Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: a systematic review and meta-analysis

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ONLINE DATA SUPPLEMENT

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 combining three groups of subjects with the Boolean operator “AND”: 1/ bronchoscopy and synonyms; 2/ guidance OR navigation; 3/ electromagnetism. All terms were exploded. Because search strategies for identifying trials reporting diagnostic accuracy are poorly sensitive,[1,2] no corresponding terms were used to select these studies. We restricted our search to trials published after 2000 because electromagnetic navigation bronchoscopy was first described in 2003. No restriction of study design, population or language was applied. For EMBASE database, the following search strategy was applied: “guid* OR navigat* AND ('bronchoscopy'/syn OR endoscop* NEAR/5 (lung OR pulmon* OR thora* OR bronchi*) OR fibroscop* NEAR/5 (lung OR pulmon* OR thora* OR bronchi)) AND electromagneti* AND [2000-2012]/py”. Reference lists of retrieved papers were independently hand-searched by two investigators for additional articles.

Statistical analysis

The aforementioned outcomes were pooled by using the inverse-variance method with random effects on the logit transformed proportions.[3] A continuity correction was applied to studies with 0% or 100% of events (a count of 0.5 was added to the number of events and a count of 1 to the sample size). Sensitivity analyses were conducted by removing the studies

one-by-one to check the robustness of the results in regard of each study. The presence of between-study heterogeneity was assessed by using the indicator I2.[4] When the I-squared indicated the presence of heterogeneity (>25%) and when the number of studies with available data was at least 10, potential heterogeneity factors were analyzed for performance outcomes by meta-regressions or Cochran tests on the between-strata heterogeneity. When one of the strata contained less than five studies, or if the heterogeneity was explained by a single study, the heterogeneity was not explored. Only significant associations were reported. Prespecified analyzed factors included *study-level characteristics*, i.e. study design (retro- versus prospective), conflict of interest, type of sedation (general anaesthesia versus conscious sedation), use of fluoroscopy, EBUS, or ROSE (Rapid on-site cytological evaluation), type of sampling tools and year of publication, as well as *patient-level characteristics*, i.e. mean age, percentage of female, percentage of nodules located in upper and lower lobes, nodule diameter, distance from nodule to visceral pleura, malignancy prevalence, AFTRE scores (average fiducial target registration error) and distance from the tip of the location sensor to the centre of the nodule. The rates of safety outcomes (pneumothorax and bleedings) were obtained by adding directly the counts reported in the studies. The inverse-variance method was not used for these outcomes because the continuity correction should have been applied to most studies, yielding an overestimation of the risk of adverse events. Publication bias was explored by using Egger's test and the trim and fill method.[5] This method detects potentially missing studies for the funnel plot to be symmetric and assesses the pooled results including these missing studies. All analyses were performed using Comprehensive Meta Analysis Version 2 and S-plus 8.0 for Windows. The significance level was 0.05.

TABLES AND FIGURES

Table E1. Extracted outcomes

Results of Electromagnetic Navigation Bronchoscopy
Total Nb of targeted nodules
Total Nb of sampled nodules (successfully accessed on multiplanar views)
Nb of malignancies (including carcinoids)
Nb of positive, definitive benign diagnoses (e.g. hamartoma, fungal infection)
Nb of benign intermediate results (diagnosis needing confirmation, e.g. chronic inflammation)
Nb of malignant intermediate results (cancer suspicion, e.g. atypical cells)
Nb of indeterminate results (e.g. normal lung tissue)
Complications
Final results after further testing
Total Nb of known final diagnoses
Nb of malignancies (including carcinoids)
Nb of benign conditions
Nb of benign intermediate results confirmed to be benign
Nb of malignant intermediate results confirmed to be malignant

Table E2. Main characteristics of selected studies (participants/nodules)

Study	Beginning of inclusion	Patient selection	Participants, No (% female)	Mean age, yrs	Lung lesions, No	Prevalence of lung cancer	Mean diameter, mm	Location in lower lobe, %	Mean distance to pleura, mm
Becker 2005	2003	PPL beyond the field of FB, regardless of lesion size	30 (23%)	65	30	83%	39.8	27	2
Hautmann 2005	2004	PPL beyond the field of FB	16 (38%)	63.7	16	ND	ND	44	ND
Gildea 2006	2004	Referral for PPL beyond the field of FB	49 (40%)	67.9	56	74%	22.8	30	ND
Schwarz 2006	2003	PPL beyond the field of FB, regardless of lesion size	13	ND	13	92%	33.5	38	ND
Makris 2007	2005	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	ND	15
Eberhardt 2007a	2005	PPL beyond the field of FB	89 (44%)	67	93	76%	24	34	ND
Eberhardt 2007b	2003	PPL beyond the field of FB	39 (49%)	55	39	74%	28	36	ND
Eberhardt 2007b EBUS	2003	PPL beyond the field of FB	40 (38%)	51	40	78%	24	45	ND
Wilson 2007	2005	PPL beyond the field of FB	222 (51%)	63.1	271	57%*	21	37	ND
Bertoletti 2008	2005	PET positive PPL beyond the field of FB, high risk surgery	54 (13%)	67	54	78%	31.2	ND	9
Eberhardt 2009	2005	Referral for small PPL suggestive of malignancy	54 (26%)	65.1	55	89%	23.3	ND	ND
Lamprecht 2009	2005	PPL beyond the field of FB and/or too small to be visible on fluoroscopy	13 (23%)	64.2	13	69%	30	31	27
Seijo 2010	2007	PPL. Straightforward Surgery or TTNA deemed suboptimal	51 (27%)	62	51	72%	25	24	11
Mahajan 2011	2006	PPL beyond the field of FB, high risk surgery	48	ND	49	57%	20	33	ND
Lamprecht 2012	2010	PPL beyond the field of FB	112 (33%)	66.7	112	85%	27.1	37	ND
Pearlstein 2012	2008	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	ND	ND

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

* High incidence of histoplasmosis in the study population (Indiana, USA); 33% unknown final diagnoses.

Table E3. Main characteristics of selected studies (methods, intervention)

Study	Study design	QUADAS scores	Conflict of interest	Type of sedation	Additional technique	AFTRE (mm)	Mean distance btw tip of sensor and center of nodule (mm)	Sampling technique	Overall duration of exam (min, mean)
Becker 2005	Prospective	3	No	GA	Fluoroscopy, radial probe EBUS	6.2	8.4	Forceps, brush, curette	ND
Hautmann 2005	Prospective	3	ND	CS	Fluoroscopy‡	ND	ND	Forceps	ND
Gildea 2006	Prospective	3	Yes	CS	Fluoroscopy	6.6	9	Forceps, brush, BAL, needle	51
Schwarz 2006	Prospective	3	Yes	CS	Fluoroscopy	5.7	ND	Forceps, brush	46
Eberhardt 2007a	Prospective	3	Yes	GA/CS	0	4.6	9	Forceps, brush, BALll, needle	26.9
Eberhardt 07b	Prospective	3	Yes	GA/CS	0	ND	ND	Forceps	ND
Eberhardt 07b EBUS	Prospective	3	Yes	GA/CS	Radial probe EBUS	ND	ND	Forceps	ND
Makris 2007	Prospective	4	No	GA	0	4	8.7	Forceps§	ND
Wilson 2007	Retrospective	3	No	CS	Fluoroscopy, ROSE	5	8	Forceps, needle	ND
Bertoletti 2008	Prospective	3	ND	CS*	0	4.7	10	Forceps, brush	29.5
Eberhardt 2009	Prospective	3	Yes	GA	0†	3.6	9	Forceps, suction**	25.7
Lamprecht 2009	Retrospective	3	ND	GA	ROSE	3.8	8.4	Forceps, brush, needle	60
Seijo 2010	Prospective	3	Yes	CS	ROSE	4	8	Forceps, needle	56
Mahajan 2011	Retrospective	3	No	CS	Fluoroscopy	ND	ND	Forceps, brush, BAL	ND
Lamprecht 2012	Prospective	4	No	GA	ROSE	ND	ND	Forceps, brush, needle	45.2
Pearlstein 2012	Retrospective	3	Yes	GA	ROSE	4	7.4	Forceps, brush, needle	70

QUADAS: Quality Assessment of Diagnostic Accuracy Studies, cf text. AFTRE: Average Fiducial Target Registration Error. GA: general anesthesia. CS: conscious sedation. ND: no data available. BAL: bronchiolo-alveolar lavage. ROSE: rapid on-site cytological evaluation

* 50%/50% nitrous oxide/oxygen mixture

† EBUS performed, but without additional navigation if PPL not seen on ultrasound

‡ Commercially unavailable ENB system, without any steerable catheter

§ 9 attempts for biopsies, instead of mostly 3 to 5 in other studies

ll Through extended working channel

** Suction of the nodule through a dedicated catheter, with back and forth moves

Table E4. Patient-level characteristics associated with significant modification of ENB's performance.

	Outcome	Regression slope	p-values	Nb of studies*
Malignancy prevalence	Diagnostic yield	0.025	0.02	15
	Negative predictive value	- 0.038	0.02	14
Publication date	Sensitivity for malignancy	0.165	<0.001	14
	Accuracy for malignancy	0.162	<0.001	14
	Negative predictive value	0.164	0.009	14
Percentage of nodules in upper lobes**	Sensitivity for malignancy	- 6.125	0.03	12
	Accuracy for malignancy	- 8.010	0.02	12
	Negative predictive value	- 8.120	0.048	14

* With available data

** Highly dependent on a single study according to sensitivity analyses

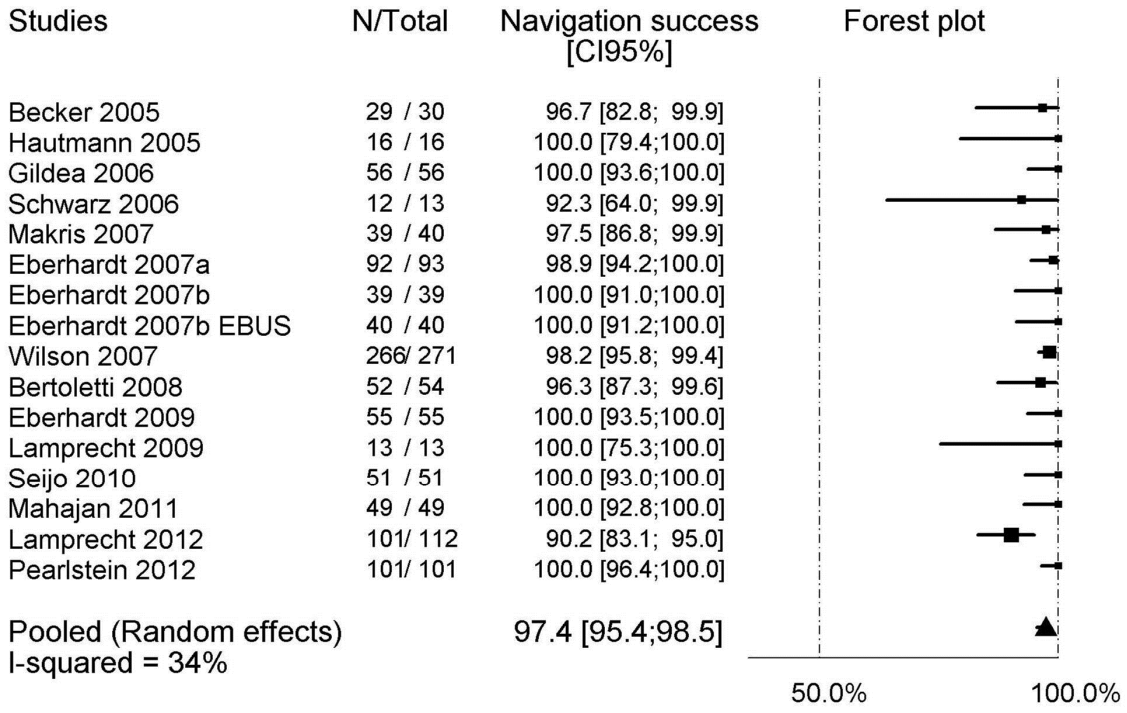

Figure E1: Successful navigation toward peripheral lung lesions with ENB

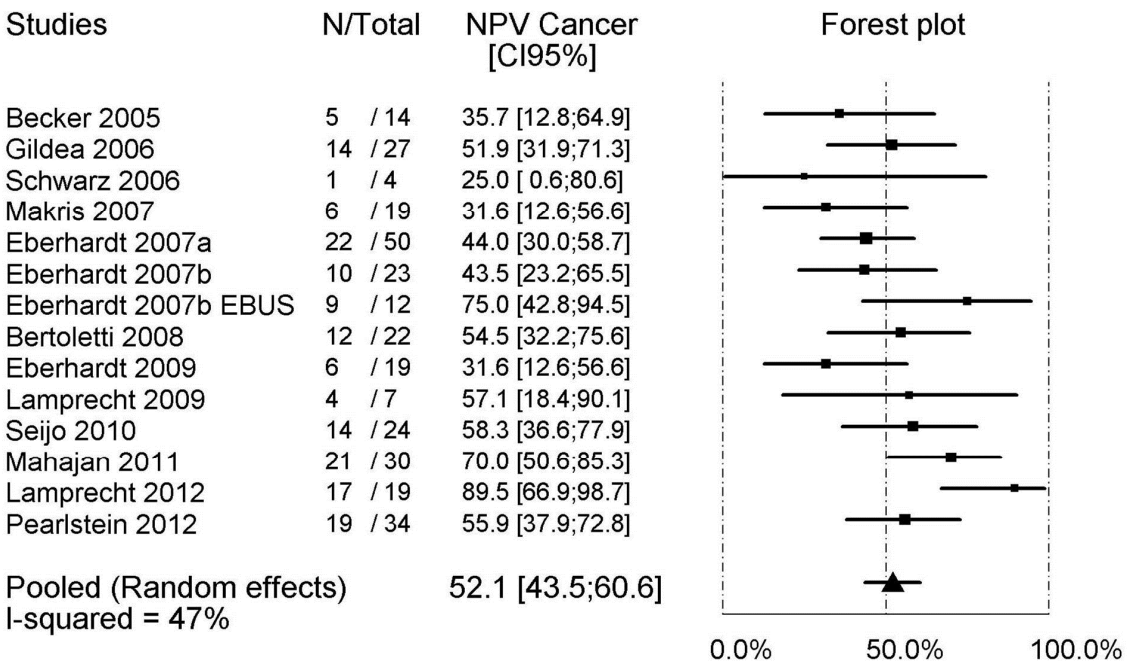

Figure E2: ENB's negative predictive value for malignancy

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