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Sensitivity and Safety of Electromagnetic Navigation Bronchoscopy for Lung Cancer Diagnosis

Systematic Review and Meta-analysis

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BACKGROUND: Bronchoscopy is a useful tool for the diagnosis of lesions near central airways; however, the diagnostic accuracy of these procedures for peripheral pulmonary lesions (PPLs) is a matter of ongoing debate. In this setting, electromagnetic navigation bronchoscopy (ENB) is a technique used to navigate and obtain samples from these lesions. This systematic review and meta-analysis aims to explore the sensitivity of ENB in patients with PPLs suspected of lung cancer.

RESEARCH QUESTION: In patients with peripheral pulmonary lesion suspected of lung cancer, what is the sensitivity and safety of electromagnetic navigation bronchoscopy compared to surgery or longitudinal follow up?

STUDY DESIGN AND METHODS: A comprehensive search of several databases was performed. Extracted data included sensitivity of ENB for malignancy, adequacy of the tissue sample, and complications. The study quality was assessed using the QUADAS-2 tool, and the combined data were meta-analyzed using a bivariate method model. A summary receiver operatic characteristic curve (sROC) was created. Finally, the quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation approach.

RESULTS: Forty studies with a total of 3,342 participants were included in our analysis. ENB reported a pooled sensitivity of 77% (95% CI, 72%-82%; I^2 = 80.6%) and a specificity of 100% (95% CI, 99%-100%; I^2 = 0%) for malignancy. The sROC showed an area under the curve of 0.955 (P = .03). ENB achieved a sufficient sample for ancillary tests in 90.9% (95% CI, 84.8%-96.9%; I^2 = 80.7%). Risk of pneumothorax was 2.0% (95% CI, 1.0-3.0; I^2 = 45.2%). We found subgroup differences according to the risk of bias and the number of sampling techniques. Meta-regression showed an association between sensitivity and the mean distance of the sensor tip to the center of the nodule, the number of tissue sampling techniques, and the cancer prevalence in the study.

INTERPRETATION: ENB is very safe with good sensitivity for diagnosing malignancy in patients with PPLs. The applicability of our findings is limited because most studies were done with the superDimension navigation system and heterogeneity was high.

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FOR EDITORIAL COMMENT, SEE PAGE 1312

ABBREVIATIONS: ENB = electromagnetic navigation bronchoscopy; FN = false negative; FP = false positive; PPL = peripheral pulmonary lesion; r-EBUS = radial endobronchial ultrasound needle aspiration; ROSE = rapid on-site examination; TN = true negative; TP = true positive; TTNA = transthoracic needle aspiration

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Lung cancer is one of the most commonly diagnosed malignancies and the leading cause of cancer-related mortality in both men and women globally.[1] Early diagnosis of lung cancer is an important proximate objective to facilitate curative intent. According to current clinical practice guidelines, a minimally invasive approach is strongly recommended for patients with pulmonary nodules or lesions suspected of lung cancer.[2] For lesions proximal to central airways, procedures such as endobronchial ultrasound needle aspiration have a sensitivity of > 90% and a specificity of > 95% for diagnosis and mediastinal staging.[2,3] Although evidence regarding suspicious lesions near the central airways is strong, accuracy for peripheral pulmonary lesions (PPLs) suspected of lung cancer is variable. Furthermore, data regarding the accuracy of radial endobronchial ultrasound needle aspiration (r-EBUS) is only fair, with the AQuIRe registry reporting a diagnostic yield of 57%.[4] In an attempt to improve the yield, several image-guided biopsy diagnostic tools have been developed in the last decade. Electromagnetic navigation bronchoscopy (ENB) allows physicians to access PPLs beyond the reach of conventional bronchoscopy through a minimally invasive method, using an image-guided flexible catheter and a dedicated navigation software system (superDimension [Medtronic], SpiNDrive [Veran], etc).[5] This procedure is an alternative to transthoracic needle aspiration (TTNA), a procedure with a sensitivity for detecting malignancy of 92.1%.[6] Despite displaying a good sensitivity for cancer diagnosis, TTNA accounts for pneumothorax rates of 25.3% when core biopsy is performed and 18.8% when fine needle aspiration is performed, requiring chest tube placement in up to 11.9% of cases.[7]

This systematic review and meta-analysis evaluated the sensitivity and safety of ENB for the sampling of PPLs suspected of lung cancer.

Materials and Methods

This systematic review and meta-analysis was performed according to the current recommendation from the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies statement.[8] Full protocol and register were previously published in the PROSPERO database (CRD 42019109449).

Literature Search

A highly sensitive database search was conducted by a review author (G. L.), without language restriction, using the following databases: PubMed (MEDLINE), Embase, LILACS (www.scielo.org), Clinical Trials (ClinicalTrials.gov), Cochrane Central Register of Controlled Trials, ScienceDirect (www.sciencedirect.com), Scirus (www.scirus.com/srsapp), ISI Web of Knowledge (www.isiwebofknowledge.com), and Google Scholar (http://scholar.google.com). An initial literature search was performed in May 2019 and updated in November 2019. References from the included studies were also manually searched along with the abstracts of potential studies presented in conferences from 2014 through 2019 by the American Thoracic Society, American College of Chest Physicians, European Respiratory Society, and American Association for Bronchology & Interventional Pulmonology. The full literature search strategy is available in e-Appendix 1.

Inclusion Criteria: Criteria for inclusion were as follows: (1) ENB used for diagnosis of PPLs, (2) diagnosis confirmed histologically or by close clinical follow-up, and (3) studies that stated a clear reference standard for establishing diagnostic sensitivity. We excluded review papers, letters, or studies in which data to calculate sensitivity for malignancy was insufficient. Studies were selected for inclusion only after both reviewers assessed the full text.

Selection of Studies: The references identified after the literature search were included in Covidence software (Veritas Health Innovation Ltd). A highly specific hand search screening of both titles and abstracts was independently performed by two review authors (G. L. and D. O.-D.). Eligible studies were evaluated in full text and selected according to our prespecified inclusion and exclusion criteria; any disagreement was resolved by discussion.

Data Extraction and Quality Assessment: Two independent reviewers (G. L. and D. O.-D.) extracted data from each study. The following information was collected: first author, publication year, publication type (retrospective or prospective), number of participants, index test, reference standard, number of techniques, true positives (TPs), false positives (FPs), true negatives (TNs), false negatives (FNs), use of rapid on-site examination (ROSE) (yes or no), nodule size, fluoroscopy use (yes or no), r-EBUS use (yes or no), cancer prevalence, and successful navigation to the target lesion. Cancer prevalence was defined as the total lung cancer cases (TPs + FNs) divided by the total population included in each study. Successful navigation was defined as the number of lesions in which navigation was successful divided by the number of lesions in which navigation was attempted.

Quality assessment was performed using the QUADAS-2 tool[9] by two reviewers (G. L. and D. O.-D.). We rated the risk of bias because of

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patient selection, index test, reference standard, flow and timing, and applicability concern in their respective domains. Finally, we rated the overall risk of bias and categorized it as low risk or high risk according to the results of the QUADAS-2 analysis. Any disagreement was resolved by a third reviewer (F. K.).

Data Analysis: Pooled data were analyzed and imported in a two-by-two contingency table. The principle outcome was defined as the pooled sensitivity of ENB for malignancy (lung cancer). Sensitivity was calculated as TP/TP + FN, including the total navigation cases (successful and nonsuccessful navigation). Specificity (TN/TN + FP), negative likelihood ratio, and positive likelihood ratio were also reported. For quantitative analyses, we performed a proportions meta-analysis after a binomial distribution.[10] We used the metaprop command with a Freeman-Tukey double arcsine transformation on STATA software version 14.2 (Stata Corp)[11] and Open Meta Analyst software (Brown University).[12] We also created a summary receiver operatic characteristic curve.[10,13] All results were expressed as a percentage and a 95% CI with an alpha value of 0.05.

Interstudy heterogeneity (percentage of total variation across studies that is caused by heterogeneity rather than chance) was measured using visual inspection of a forest plot and an I^2 test. Significant heterogeneity was defined as an $I^2 > 75\%$ and nonsignificant was defined as $I^2 < 40\%$ according to previous publications.[14] In the case of significant heterogeneity, subgroup analysis evaluating possible explanations of the difference between groups was explored.[15] We prespecified the following variables as potential subgroups: (1) risk of bias of included studies, (2) type of navigation system used (superDimension or others), (3) use of ROSE, (4) use of fluoroscopy guidance, (5) type of anesthesia (general, conscious sedation, or both), (6) r-EBUS use, (7) time interval in which the study was performed, and (8) number of sampling techniques used in association to ENB. Finally, heterogeneity between subgroups was assessed with a Q test.

The potential for publication bias was evaluated through both visual inspection of the funnel plot and Egger test. Asymmetry in the distribution of the studies in the funnel plot raised concerns about serious publication bias.[16]

Complementary Analysis: Adequacy of the Sample Achieved by ENB and Association Between Sensitivity and Covariables: A random effects model was used in cases in which heterogeneity between studies was high. A fixed random effects model was used in cases in which this heterogeneity was low. For overall sensitivity, both models were used, and results were compared. We performed two complementary data analyses. For the first analysis, we explored the association between pooled sensitivity for the diagnosis of malignancy and continuous variables related to ENB procedure through a meta-regression. The dependent variable was defined as the pooled sensitivity for lung cancer. We used the following independent continuous covariables related to ENB procedures to run the model: cancer prevalence, distance between tip of sensor and center of nodule, duration of the procedure, number of sampling techniques used in association to ENB, and nodule size.[17] For the second complementary analysis, we explored the adequacy of samples obtained through ENB to test for driver oncogenes. In this case, we performed a binary effect meta-analysis after a maximum likelihood method. A sufficient sample was defined as a sample obtained using ENB that allowed the performance of the ancillary test. For calculation, we used the proportion of participants in which a sufficient sample was achieved relative to all participants in which a sample for ancillary testing was attempted as an effect measure.

Safety Analysis: Additionally, we reviewed the safety of ENB by assessing the proportion of patients that developed the following adverse events: (1) pneumothorax requiring chest tube placement; (2) minor bronchopulmonary bleeding, defined as bleeding that stopped spontaneously in < 5 min or with the use of a Fogarty balloon; (3) major bronchopulmonary bleeding, defined as bleeding that did not meet minor bleeding criteria; (4) acute respiratory failure; and (5) need for a repeat biopsy.

The effect measure used was the proportion of participants who developed the adverse event relative to all the participants included in each study.

Finally, we created a summary of findings table of the diagnostic test results,[18] and the quality of evidence was rated by a panel (G. L. and F. K.) following the Grading of Recommendations Assessment, Development and Evaluation approach.

Results

Overview of Eligible Trials

A thorough electronic database search retrieved 2,198 citations from different sources and 160 potential studies were identified for analysis. After examining those articles, 75 articles were suitable for full-text review, and 35 articles were excluded. A total of 40 studies were included in the qualitative and quantitative analyses.[19-58] A summary of the literature search following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies statement is shown in Figure 1.

Study Characteristics

The summary of the study characteristics is shown in Table 1. A total of 3,342 participants were extracted from the selected articles with a mean age of 64.5 years. Out of 40 studies, 18 were conducted in North America (45%), 10 in Europe (25%), nine in Asia (22.5%), two in both the United States and Europe (5%), and one in Oceania (2.5%). The median number of participants per study was 35 (range, 10-1,157), and successful navigation to the target lesion was achieved in 3,290 of 3,356 PPLs (98%) included. When the number of centers was evaluated, 37 (92.5%) studies were conducted in a single center and three (7.5%) were multicenter (range, 2-29 centers). Regarding study design, 21 (52.5%) were retrospective and 19 (47.5%) were prospective trials. Two studies were double-arm.[23,53] The superDimension system was used in 38 studies (95%). The average lesion size was 23.2 mm (range, 15-39.8 mm), the average mean distance between the tip of the sensor and the center of the nodule was 8.2 mm (range, 6.3-12.2 mm), and the mean duration of the procedure was 46.3 min (range, 16.8-95.3 min). The average cancer prevalence

was 66% (median, 48.2%; range, 20%-92%), and the mean follow-up period was 14.3 months (median, 12; range, 3-24 months).

Quality Assessment

The risk of bias was evaluated in all studies using the QUADAS-2 tool. Out of 40 studies, 19 reported low risk of bias in most aspects; however, a high or unclear risk of bias regarding patient selection, index test, and the reference standard was found in most studies because no proper reference standard was used. The definition of navigation success varied across the studies, possibly resulting in selective reporting. A full report of the risk of bias assessment is shown in Table 2.

Sensitivity of ENB

A total of 40 studies were included in the quantitative analysis, including 3,342 participants pooled in the meta-analysis. The overall sensitivity of ENB for the diagnosis of lung cancer was 77% (95% CI, 72%-82%; $I^2 = 80.6\%$) using a random effects model (Fig 2); when a fixed effects model was done, sensitivity only dropped to 76% (95% CI, 74%-78%; $I^2 = 0\%$). Specificity was 100% (95% CI, 99%-100%; $I^2 = 0\%$) (Fig 2). The negative likelihood ratio was 0.2 (95% CI, 0.1-0.3; $I^2 = 0\%$) and the positive likelihood ratio was 15.8 (95% CI, 10.3-24.2; $I^2 = 0\%$). The summary receiver operatic characteristic curve showed an area under the curve of 0.95 (SE, 0.01; $P = .03$) (e-Fig 1). Based on a visual inspection of the funnel plot (e-Fig 2), publication bias was low. Egger test was nonsignificant ($P = .16$). Finally, using the Grading of Recommendations Assessment, Development and Evaluation approach, diagnostic sensitivity and specificity were determined to be low because of the risk of bias and imprecision (high heterogeneity between studies) (Table 3).

Subgroup Analysis and Explaining Heterogeneity

A summary of the subgroup analysis is presented in Table 4. Analysis according to the risk of bias showed that studies with high risk had a sensitivity of 66.9% (95% CI, 59%-74%; $I^2 = 78.5\%$), whereas sensitivity increased to 77.1% (95% CI, 71.2%-82.1%; $I^2 = 60.2\%$) when studies had a low risk. There was significant heterogeneity between subgroups with a Q statistic of $P < .01$.

A subgroup analysis of studies over time showed no differences in sensitivity when studies were grouped in 2-year intervals. The time interval with the lowest sensitivity was 2015 to 2016, with only a 64% pooled

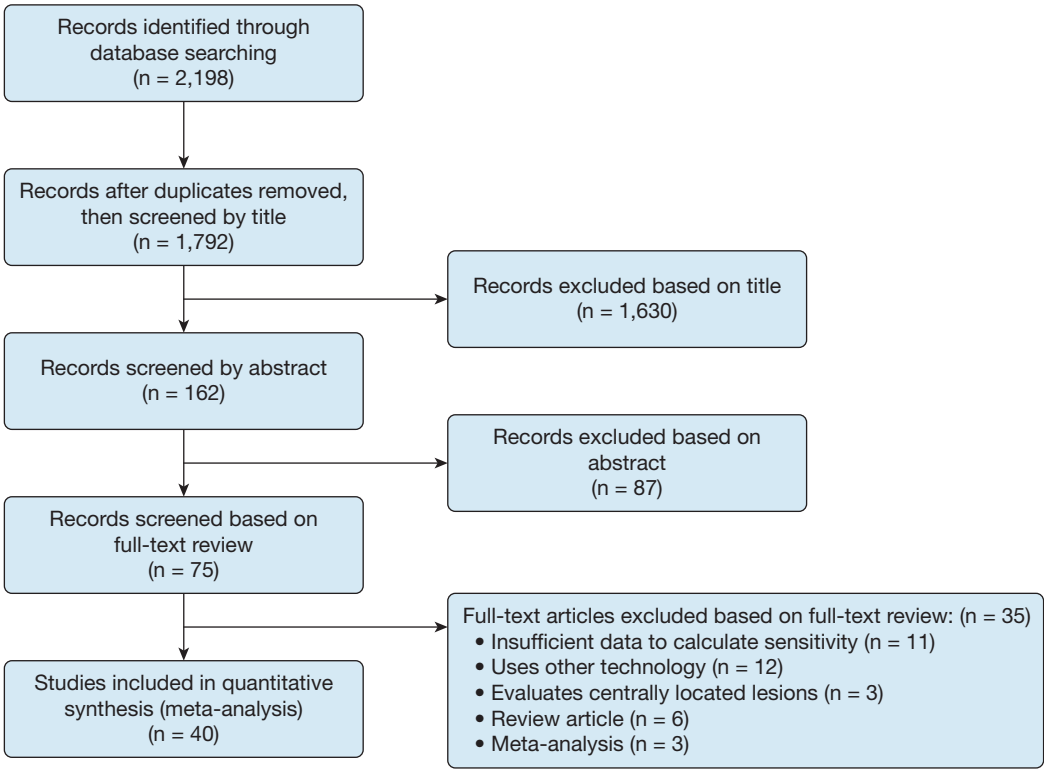

Figure 1 – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.*

TABLE 1] Characteristics of Studies Included in Meta-analysis

Study	Country	Enrolled Participants With PPL	Sensitivity	Mean/Median Age (y)	No. of Centers	Design (Retro-/Prospective)	Nodule Size Average (mm)	Duration of Follow-up (mo)	Criterion Standard (Thoracoscopy, CT Punction, Other)
Becker et al[19]	Germany	30	0.63	65	1	Prospective, single arm	39.8	Not reported	Surgery, follow-up
Hautmann et al[20]	Germany	16	1.00	63.7	1	Prospective, single arm	Not reported	Not reported	Not reported
Gildea et al[21]	USA	49	0.74	67.9	1	Prospective, single arm	22.8	10.5	Thoracotomy, CT scan-fine needle aspiration, mediastinoscopy, and PET scan
Schwarz et al[22]	Israel	15	0.64	Not reported	1	Prospective, single arm	33.5	Not reported	CT scan-fine needle aspiration, surgery
Eberhardt et al[23]	Germany/ USA	39	0.55	55	2	Prospective, RCT (EBUS only, ENB only, or combined)	28	Not reported	Surgery
Eberhardt et al[23]	Germany/ USA	40	0.90	51	2	Prospective, RCT (EBUS only, ENB only, or combined)	24	Not reported	Surgery
Eberhardt et al[24]	Germany/ USA	89	0.74	67	2	Prospective, single arm	24	16.1	CT scan-fine needle aspiration, surgery
Makris et al[25]	France	40	0.61	60	1	Prospective, single arm	23.5	Not reported	Open lung biopsy, mediastinoscopy, TTNA
Wilson and Bartlett[26]	USA	222	0.90	63.1	1	Retrospective, single arm	21	6	CT scan-fine needle aspiration, surgery
Bertoletti et al[27]	France	54	0.71	67	1	Prospective, single arm	31.2	> 18	Surgery, TTNA
Lamprecht et al[28]	Austria	13	0.67	64.2	1	Retrospective, single arm	30	Not reported	Surgery, CT scan-fine needle aspiration
Eberhardt et al[29]	Germany	54	0.72	65.1	1	Prospective, single arm	23.3	Not reported	Surgery, CT scan-fine needle aspiration, follow-up
Seijo et al[30]	Spain	51	0.74	62	1	Prospective, single arm	25	Not reported	Surgery, CT scan-fine needle aspiration, follow-up
Mahajan et al[31]	USA	48	0.67	Not reported	1	Retrospective, single arm	20	Not reported	

(Continued)

TABLE 1] *(Continued)*

Study	Country	Enrolled Participants With PPL	Sensitivity	Mean/Median Age (y)	No. of Centers	Design (Retro-/ Prospective)	Nodule Size Average (mm)	Duration of Follow-up (mo)	Criterion Standard (Thoracoscopy, CT Punction, Other)
									VATS, CT scan-fine needle aspiration, follow-up
Brownback et al[32]	USA	55	0.69	63	1	Retrospective, single arm	30	Not reported	Surgery, CT scan-fine needle aspiration
Pearlstein et al[33]	USA	104	0.82	69	1	Retrospective, single arm	28	24	Surgery, CT scan-fine needle aspiration, follow-up
Balbo et al[34]	Italy	40	0.76	71.5	1	Retrospective, single arm	23.5	Not reported	Surgery, CT scan-fine needle aspiration
Karnak et al[35]	Turkey	35	1.00	55.4	1	Prospective, single arm	23.1	24	Surgery, follow-up
Mohanasundaram et al[36]	USA	41	0.88	65	1	Retrospective, single arm	30.1	24	Surgery, CT scan-fine needle aspiration, follow-up
Loo et al[37]	USA	40	0.88	67	1	Retrospective, single arm	26	Not reported	Surgery, CT scan-fine needle aspiration, follow-up
Odronic et al[38]	USA	91	0.63	66	1	Retrospective, single arm	27	12	Surgery, CT scan-fine needle aspiration, follow-up
Bowling et al[39]	USA	96	0.84	67	1	Retrospective, single arm	Not reported	> 18	Surgery, TTNA, follow-up
Steinfort et al[40]	Australia	57	0.19	69	1	Prospective, single arm	19.1	12	Surgery, CT scan-fine needle aspiration, follow-up
Garwood et al[41]	USA	90	0.69	65.6	1	Retrospective, single arm	22.7	24	Surgery, follow-up
Ozgul et al[42]	Turkey	56	0.65	60	1	Prospective, single arm	30	24	Surgery, CT scan-fine needle aspiration
Raval and Amir[43]	USA	50	0.58	67.7	1	Retrospective, single arm	19.3	24	Surgery, TTNA, follow-up
Flenaugh and Mohammed[44]	USA	41	0.80	62.4	1	Retrospective, single arm	22.1	12	Surgery, TTNA
Bowling et al[45]	USA	14	0.43	58.6	1	Retrospective, single arm	23.5	Not reported	Follow-up

(Continued)

TABLE 1] *(Continued)*

Study	Country	Enrolled Participants With PPL	Sensitivity	Mean/Median Age (y)	No. of Centers	Design (Retro-/Prospective)	Nodule Size Average (mm)	Duration of Follow-up (mo)	Criterion Standard (Thoracoscopy, CT Punction, Other)
Sun et al[46]	China	40	0.87	59	1	Prospective, single arm	21.1	12	Surgery, CT scan-fine needle aspiration, follow-up
Huang et al[47]	China	18	1.00	68	1	Prospective, single arm	Not reported	Not reported	Not reported
Gu et al[48]	China	78	1.00	53.5	1	Prospective, single arm	19	12	Follow-up
Mukherjee and Chacey[49]	USA	31	0.96	66	1	Retrospective, single arm	18	12	FNA, follow-up
Patrucco et al[50]	Italy	113	0.75	72.4	1	Retrospective, single arm	24.6	24	Surgery, CT scan-fine needle aspiration, follow-up
Panchabhai et al[51]	USA	10	1.00	64.3	1	Retrospective, single arm	20.5	Not reported	Follow-up
Sato et al[52]	Japan	35	0.81	…	1	Prospective, single arm	15.2	3	Surgery, follow-up
Taton et al[53]	Belgium	32	0.32	68	1	Prospective, double arm	16	6	Surgery, follow-up
Taton et al[53]	Belgium	32	0.56	68	1	Prospective, double arm	16	6	Surgery, follow-up
Pritchett et al[54]	USA	75	0.91	70	1	Retrospective, single arm	16	Not reported	Surgery, follow-up
Sobieszczyk et al[55]	USA	22	1.00	69	1	Retrospective, single arm	21	6	Follow-up
Cho et al[56]	South Korea	30	0.75	64	1	Retrospective, single arm	18.4	8	TTNA, follow-up
Folch et al[57]	USA	1,157	0.71	67.6	29	Prospective, single arm	20	12	Surgery, TTNA, follow-up
Cheng and Chu[58]	China	99	0.75	69.1	1	Retrospective, single arm	26	12	Surgery, TTNA

EBUS = endobronchial ultrasound needle aspiration; ENB = electromagnetic navigation bronchoscopy; FNA = fine needle aspiration; PPL = peripheral pulmonary lesion; RCT = randomized controlled trial; TTNA = transthoracic needle aspiration; VATS = video-assisted thoracoscopic surgery.

TABLE 2] QUADAS-2 Electromagnetic Navigation Bronchoscopy

Study	Risk of Bias				Applicability Concerns			Overall
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard	
Becker et al[19]	L	L	L	H	H	L	L	H
Hautmann et al[20]	L	L	U	U	H	L	U	H
Gildea et al[21]	L	L	L	H	L	L	L	L
Schwarz et al[22]	L	L	L	H	H	L	L	H
Eberhardt et al[23]	L	L	L	L	L	L	L	L
Eberhardt et al[24]	L	L	L	H	L	L	L	L
Makris et al[25]	L	L	L	H	L	L	L	L
Wilson and Bartlett[26]	H	L	L	H	H	L	L	H
Lamprecht et al[28]	H	L	L	H	H	L	L	H
Bertoletti et al[27]	L	L	L	H	H	L	L	H
Eberhardt et al[29]	L	L	L	H	L	L	L	L
Seijo et al[30]	L	L	L	H	L	L	L	L
Mahajan et al[31]	H	L	L	H	L	L	L	L
Brownback et al[32]	H	L	L	H	L	L	L	L
Pearlstein et al[33]	H	L	L	H	L	L	L	L
Balbo et al[34]	H	L	L	H	H	L	L	H
Karnak et al[35]	L	L	L	H	L	L	L	L
Mohanasundaram et al[36]	H	L	L	H	L	L	L	L
Loo et al[37]	H	L	L	H	L	L	L	L
Odronic et al[38]	H	L	L	H	L	L	L	L
Bowling et al[39]	H	L	L	H	L	L	L	L
Steinfort et al[40]	L	L	L	H	H	L	L	L
Garwood et al[41]	H	L	L	H	L	L	L	L
Ozgul et al[42]	L	L	L	H	L	L	L	L
Raval and Amir[43]	H	L	L	H	L	L	L	L
Flenaugh and Mohammed[44]	H	L	L	H	L	L	L	L
Bowling et al[45]	H	L	L	H	L	L	L	L
Sun et al[46]	L	L	L	H	L	L	L	L
Huang et al[47]	L	L	U	U	L	L	U	L
Gu et al[48]	H	L	L	H	H	L	L	H
Mukherjee and Chacey[49]	H	L	L	H	L	L	L	L
Patrucco et al[50]	H	L	L	H	L	L	L	L
Panchabhai et al[51]	H	L	L	H	H	L	L	H
Sato et al[52]	L	L	L	H	L	L	L	L
Taton et al[53]	L	L	L	H	L	L	L	L
Pritchett et al[54]	H	L	L	H	L	L	L	L
Sobieszczyk et al[55]	H	L	L	H	L	L	L	L
Cho et al[56]	H	L	L	H	L	L	L	L
Folch et al[57]	L	L	L	H	L	L	L	L
Cheng and Chu[58]	H	L	L	H	L	L	L	L

H = high risk of bias; L = low risk of bias; U = unclear risk of bias.

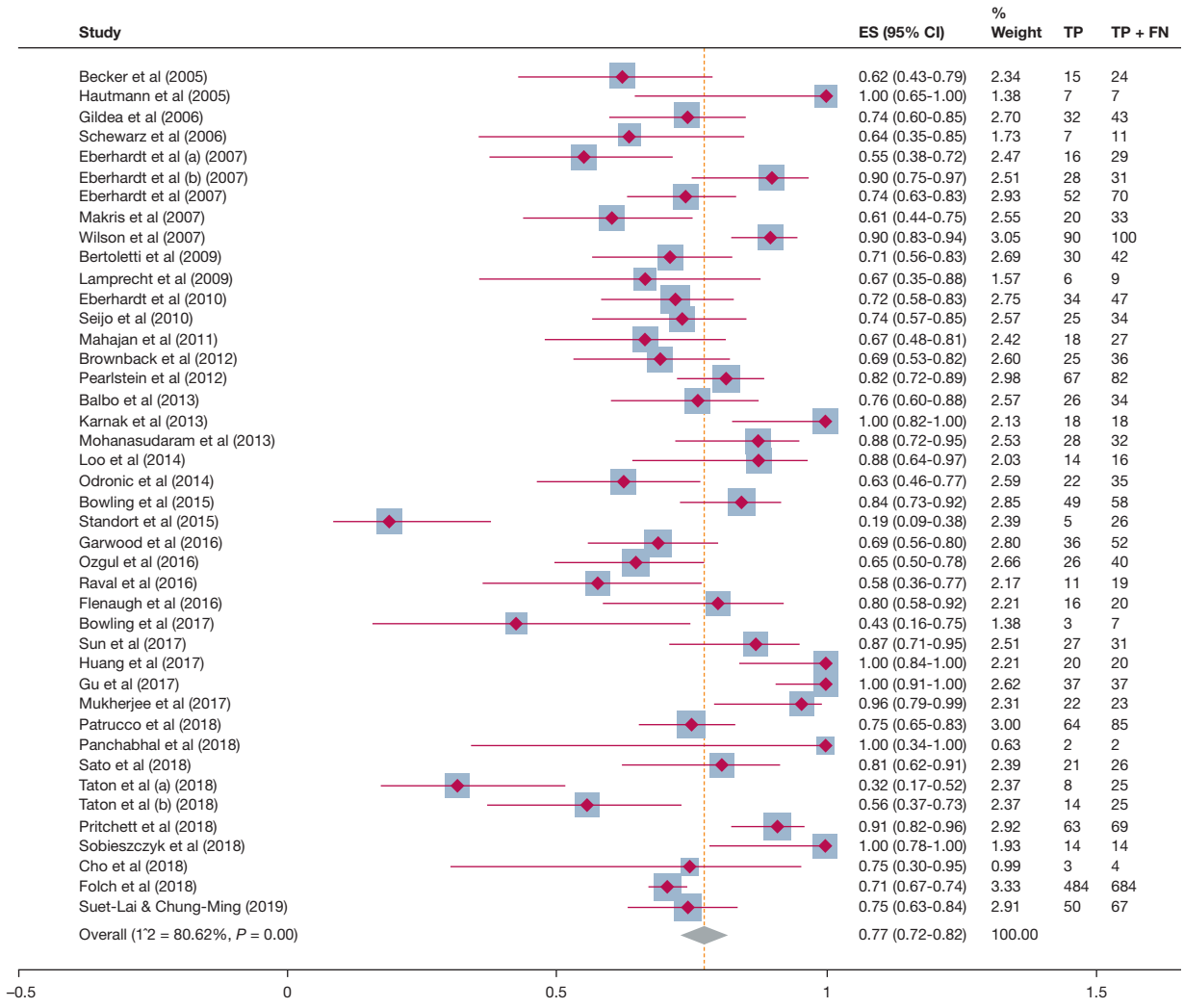

Figure 2 – *Forest plots of sensitivity and specificity of electromagnetic navigation bronchoscopy in suspected lung cancer. ES = effect size; TP = true positive; TP+FN = true positive and false negative.*

sensitivity. The heterogeneity between subgroups was nonsignificant with a Q statistic of $P = .55$.

Although different navigation systems were used, similar sensitivities were reported. Used in 38 studies, the superDimension system had a pooled sensitivity of 78% (95% CI, 73%-83%; $I^2 = 81.31$). Two studies included in the analysis used other navigation systems, with a pooled sensitivity of 70% (95% CI, 54%-84%; $I^2 =$ not applicable). There was no significant heterogeneity between subgroups with a Q statistic of 0.37.

The type of sedation used showed no difference in the pooled sensitivity between subgroups. General anesthesia was used in 16 studies; the pooled sensitivity for this group was 74% (95% CI, 66%-81%; $I^2 = 69.3\%$). On the other hand, 15 studies used only conscious sedation, with a pooled sensitivity of 75% (95% CI, 65%-84%; $I^2 = 81.8\%$). Four studies used a mix of general anesthesia and conscious sedation, with a pooled sensitivity of 74% (95% CI, 65%-81%; $I^2 = 62.7\%$). However, there was no significant heterogeneity between subgroups with $P = .09$.

Using complementary techniques such as ROSE, r-EBUS, or fluoroscopy did not result in differences in pooled sensitivity between subgroups. First, use of ROSE was reported in 20 studies, and pooled analysis showed a sensitivity of 76% (95% CI, 69%-83%; $I^2 = 83.0\%$), whereas sensitivity for ENB without ROSE was reported in 14 studies, with a pooled sensitivity of 81% (95% CI, 74%-88%; $I^2 = 67.7\%$), with no significant heterogeneity between subgroups ($P = .51$). A total of 19 studies

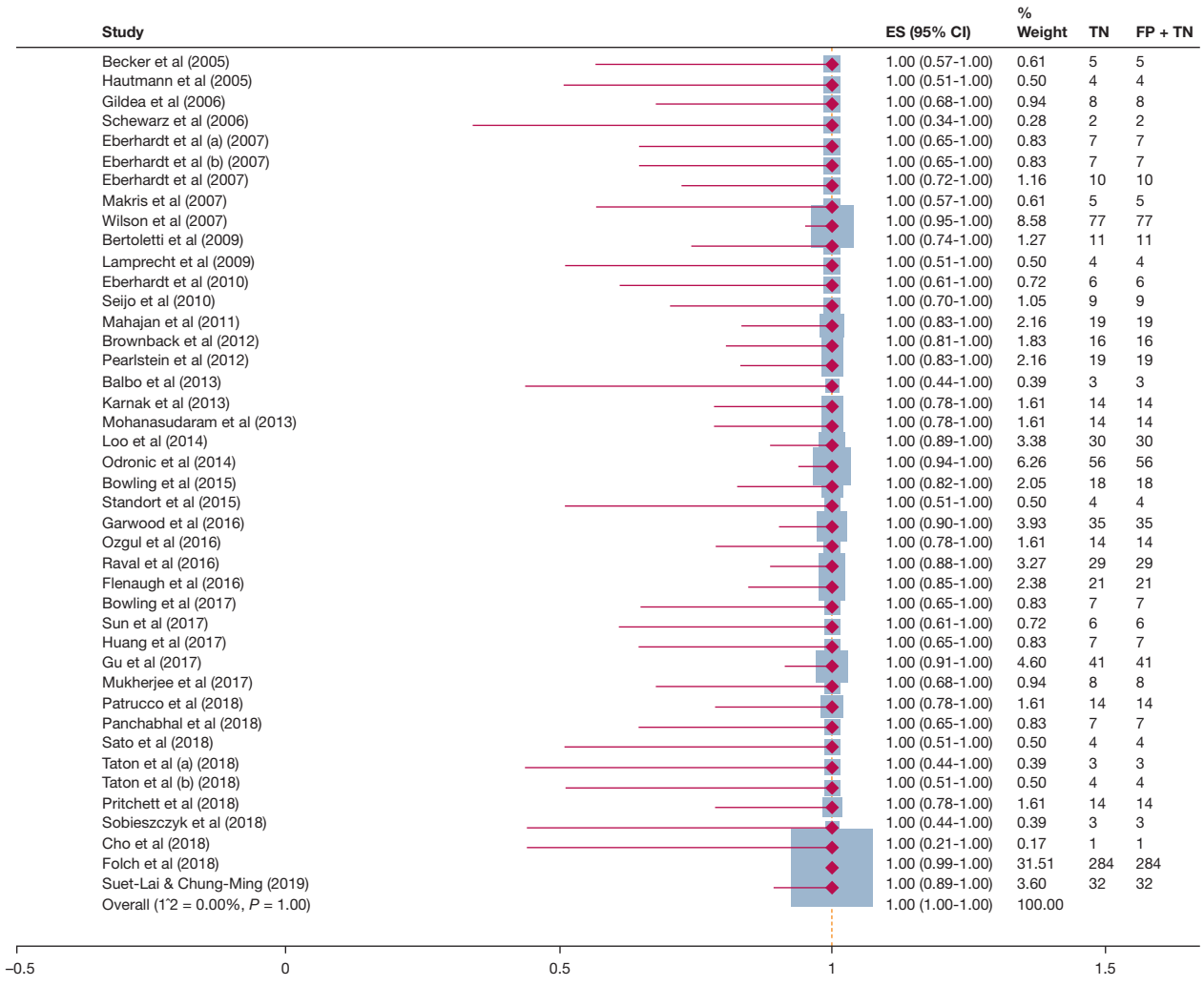

Figure 2 – *Continued*

reported fluoroscopy guidance in association with ENB, with a sensitivity of 74% (95% CI, 65%-81%; $I^2 = 84.2\%$) compared with 15 studies that reported ENB without fluoroscopy, with a pooled sensitivity of 83% (95% CI, 71.7%-89%; $I^2 = 62.7\%$), without significant heterogeneity between subgroups ($P = .09$). Finally, the use of r-EBUS reported a pooled sensitivity of 80% (95% CI, 74%-83%; $I^2 = 73\%$) compared with 72% (95% CI, 66%-76%; $I^2 = 85.5\%$) without r-EBUS.

Regarding the number of sampling techniques used in association with ENB, different combinations of forceps, brush, needle, cryoprobe, GenCut (Medtronic), and triple needle brush were reported, including seven studies reporting one technique with a pooled sensitivity of 67% (95% CI, 53%-79%; $I^2 = 75.8\%$), 11 studies reporting two techniques with a pooled sensitivity of 72% (95% CI, 60%-83%; $I^2 = 82.2\%$), 19 studies reporting three techniques with a pooled sensitivity of 83% (95% CI, 76%-89%; $I^2 = 75.1\%$), one study using four sampling techniques with a sensitivity of 91% (95% CI, 82%-96%), and two studies using five different techniques, with a pooled sensitivity of 72% (95% CI, 69%-76%; $I^2 =$ not applicable).

We found significant heterogeneity between subgroups ($P < .01$).

Sensitivity Analysis: Meta-Regression Report

We found statistically significant positive associations between sensitivity and cancer prevalence reported as a beta regression coefficient of 3.45 (95% CI, 2.28-4.61; SE, 0.59; $P \leq .001$), and between sensitivity and number of sampling techniques with a beta coefficient of 0.32 (95% CI, 0.07-0.58; SE, 0.13; $P = .011$). We also found a statistically significant negative association between sensitivity and mean distance between the tip of sensor and center of nodule, with a beta regression coefficient

TABLE 3] Summary of Findings Using the Grading of Recommendations Assessment, Development and Evaluation Approach

Outcome	No. of Studies (No. of Patients)	Study Design	Factors That May Decrease Certainty of Evidence					Effect per 1,000 Patients Tested	Test Accuracy Confidence of Evidence
			Risk of Bias	Indirectness	Inconsistency	Imprecision	Publication Bias	Pretest Probability of 66%[a]	
Specificity	40 (3,342)	Cross-sectional (cohort-type accuracy study)	Serious[b]	Not serious	Not serious	Not serious	None	152 (119-185)	Moderate
Sensitivity	40 (3,342)	Cross-sectional (cohort-type accuracy study)	Serious[b]	Not serious	Very serious[c]	Not serious	None	508 (475-541)	Low

Sensitivity was 0.77 (95% CI, 0.72-0.82), specificity was 1.00 (95% CI, 0.99-1.00), and prevalence was 66%. Prevalence was estimated using a pooled analysis of included studies.
[a]Pretest probability from the pooled prevalence of lung cancer from included studies. Values shown are number of positive tests reported as test per 1,000 participants, and 95% CI is included in parentheses.
[b]Bias because of difference regarding the navigation success definition used across studies, which is a potential source of selective reporting.
[c]We downgraded because of significant residual heterogeneity in each subgroup.

of −0.38 (95% CI, −0.66 to −0.19; SE, 0.14; $P = .006$). Finally, we found no statistically significant association between sensitivity and average nodule size. A summary of meta-regression results is shown in Table 5.

Adequacy of Samples Obtained by ENB

A total of three studies,[46,50,57] including 610 participants, reported data on the adequacy of samples obtained by ENB to perform driver oncogene testing in patients with a positive biopsy result. All studies were published after 2015. The meta-analysis reported an adequate sample proportion of 90.9% (95% CI, 84.8%-96.9%; $I^2 = 80.7\%$).

Safety Analysis

A summary of adverse events reported in each study is available in e-Table 1. Complication rates after ENB were reported in 39 studies, including a total of 3,253 participants with 3,204 PPLs from data analyses across individual studies (exclusion criteria for individual studies were broad). One study did not report adverse events.[40] Pooled analysis showed a 2.0% rate of pneumothorax (95% CI, 1.0%-3.0%; $I^2 = 42.5\%$) (Fig 3), risk of minor bronchopulmonary bleeding of 1.0% (95% CI, 0.6%-1.3%; $I^2 = 0\%$), risk of major bronchopulmonary bleeding of 0.8% (95% CI, 0.5%-1.1%; $I^2 = 0\%$), and risk of acute respiratory failure of 0.6% (95% CI, 0.4%-0.9%; $I^2 = 0\%$.) Forest plots for different complications are shown in e-Figs 3-6.

Discussion

This systematic review and meta-analysis showed the following: (1) ENB has an overall sensitivity of 77%, a specificity of 100%, a positive likelihood ratio of 15.79, and a negative likelihood ratio of 0.23 for diagnosing PPLs suspected of lung cancer; (2) potential sources of heterogeneity were seen in both risk of bias and number of sampling techniques, with no significant heterogeneity between subgroups noted when navigation system, ROSE, fluoroscopy guidance, anesthesia type, EBUS, or time interval in which the study was performed; (3) sensitivity was associated with lung cancer prevalence, number of sampling techniques used, and mean distance between the tip of the sensor and the center of the nodule; (4) ENB is a very safe procedure with a 2.0% risk of pneumothorax and a risk of any bleeding or respiratory failure of < 1%; and (5) ENB can obtain adequate samples for testing driver oncogenes in 90% of positive biopsies in which additional testing is needed.

TABLE 4] Summary of Subgroup Analysis

Subgroup	Sensitivity (%)	95% CI (%)	I^2 Value (%)	Intergroup heterogeneity
Risk of bias				
Low risk of bias	77	71.2-82.1	60.10	Significant
High risk of bias	67	59-74	78.50	
ROSE				
Yes	72	66-76	34.07	Nonsignificant
No	74	65-80	84.92	
EBUS use				
Yes	80	74-83	73.1	Nonsignificant
No	72	66-76	85.5	
Fluoroscopy guidance				
With fluoroscopy	71	60-79	85.25	Nonsignificant
Without fluoroscopy	74	69-77	24.66	
Navigation system				
Super dimension	78	73-83	81.30	Nonsignificant
Another platform	70	54-84	N.A.	
No. of techniques				
1	67	53-79	75.14	Significant
2	72	60-83	82.24	
3	83	76-89	75.14	
4	91	82-96	N.A.	
5	72	69-76	N.A.	
Type of anesthesia				
General anesthesia	74	66-81	69.29	Nonsignificant
Conscious sedation	75	65-84	81.75	
Combined	74	65-81	62.65	
Time interval				
2005-2006	75	58-88	49.32	Nonsignificant
2007-2008	76	61-89	84.52	
2009-2010	72	64-80	0.00	
2011-2012	75	64-84	N.A.	
2013-2014	84	70-95	74.94	
2015-2016	64	45-81	86.55	
2017-2018	84	73-93	88.03	
2019-2020	75	63-84	N.A.	

N.A. = not applicable; ROSE = rapid on-site examination. See Table 1 legend for expansion of other abbreviation.

Previously, three systematic reviews have been published on the topic. Wang Memoli et al[59] quantitatively analyzed 39 studies (prior to 2010) that described alternative PPL exploration techniques (r-EBUS, ENB, etc). The authors reported a diagnostic yield for any diagnoses of 70%, with a pneumothorax rate of 1.5%.[59] A study by Gex et al[60] described the diagnostic accuracy for any diagnoses of ENB including 15 trials with an overall accuracy of 73.9%, a sensitivity of 71.1%, and a risk of pneumothorax of 3.1%. Finally, Zhang et al[61] included 17 studies of ENB with a pooled sensitivity for cancer diagnoses of 82%, a specificity of 100%, a positive likelihood ratio of 19.36, and a negative likelihood ratio of 0.23. In the present meta-analysis, 40 studies were quantitatively analyzed, including the results of the US cohort for the largest prospective multicenter study, NAVIGATE.[57]

Heterogeneity was high, likely because of a number of factors, including the prevalence of cancer in each study, the average distance between the tip of the sensor and

TABLE 5] Summary of Meta-Regression Analysis

Variable	β Coefficient	95% CI	SE	*P* Value
Cancer prevalence (%)	3.45	2.28 to 4.61	0.59	**< .001**
Distance from tip (mm)	−0.38	−0.66 to −0.19	0.14	**.006**
No. of techniques	0.32	0.07 to 0.58	0.13	**.011**
Nodule size (mm)	−0.018	−0.06 to −0.032	0.02	.484

Boldface indicates statistically significant.

the center of the nodule, and the number of sampling techniques used in each study. These variables are related to differences in sensitivity across studies. Other variables with nonsignificant statistical differences included fluoroscopy use, ROSE use, r-EBUS, anesthesia type, the time interval in which the study was performed, and average nodule size. Different time intervals had similar pooled sensitivities except for 2015 to 2016.

The present analysis also explored the role of the specific navigation software used (superDimension vs others). Different navigation software have described similar sensitivity; however, there was a wide variation in diagnostic definitions. Research on other systems is sparse compared with superDimension; therefore, the conclusion of these analyses is not applicable to other navigation systems. Our data are only applicable for ENB using the superDimension system.

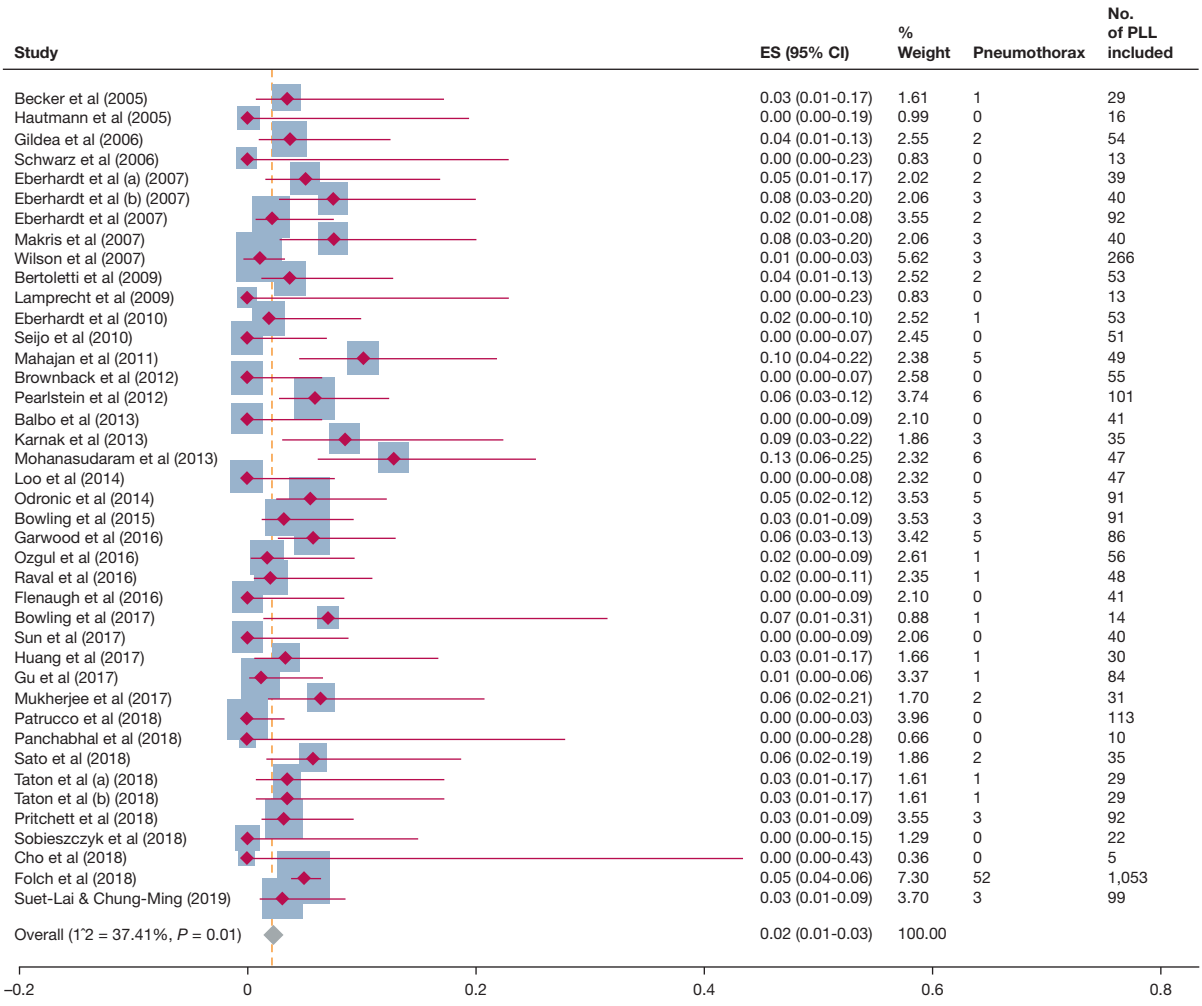

Figure 3 – *Forest plot. Risk of pneumothorax after electromagnetic navigation bronchoscopy. PPL = peripheral pulmonary lesion. See Figure 2 legend for expansion of other abbreviation.*

Compared with other methods, TTNA has historically been the preferred diagnostic method to explore PPLs to avoid unnecessary surgery. TTNA has a pooled sensitivity for cancer diagnosis of 92.1%, with a trend toward lower sensitivity in lesions < 2 cm and in lesions located in the lower lobes, making this an attractive choice in patients with solitary lung lesions without mediastinal or hilar adenopathy.[6,62] However, the overall rate of complications is 24% to 39%, with a risk of pneumothorax ranging between 19% and 25%, depending on the sampling method used.[63] Alternatively, we found that ENB is a safe procedure with < 3% overall complications. These findings are similar to previously reported ones, with the most common complication being pneumothorax, occurring in approximately 2% of patients. Considering these factors, it can be said that the use of ENB is a safe alternative to TTNA, especially in those patients with an increased risk of complications because of comorbidities.

On the other hand, traditional bronchoscopy has shown variable diagnostic accuracy for total diagnoses for PPLs, as shown by the AQuIRE database.[4] r-EBUS has been proposed in the literature as an alternative to increase the diagnostic yield of the previously mentioned technique. A recent systematic review and meta-analysis reported a pooled sensitivity for cancer diagnosis of 72% for PPLs (95% CI, 70%-75%; $I^2 = 76\%$), with a pooled risk of pneumothorax of 0.7% (95% CI, 0.3%-1.1%).[64] Although sensitivity improved when r-EBUS was used, it is difficult to draw conclusions because heterogeneity in the mentioned meta-analysis was high. The addition of other techniques, such as ROSE, endobronchial ultrasound needle aspiration, or fluoroscopy did not increase diagnostic sensitivity, as seen in previous studies.[65]

ENB should be performed with biopsy tools designed to achieve a sufficient sample size for analysis. Our data suggest that the use of three biopsy tools may increase sensitivity to 83%. However, whenever more than four biopsy tools were used, sensitivity dropped to 71%. Drawing conclusions based on these data is difficult given the significant heterogeneity between groups as seen with a positive Q test. A prospective study designed to look at this is necessary to corroborate these findings.

Precision medicine requires a comprehensive approach including the determination of driver oncogenes. Studies describe the percentage of adequate samples where these ancillary tests were performed (molecular testing, flow cytometry, etc). Pooled data from 610 participants showed that when ENB was used, 90% of samples were sufficient for ancillary tests; this proportion is similar to other minimally invasive methods such as endobronchial ultrasound needle aspiration.[66,67] However, only three studies included data about this topic, and future research incorporating data on the ability to achieve a sufficient sample for ancillary tests is necessary. At the time of this publication, international guidelines do not recommend the analysis of driver oncogenes in stage I non-small cell lung cancer, and this is likely to impact the number of available cases for analysis.

This paper was performed according to current recommendations. In the present meta-analysis, a random effects model was predefined because of high heterogeneity between subgroups. This method is strongly recommended in cases of significant interstudy heterogeneity.[14] This approach was based on the binomial distribution as the bivariate model, rather than the DerSimonian and Laird random effects model, because the latter model approximates within-study variability of an outcome by a normal distribution, a method that biases diagnostic test results.[10]

We found the following limitations. First, the presence of an airway sign and distance of the nodule from the pleura were inconsistently reported between different studies; therefore, it was not possible to do subgroup analyses of sensitivity with these variables. Second, we used a trial-level analysis (both subgroup and meta-regression analysis) without patient-specific data; therefore, our findings should be viewed as exploratory.[68] Although we found a biological plausibility between studies with both increased prevalence and average nodule size, those variables are strongly associated with an increased pretest probability of positive samples achieved by any bronchoscopic procedure. However, the results of our meta-regression should be interpreted with caution, and further patient-level data would be necessary to evaluate the potential predictive value of these variables and sensitivity.

Finally, the findings of this systematic review and meta-analysis should inform future research on minimally invasive procedures after a precision medicine approach. We emphasize the importance of considering the human and technologic capital available at each institution to provide patients with the lowest procedural risk while maintaining an adequate sensitivity for tissue diagnosis. In some cases, the presence of mediastinal involvement or pleural effusion will dictate a different diagnostic strategy or a procedure that can be combined under the same anesthetic episode.

Conclusions

ENB is a safe procedure that has good sensitivity for identifying lung cancer, especially in patients with a high pretest probability of malignancy. Significant limitations for this study include the high heterogeneity in several analyses, despite the explanation of potential causes. Further research is needed to improve the evidence of this diagnostic technique.

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Additional information: The e-Appendix, e-Figures, and e-Table can be found in the Supplemental Materials section of the online article.

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