclusion [17, 18]. Surprisingly, trials combining ENB with fluoroscopy reported significantly lower diagnostic yields. Nevertheless, one cannot conclude from these data that fluoroscopy decreases the yield of ENB. Indeed, this observational association emerges from a univariate analysis and therefore may be attributed to confounding factors (type I error). Finally, making use of EBUS or the catheter suction technique was not significantly associated with better outcomes in our meta-analysis, despite promising results from individual trials. This is easily explained by a lack of statistical power, as these techniques were only used in a few trials.

In contrast to the aforementioned study-level characteristics, analysis of patient-level characteristics is notoriously subject to caution in meta-analyses, because of potential ecological biases. With that reservation, 3 patient-level characteristics were significantly associated with fluctuations in ENB's performance. First, better yields were seen in more recent trials, which could be attributed to technological improvements in the quality of the ENB (e.g. software updates) and/or overcoming the institutional and operator-dependent learning curves. Also, studies with a higher prevalence of malignancy reported better diagnostic yields. However, the underlying etiology of lung nodules has only been inconsistently identified as a predicting factor of the yield of any sampling modality for lung lesions. Finally, trials with higher percentages of nodules located in the upper lobes reported lower ENB yields; this contrasts with the opposite finding in an original study by Eberhardt et al. [18]. Nevertheless, this was not a statistically robust finding (see above) and it contrasts with expected outcomes, since alignment between CT images and actual anatomy should be more accurate a priori in the upper lobes, where respiratory movement artifact is minimal.

Strengths and Limitations

Trials assessing the diagnostic accuracy of tissue sampling techniques usually report very different outcomes,

which may be variably defined. Pooling or comparing these outcomes to other techniques can therefore be problematic. For example, many studies overestimate the diagnostic yield by defining it as the rate of initial malignancy status (malignant vs. not malignant) confirmed by further testing (i.e. what we defined as malignancy status accuracy). A stricter definition of diagnostic yield such as the one we chose (i.e. a definitive diagnosis precluding further testing or follow-up), is associated with lower yields as evidenced by our analysis (64.9 vs. 78.6%). To overcome this problem, we reconstructed a relatively large panel of well-defined performance outcomes from the reported results of ENB. This approach provides yields which can be reliably compared to those of other sampling techniques.

The lack of well-defined inclusion criteria in selected studies is a limitation of this meta-analysis. The choice of ENB as a sampling technique remains inconsistent between centers and cannot be definitively addressed by our study. In addition, factors influencing the performance of ENB still need clarification, because heterogeneity exploration in meta-analysis is a univariate method subject to confounding factors. Moreover, the limited number of original trials evaluating similar variables precludes a definitive assessment of predictive factors. Pooling data from each nodule in an individual patient data meta-analysis might be the solution to accurately identify predicting factors of ENB's yield.

Conclusion

ENB is an effective and safe procedure to sample peripheral pulmonary lesions. The yield of this technique seems to be similar to other guided endoscopic procedures. The combination of ENB and radial EBUS may lead to significantly better yields. ENB's performance seems slightly inferior to reported outcomes with CT-guided transthoracic needle biopsies. The same can be said for other guided bronchoscopic techniques. However, the major strength of the ENB approach is clearly its safety profile, especially regarding the risk of procedure-related pneumothorax, which is about 10 times lower. Further analysis and adequately powered prospective studies are needed to clarify the role of several variables conditioning the diagnostic yield of this emerging endoscopic technique.

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