Utility of Elastography for Differentiating Malignant and Benign Lymph Nodes During EBUS-TBNA

A Systematic Review and Meta-analysis

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Background: **Ultrasound elastography noninvasively estimates tissue hardness. Studies have evaluated elastography for differentiating malignant from benign lymph nodes during endobronchial ultrasound-guided transbronchial needle aspiration. Several methods of performing elastography are described with variable diagnostic accuracy.**

Methods: **The aim of this study was to evaluate endobronchial ultrasound-guided elastography in differentiating malignant from benign mediastinal lymphadenopathy. We performed a systematic search of the PubMed and Embase databases to extract the relevant studies. A diagnostic accuracy meta-analysis was carried out to calculate the pooled sensitivity and specificity [with 95% confidence intervals (CIs)], and positive and negative likelihood ratios of elastography.**

Results: **After a systematic search, 20 studies (1600 patients, 2712 nodes) were selected. The pooled sensitivity and specificity of elastography were 0.90 (95% CI, 0.84-0.94) and 0.79 (95% CI, 0.73-0.84), respectively. The summary receiver operating curve demonstrated an area under the curve for elastography of 0.90 (0.88-0.93). The positive and negative likelihood ratios and the diagnostic odds ratio were 4.3 (95% CI, 3.3-5.5), 0.12 (95% CI, 0.07-0.20), and 35 (95% CI, 19-63), respectively. Of the most commonly described methods, the color classification method (type 3 malignant vs. type 1 benign) demonstrated the highest area under the curve of 0.91 (0.88-0.93). There was significant heterogeneity and publication bias. Subgroup analyses indicated no significant difference between the sensitivity and specificity of quantitative and qualitative elastography methods.**

Conclusions: **Ultrasound elastography is useful in differentiating malignant and benign lymph nodes during endobronchial ultrasound-guided transbronchial needle aspiration. However, elastography does not replace the requirement of lymph node aspiration.**

Key Words: endobronchial ultrasound, elastography, lung cancer, bronchoscopy, ultrasound, meta-analysis

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Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a well-established modality for the diagnosis and staging of non-small-cell lung cancer. It is also efficacious to evaluate mediastinal lymphadenopathy of unclear etiology.[1] During the endosonographic evaluation of lymph nodes, specific B mode ultrasound characteristics, lymph node size, and power Doppler vascular patterns have been studied for prediction of malignant lymph node involvement.[2–4] However, these characteristics are not sensitive, and assessment is dependent on operator expertise. Individual nodes may be avascular, and B mode features are often equivocal.[5] Imaging modalities, such as PET-CT scanning, have poor sensitivity and lack specificity for malignant mediastinal lymph node involvement.[6] During EBUS-TBNA, multistation node involvement or multiple nodes at a single station is commonly observed. Under these circumstances, the operator needs to identify the potentially malignant

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nodes to reduce the duration of the procedure and prevent unnecessary punctures.[7]

Ultrasound elastography is a technology that noninvasively assesses tissue stiffness and its distribution in the selected region of interest (ROI).[8] The stiffness of tissue is measured in response to mechanical stress that may be due to the application of local pressure or vibration. Elastography has also been described as computer-assisted palpation.[9] After the development of technology to image elasticity in 1991, elastography was first used for the characterization of malignant breast lesions.[10,11] Subsequently, use was described in the pancreas and thyroid nodules. A harder tissue, like one infiltrated by malignancy, is stiffer and less deformable. The hardness is analyzed as a color-based output that is interpreted in different methods based on the equipment. Before EBUS-TBNA, elastography had been used in endoscopy-ultrasound (EUS)-FNA for differentiation between benign and malignant abdominal lymphadenopathy.[12]

The first feasibility study of EBUS elastography was reported in 2013.[9] Since then, various methods of elastography assessment have been described. These broadly include 2 categories: qualitative and quantitative methods. The most commonly described method of EBUS elastography categorized the elastography images into 3 patterns. This method divides elastography images into 3 color patterns, as defined by Izumo et al[5]: (type 1) predominant nonblue, (type 2) part blue part nonblue, and (type 3) predominantly blue. Hard tissue like malignancy displays mostly blue color, whereas softer tissues like benign lesions display mainly nonblue (red-green) color. Other qualitative methods include a 4-color or 5-color classification on similar principles. The later-described quantitative methods include the strain ratio (SR), blue color proportion (BCP), stiff area ratio (SAR), and strain histogram methods.[8,13–15]

A meta-analysis reported the findings from 7 published studies on EBUS elastography.[16] Many other recent studies have reported variable sensitivity and specificity of elastography. The studies have methodological variability and have used different measures for reporting diagnostic accuracy. Therefore, we performed a systematic review to summarize the studies describing the utility of EBUS elastography. We also carried out a meta-analysis to calculate the pooled sensitivity and specificity of EBUS elastography. We also carried out summary receiver operating curve (SROC) analysis and meta-regression to study the effect of various characteristics affecting the sensitivity and specificity.

METHODS

Search Strategy and Initial Review

Two authors (K.M. and M.M.) performed a systematic search of 2 databases: PubMed and EMBASE (January 1, 2004 up to July 30, 2020) to identify the original, peer-reviewed, full-length, human participant articles describing the use of EBUS elastography. The following database-specific Boolean search strategy was used. Free text search terms were (ebus OR ebus-tbna OR ebus tbna OR tbna OR endobronchial ultrasound OR endobronchial ultrasonography OR endobronchial ultrasound-guided OR endobronchial ultrasound-guided) AND (elastography OR elastographic). All the retrieved studies were imported into reference management software (EndNote). Duplicate citations were discarded. The studies were screened by title and abstract. Full texts were downloaded for review, wherever required. The reference lists of the extracted studies were also reviewed, and the authors also searched their files. The finally selected studies were independently screened by 2 authors (K.M. and M.M). Studies on utilization of EBUS elastography for differentiation between malignant and benign mediastinal lymphadenopathy were included. For inclusion, sufficient data for calculating sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were required. The following studies were excluded: (a) studies that did not report the utilization of elastography in EBUS-TBNA; (b) utilization of EBUS-TBNA without elastography or vice versa; (c) elastography in EUS; (d) studies not in the English language; (e) review articles, editorials, abstracts, and letters without any case description; and (f) case reports or series with ten or fewer patients. Any disagreement between the authors was resolved after mutual discussion.

Data Abstraction

Data from the finally selected studies were abstracted on a data extraction form. The following information was retrieved after a thorough review of the full text: (a) author, (b) year, (c) number of patients, (d) sex, (e) number of centers, (f) study design, (g) age, (h) EBUS bronchoscope type, (i) anesthesia, (j) number of nodes sampled, (k) ultrasound processor and scanning frequency, (l) elastographic classification system used

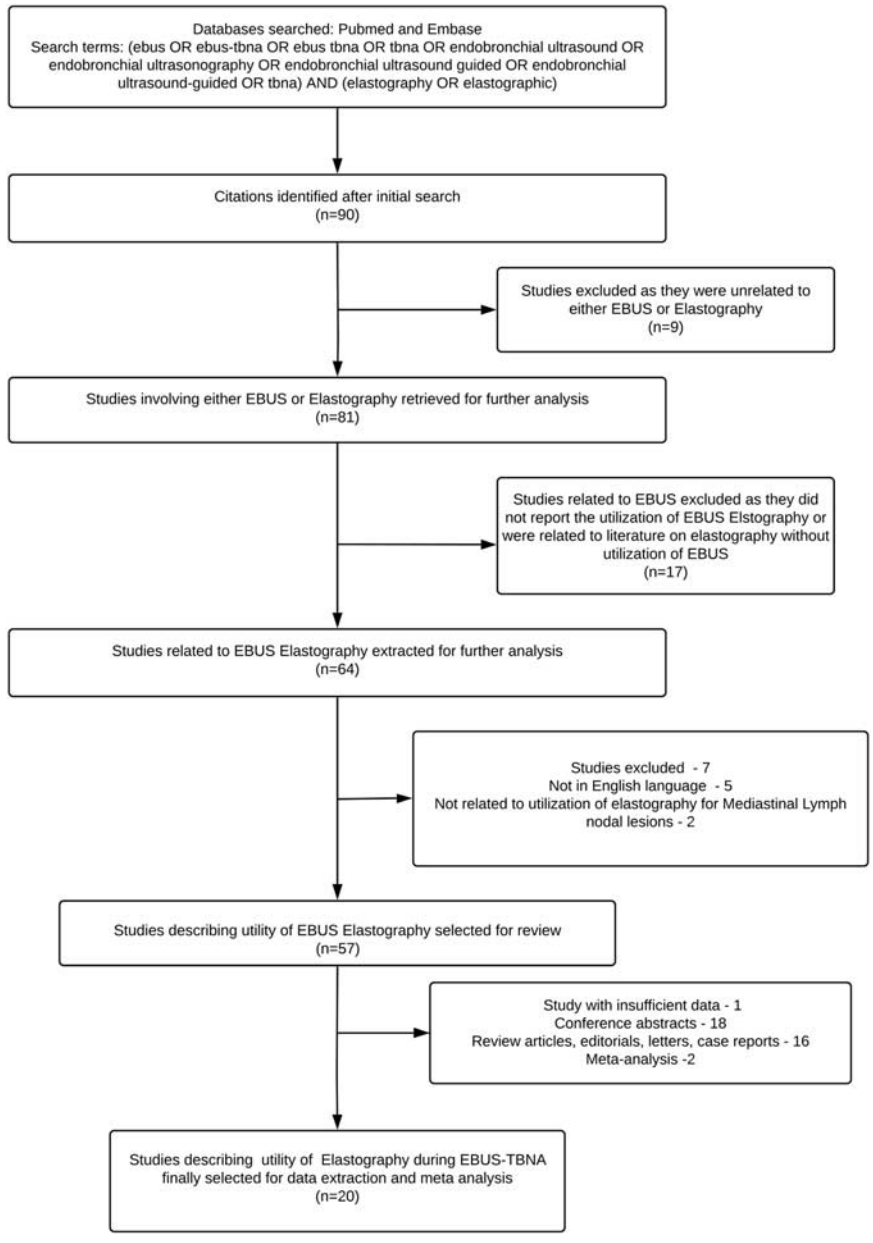

FIGURE 1. Flow diagram describing the process of systematic review and selection of relevant studies for meta-analysis. EBUS-TBNA indicates endobronchial ultrasound-guided transbronchial needle aspiration.

(quantitative or qualitative) and number of interpreters, (m) suction use, (n) rapid on-site evaluation, (o) lymph node size, (p) lymph node stations sampled, (q) needle gauge, (r) diagnostic comparators, (s) true positives, (t) false negatives, (u) false positives (FP), and (v) true negatives. The sensitivity, specificity, positive and negative predictive values, diagnostic accuracy, PLR, and NLR and DOR were calculated manually individually for each study and cross-checked with the author reported values. The systematic review methodology is summarized in Figure 1.

Assessment of Study Quality

The Quality Assessment of Diagnostic Accuracy Studies tool was used to assess the quality of studies. Two authors (M.M. and H.I.) evaluated the quality of the selected studies for meta-analysis. The interobserver agreement for the quality assessment of the selected studies was determined.

Statistical Analysis

Statistical analyses were carried out using the STATA statistical analysis software (Stata Statistical Software: Release 15, 2017; StataCorp LLC,

TABLE 1. Baseline Characteristics of the Study Participants, Study Design, and Technical Details of the EBUS-TBNA Procedure

References	Country	Design	Patients (N) Age (y) Sex (Male, Female) % Male	Nodes (N) Lymph Node Size (mm) Primary Stations Sampled Benign/ Malignant Nodes	Anesthesia Type	EBUS Bronchoscope Scanning Frequency (MHz) Route of Insertion	Rapid On-site Evaluation	Needle Type
Izumo et al[5]	Japan	Retrospective Single center	30 67.1 ± 15.5 17 male, 13 female 0.57	75 Median-15 (5-50) Lower paratracheal (4R/4L) and subcarinal 32/43	Moderate sedation	Olympus BF-UC-260 FW 7.5 Oral	Yes	NR
He et al[13]	China	Prospective Single center	40 65 ± 11 26 male, 14 female 0.65	68 Median-17 Lower paratracheal (4R/4L) and subcarinal 26/42	GA with LMA	Pentax EB-1970-UK 7.5 Oral	No	22 G
Nakajima et al[8]	Japan	Retrospective Single center	21 63 (30-80) 15 male, 6 female 0.71	49 Mean-8.44 (5-21.7) Lower right paratracheal, 11 and subcarinal 33/16	Moderate sedation	Olympus BF-UC-260 FW 10 NR	Yes	NR
Rozman et al[21]	Slovenia	Prospective Single center	33 67.5 ± 8.2 25 male, 8 female 0.76	80 Mean-11.1 ± 4.8 (4-26) NR 46/34	Deep sedation	Olympus BF-UC-180F NR NR	No	22 G
Gu et al[7]	China	Prospective Single center	60 62 (26-82) 49 male, 11 female 0.82	133 NR Lower paratracheal (4R/4L) and subcarinal 44/89	Topical anesthesia	Olympus BF-UC260FOL8 7.5 Oral or Nasal	Yes	22 G
Huang et al[22]	China	Retrospective Single center	47 60.19 ± 11.03 (25-77) 29 male, 18 female 0.62	78 Mean-19.78 Lower right paratracheal, subcarinal and 11L 45/33	Moderate to deep sedation	Olympus BF-UC-260 F NR Nasal	Yes	22 G
Korrungruang et al[23]	Thailand	Prospective 2 centers	72 58.3 ± 12.5 41 male, 31 female 0.57	120 Mean-18.8 ± 7.9 NR 24/96	Moderate sedation	Olympus BF-UC-180F 10 Oral	No	22 G
Sun et al[24]	China	Prospective Single center	56 56.07 32 male, 24 female 0.57	68 Mean-19.92 ± 9.09 Lower right paratracheal, subcarinal 33/35	Moderate sedation	Pentax EB-1970 7.5 NR	No	22 G

TABLE 1. (*continued*)

References	Country	Design	Patients (N) Age (y) Sex (Male, Female) % Male	Nodes (N) Lymph Node Size (mm) Primary Stations Sampled Benign/ Malignant Nodes	Anesthesia Type	EBUS Bronchoscope Scanning Frequency (MHz) Route of Insertion	Rapid On-site Evaluation	Needle Type
Ma et al[14]	China	Retrospective Single center	60 61.6 40 male, 20 female 0.67	79 Mean-14.7 Lower right paratracheal, Subcarinal 40/39	Topical anesthesia	Olympus BF-UC260FW 7.5 Oral	No	NR
Fournier et al[25]	France	Prospective Single center	114 60.2 ± 12.2 80 male, 34 female 0.70	217 Mean-16.2 ± 8.5 Lower right paratracheal, 11R and subcarinal 97/120	Mild sedation	Olympus BF-UC-180F NR NR	No	22 G
Fujiwara et al[26]	Japan	Retrospective Single center	122 68.4 (37-84) 94 male, 28 female 0.77	228 Mean-11.7 Lower paratracheal (4R/4L) and subcarinal 150/78	Moderate sedation	Olympus BF-UC-260 FW 10 NR	Yes	22 G
Hernández Roca et al[27]	Spain	Prospective Single center	27 68 ± 10 16 male, 11 female 0.59	43 Mean-15 ± 6 Lower right paratracheal, subcarinal 24/18	GA with orotracheal intubation	Pentax EB-1970-UK NR Oral	Yes	NR
Lin et al[28]	Taiwan	Retrospective Single center	94 62.8 (20-97) 65 male, 29 female 0.69	206 Mean-13.6 (2.0-56.3) Lower right paratracheal, subcarinal, and 11L 132/74	Moderate sedation	Olympus BF-UC-260 FW 7.5 Oral	No	NR
Trosini-Desert et al[29]	France	Prospective Single center	79 61.1 ± 11.4 58 male, 21 female 0.73	110 Mean-19 ± 8 Lower right paratracheal, subcarinal and 11R 66/44	GA	Pentax EB-1970 NR NR	No	22 G
Verhoeven et al[15]	The Netherlands	Prospective Single center	63 64.3 (41-83) 39 male, 24 Female 0.62	120 Mean-9.95 (4-26) Lower paratracheal (4R/4L), subcarinal and 11R 75/45	NR	Pentax EB-1970-UK NR NR	No	NR
Caglayan et al[30]	Turkey	Prospective Single center	119 63.2 ± 12.4 (16-86) 69 male, 50 female 0.58	221 Mean-16.2 ± 11.1 (3-80) Lower paratracheal (4R/4L), subcarinal 114/92	Moderate/deep sedation or GA	Olympus BF-UC-180F 10 Oral	Yes	22 G

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Hernández Roca et al[31]	Spain	Prospective Single center	24 68 ± 10 14 male, 10 female 0.58	38 Mean-15.8 ± 6 Subcarinal, Left interlobar (11L), Lower right paratracheal (4R) 21/17	GA and orotracheal intubation	Pentax EB-1970-UK NR Oral	Yes	NR
Verhoeven et al[32]	The Netherlands, Italy, Denmark	Prospective 5 centers	327 66 (26-90) 200 male, 127 female 0.61	525 Mean-12.3 (3-50) NR 272/253	NR	Pentax EB-1970-UK, EB19-J10U NR NR	No	NR
Gupta et al[33]	India	Retrospective Single center	80 43.73 ± 14.93 55 male, 25 female 0.69	105 NR Lower right paratracheal, Subcarinal and 10R 79/26	Conscious sedation	Olympus BF-UC-260 FW NR Oral	No	NR
Uchimura et al[34]	Japan	Retrospective Single center	132 71(27-87) 91 male, 41 female 0.69	149 Mean-8.0 (4.9-16.0) Lower paratracheal (4R/4L), Subcarinal 81/68	Topical anesthesia/ conscious sedation	Olympus BF-UC-260 FW NR Oral	No	22 G

GA indicates general anesthesia; LMA, laryngeal mask airway; NR, not reported.

College Station, TX). The standard guidelines for carrying out a meta-analysis of a diagnostic test were followed and the required items in the PRISMA checklist were addressed.[17] Data were imported into a 2-by-2 table and initially analyzed manually. The program calculated summary estimates of sensitivity and specificity [with 95% confidence intervals (CIs)] after antilogit transformation of the mean logit sensitivity and logit specificity with respective SEs considering the heterogeneity between studies. Results were expressed as sensitivity, specificity, negative predictive value, positive predictive value, and likelihood ratios. A binary random-effects model was then constructed. In Stata, several summary receiver operating curve (ROC) linear regression lines based on either the regression of logit sensitivity on specificity, the regression of logit specificity on sensitivity, or an orthogonal regression line by minimizing the perpendicular distances may be derived, based on parameters estimated by the bivariate model. These lines can be transformed back into the original ROC scale to obtain a summary ROC. We reported the overall sensitivity and specificity of endobronchial ultrasonographic elastography, and the results were expressed as a percentage and CI. We also carried out a sensitivity and specificity analysis (meta-regression) across various subgroups to assess the influence of baseline characteristics on heterogeneity.

Heterogeneity Assessment

The impact of heterogeneity on the pooled estimates of the outcome was assessed using the Cochran Q statistic and the I^2 test. I^2 is the traditional statistical tool to evaluate the impact of unobserved heterogeneity.[18] It describes the percentage of total variation across studies that is attributable to heterogeneity rather than chance. An I^2 value of $\geq 50\%$ indicates significant heterogeneity. For the Cochran Q test, which has a low sensitivity for detecting heterogeneity, a P-value <0.1 was significant for the presence of statistical heterogeneity.

Assessment of Publication Bias

Publication bias was assessed using Deek funnel plot (statistically significant publication bias when $P < 0.1$).[19]

RESULTS

The initial literature search yielded 90 articles, from which 20 studies were selected for data abstraction and included in the meta-analysis. One study on EBUS elastography was excluded

TABLE 2. Methodological Quality of Included Studies According to the Revised Quality Assessment for Studies of Diagnostic Accuracy Tool-2

	Risk of Bias				Applicability Concerns		
References	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Uchimura et al[34]	+	−	+	+	+	+	+
Gupta et al[33]	+	+	+	+	?	+	+
Verhoeven et al[32]	+	−	?	+	+	+	+
Hernández Roca et al[27]	+	?	+	-	+	+	+
Caglayan et al[30]	+	−	+	+	+	+	+
Verhoeven et al[15]	+	−	?	+	+	+	+
Trosini-Desert et al[29]	+	?	?	+	+	+	+
Lin et al[28]	+	?	?	−	+	+	+
Hernández Roca et al[31]	+	?	?	+	?	+	+
Fujiwara et al[26]	+	+	?	+	?	+	+
Fournier et al[25]	+	+	+	−	+	+	+
Ma et al[14]	+	−	+	+	+	+	+
Sun et al[24]	?	+	?	+	+	+	+
Korrungruang et al[23]	+	−	?	+	+	+	+
Huang et al[22]	+	?	+	−	+	+	+
Gu et al[7]	+	+	+	−	+	+	+
Rozman et al[21]	+	−	+	+	+	+	+
Nakajima et al[8]	−	−	+	+	+	+	+
He et al[13]	?	−	+	+	+	+	+
Izumo et al[5]	+	?	+	−	+	+	+

− indicates high risk of bias; +, low risk of no bias; ?, unclear.

due to lack of sufficient information to verify and extract the true positive, FP, false negative, and true negative values required for summary statistics of diagnostic accuracy.[20]

Description of Studies and Quality Assessment

The study and procedural characteristics are summarized in Table 1. Overall, the 20 studies described EBUS elastography performance on 1600 patients (males 1055, 65.9%), with 2712 lymph nodes sampled overall. The methodological quality of the studies using the Quality Assessment of Diagnostic Accuracy Studies tool is summarized in Table 2.

Twelve studies (60%) were prospective and 8 (40%) were retrospective. 18 (90%) were single center [except Korrungruang and Boonsarngsuk[23] (2 centers) and Verhoeven et al[32] (5 centers)]. In 11 studies (55%), mild to deep sedation was used, 4 (20%) used general anesthesia (GA), and in one, use of both sedation and GA (5%) was described for performing EBUS-TBNA. The majority of studies used the Olympus EBUS bronchoscope (13, 65%). A scanning frequency of 7.5 MHz was most commonly used. The rest of the equipment and procedure-related data are summarized in Table 1. The most frequently sampled lymph node stations were subcarinal (station 7) and lower right paratracheal (Station 4R). Rapid on-site evaluation was available in 12 (60%) studies and a 22 G needle (100%) was used in all studies, where needle-use data were reported.

Eight studies reported the use of both qualitative and quantitative parameters for analysis of elastography images. Six studies each reported the use of only a single quantitative or qualitative parameter alone for elastography assessment (Table 3). For primary reporting and the meta-analysis, the most accurate parameter reported by the authors was used for summary statistics (10 qualitative and 10 quantitative). Among the qualitative methods, the 3-color classification system (type 1, 2, 3) was used most commonly. Other qualitative methods included either a 4-color or 5-color code pattern. The most used parameter for quantitative assessment was SR. Percentage of hard areas or BCP, SAR or blue pixel ratio, and strain histogram were the other quantitative methods described. The median number of elastography performers/interpreters in the studies was 2 (interquartile range: 1 to 2).

Meta-analysis

The overall pooled sensitivity and specificity of EBUS elastography were 0.90 (95% CI, 0.84-0.94) and 0.79 (95% CI, 0.73-0.84), respectively (Fig. 2). SROC analysis showed an area under the curve (AUC) of 0.90 (0.88-0.93) (Fig. 3).

TABLE 3. Type of Elastography Methods Used in Various Studies and the Diagnostic Comparisons Reported

References	Types of Elastography Assessments Performed	Type of Primary Elastography Method	Primary Method Used	No. Elastography Interpreters	Diagnostic Comparison Reported	True Positive	False Negative	False Positive	True Negative	Gold Standard for Comparisons
Izumo et al[5]	3 color (T1/T2/T3)	Qualitative	3 color	1	T3 vs. T1 for malignancy	35	0	2	24	EBUS-TBNA
He et al[13]	4 color (1-4) Strain Ratio	Quantitative	Strain ratio	NR	SR > 32.07 for malignancy	37	5	5	21	EBUS-TBNA, thoracoscopy or thoracotomy in each negative case
Nakajima et al[8]	Stiff area ratio on Image analysis	Quantitative	Stiff area ratio	2	SAR > 0.311 for malignancy	13	3	5	28	EBUS-TBNA, For negatives, surgical pathology or radiology follow-up for 6 mo
Rozman et al[21]	Strain ratio	Quantitative	Strain ratio	NR	SR > 8 for malignancy	30	4	7	39	EBUS-TBNA, surgical sampling for confirmation in nondiagnostic EBUS-TBNA
Gu et al[7]	3 color (T1/T2/T3)	Qualitative	3 color	2	T3 vs. T1 for malignancy	89	0	15	29	EBUS-TBNA
Huang et al[22]	3 color (T1/T2/T3)	Qualitative	3 color	NR	T3 vs. T1 for malignancy	27	1	4	26	EBUS-TBNA
Korrungruang et al[23]	3 color (T1/T2/T3) Strain ratio	Quantitative	Strain ratio	2	SR > 2.5 for malignancy	96	0	7	17	EBUS-TBNA, video-assisted thoracoscopy, clinical radiologic follow-up for 6 mo
Sun et al[24]	5 color (1-5) mean gray value	Qualitative	5 color	3	T (4-5) vs. T (1-3) for malignancy	30	5	6	27	EBUS-TBNA, bronchoscopy, CT-guided TTNA, thoracotomy/thoracoscopy, mediastinoscopy, clinical radiologic follow-up for 12 mo
Ma et al[14]	Blue color proportion	Quantitative	Blue color proportion	1	BCP > 36.7% for malignancy	36	3	14	26	EBUS-TBNA
Fournier et al[25]	3 color (T1/T2/T3)	Qualitative	3 color	3	T3 vs. T1 for malignancy	67	10	16	34	EBUS-TBNA, mediastinoscopy
Fujiwara et al[26]	Stiff area ratio on Image analysis	Quantitative	Stiff area ratio	2	SAR > 0.311 for malignancy	56	22	24	126	EBUS-TBNA, surgical sampling for confirmation in nondiagnostic EBUS-TBNA, clinical follow-up for 12 mo
Hernández Roca et al[27]	3 color (T1/T2/T3) Strain ratio Mean strain histogram Blue pixel ratio	Qualitative	3 color	1	T3 vs. T1/T2 for malignancy	13	5	2	22	EBUS-TBNA, MDD by thoracic tumor board, mediastinoscopy, change in PET-SUV or node size on CT, 6 mo follow-up

TABLE 3. (*continued*)

References	Types of Elastography Assessments Performed	Type of Primary Elastography Method	Primary Method Used	No. Elastography Interpreters	Diagnostic Comparison Reported	True Positive	False Negative	False Positive	True Negative	Gold Standard for Comparisons
Lin et al[28]	3 color (T1/T2/T3)	Qualitative	3 color	2	T3 vs. T1 for malignancy	48	5	19	90	EBUS-TBNA, surgical pathology or radiology follow-up for 6 mo
Trosini-Desert et al[29]	5 color (1-5) colorimetric Average elasticity Strain ratio Percentage of hard areas	Qualitative	5 color	NR	T (4-5) vs. T (1-3) for malignancy, colorimetric	34	10	3	63	EBUS-TBNA, mediastinoscopy, change in PET or on CT, 6 mo follow-up
Verhoeven et al[15]	Mean strain histogram 5 color (1-5) reverse Modified Tsukuba method Strain ratio	Quantitative	Mean strain histogram	1	Mean strain < 78 on strain histogram	42	3	19	56	EBUS-TBNA, clinical follow-up
Caglayan et al[30]	4 color (1-4) Strain ratio	Quantitative	Strain ratio	2	SR ≥ 2.47 for malignancy	64	21	38	72	EBUS-TBNA
Hernández Roca et al[31]	3 color (T1/T2/T3) Strain Ratio Mean Strain histogram Blue Pixel Ratio	Qualitative	3 color	3	T3 vs. T1 for malignancy	12	0	2	4	EBUS-TBNA
Verhoeven et al[32]	Mean strain histogram	Quantitative	Mean strain histogram	1	Mean strain < 115 on strain histogram	227	26	154	118	EBUS-TBNA, surgical sampling, clinical follow-up and imaging at 6 mo
Gupta et al[33]	3 color (T1/T2/T3)	Qualitative	3 color	2	T3 vs. T1/2 for malignancy	16	10	13	66	EBUS-TBNA
Uchimura et al[34]	Stiff area ratio	Quantitative	Stiff area ratio	2	SAR > 0.41 for malignancy	60	8	16	65	EBUS TBNA, surgery, bacterial culture, clinical and radiologic follow-up at 6 mo

BCP indicates blue color proportion; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; MDD, multidisciplinary discussion; NR, not reported; SAR, stiff area ratio; SR, strain ratio; TTNA, transthoracic needle aspiration.

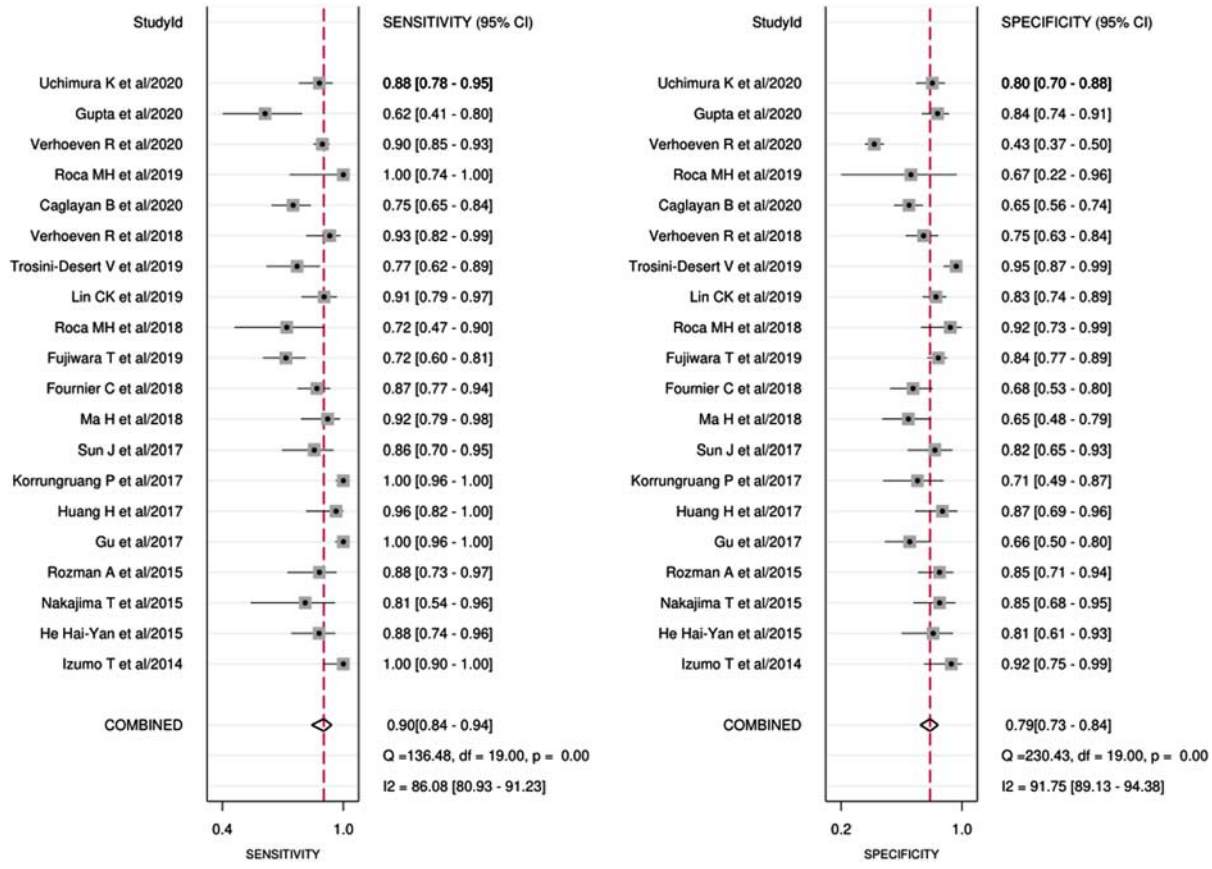

FIGURE 2. Picture showing the pooled and individual study, sensitivity, and specificity values along with heterogeneity statistics.

PLR, NLR, and DOR were 4.3 (95% CI, 3.3-5.5), 0.12 (95% CI, 0.07-0.20), and 35 (95% CI, 19-63), respectively. These values for overall assessment and individual methods are summarized in Table 4. The SROC analysis for individual methods is shown in Figure 3. The AUC for elastography (overall), the 3-color pattern (type 3 vs. type 1), SR, and SAR were 0.90, 0.91, 0.83, and 0.86, respectively. The color classification method, as described by Izumo and colleagues (type 3 malignant vs. type 1 benign), had the highest AUC among the individual methods [AUC 0.91 (0.88-0.93)], whereas the SR had the lowest AUC, 0.83 (0.80-0.86) (Table 4, Fig. 3).

Heterogeneity Assessment and Publication Bias

Significant heterogeneity was present in the sensitivity and specificity [$I^2 = 86.08$ (95% CI, 80.93-91.23) for sensitivity, $I^2 = 91.75$ (95% CI, 89.13-94.38) for specificity]. There was evidence of publication bias, Deek funnel plot ($P = 0.01$) (Fig. 4).

Subgroup Analysis

Meta-regression was performed to study the possible source of heterogeneity. The analysis was carried out to assess the influence of the following characteristics:: number of patients, number of lymph nodes, study design, sedation versus GA, type of EBUS scope, and type of elastography (qualitative vs. quantitative). The number of patients and number of lymph nodes analyzed had an influence on the heterogeneity in sensitivity and specificity (Fig. 5). Studies that used GA and those that were retrospective influenced the heterogeneity in specificity. Borderline significance was also observed for influence on specificity using the Olympus EBUS bronchoscope (Fig. 5). Subgroup analyses did not show any difference in sensitivity and specificity between the qualitative and quantitative elastography methods (Table 5).

DISCUSSION

In this systematic review and meta-analysis, we found that EBUS elastography is a useful modality for differentiating between benign and

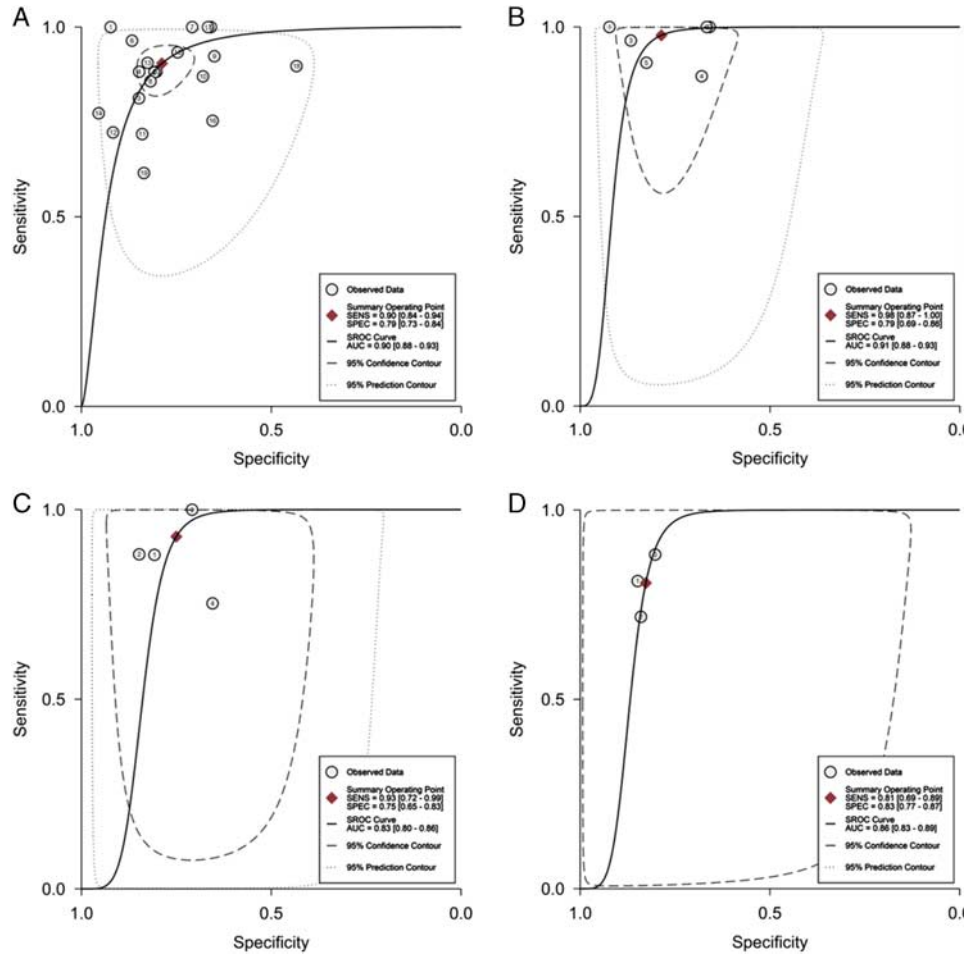

FIGURE 3. SROC curves for the diagnostic accuracy of elastography, overall (A), color classification method (type 3 vs. type 1) (B), strain ratio (C), and stiff area ratio (D). AUC indicates area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating curve.

malignant mediastinal lymph nodes during EBUS-TBNA. The pooled diagnostic sensitivity and specificity of EBUS elastography were 0.90 (95% CI, 0.84-0.94) and 0.79 (95% CI, 0.73-0.84), respectively. Significant heterogeneity in sensitivity ($I^2 = 86.08$, $Q = 136.48$, $P < 0.01$) and specificity ($I^2 = 91.75$, $Q = 230.43$, $P < 0.01$) was observed. Subgroup analyses strongly suggested that the number of patients strongly influenced the sensitivity, while the number of lymph nodes studied, GA, and retrospective study design influenced the heterogeneity in specificity. There was no difference between the sensitivity and specificity of qualitative versus quantitative methods of elastography assessment.

The elastographic classification of lymph nodes into 3 color types, type 1 (predominantly nonblue pattern), type 2 (part blue and part nonblue pattern), and type 3 (predominantly blue pattern), is the most frequently described method on EBUS elastography (8 of the 20 published studies).[5] This method is qualitative and operator dependent. The blue pattern signified a hard node with a higher probability of malignancy. In this meta-analysis, the Izumo method (type 3 vs. type 1 for malignancy) demonstrated the highest AUC among all techniques. In the initial study, there was also a good correlation between FDG-PET SUV_{max} and the color classifications.[5] However, a significant drawback of this method is that the type 2 pattern is not included in diagnostic comparison (only type 3 was compared with type 1 for malignancy).[5,7,22,25,28,31] This choice leaves a large proportion of lymph nodes (part blue part nonblue) as unclassified and does not add to clinical decisions. A large percentage of nodes in real-life settings will not fit into either a type 3 or type 1 pattern. Despite the high AUC, potential limitations of the method have been highlighted. Fournier et al[25] found a 23% prevalence of malignancy in type 1 nodes. Two of the 8 studies analyzed the data, including the type 2

TABLE 4. Summary of Sensitivity, Specificity, PLR, NLR, DOR, and AUC of Elastography (Overall) and the Most Frequently Described Methods

Type of Elastography Assessment	No. Studies	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC
Elastography (overall)	20	0.90 (0.84-0.94)	0.79 (0.73-0.84)	4.3 (3.3-5.5)	0.12 (0.07-0.20)	35 (19-63)	0.90
Type 3 vs. type 1 color for malignancy	6	0.98 (0.87-1.00)	0.79 (0.69-0.86)	4.6 (3.1-6.8)	0.03 (0.00-0.17)	164 (23-1147)	0.91
Strain ratio	4	0.93 (0.72-0.99)	0.75 (0.65-0.83)	3.7 (2.5-5.6)	0.09 (0.02-0.43)	39 (7-226)	0.83
Stiff area ratio	3	0.81 (0.69-0.89)	0.83 (0.77-0.87)	4.7 (3.5-6.2)	0.23 (0.14-0.38)	20 (11-38)	0.86
Strain histogram	2	0.90 (0.86-0.93)	0.50 (0.45-0.56)	2.37 (1.01-5.50)	0.17 (0.06-0.43)	15.02 (2.54-88.87)	SROC could not be plotted as only 2 studies
Type 3 vs. type 1/2	2	0.66 (0.50-0.80)	0.85 (0.77-0.92)	4.64 (2.15-10.01)	0.41 (0.27-0.61)	12.18 (3.83-38.72)	SROC could not be plotted as only 2 studies
Type 4/5 vs. type 1/3	2	0.81 (0.71-0.79)	0.91 (0.83-0.96)	8.37 (2.29-30.57)	0.22 (0.14-0.34)	42.98 (16.57-111.49)	SROC could not be plotted as only 2 studies

AUC indicates area under the curve; DOR, diagnostic odds ratio; NLR, negative likelihood ratio; PLR, positive likelihood ratio; SROC, summary receiver operating curve.

pattern, in which type 3 was considered malignant, while type 1/type 2 was deemed to be benign for calculations.[27,33] However, this comparison was associated with reduced sensitivity. Two studies used a 5-color group classification.[24,29] Increasing the color groups increases subjectivity and decreases reproducibility. Another major limitation of color classification is the probability of fibrotic lymph nodes (like post TB nodes) to appear as blue.[24] This overlap may significantly affect elastography interpretation in populations with a high prevalence of granulomatous conditions such as TB, sarcoidosis, and anthracosis.[22,35,36]

The SR is the most reported (4 studies) quantitative elastography method.[13,21,23,30] However, this method has considerable heterogeneity in the cutoffs used and is one of the most variable parameters.[31] Also, there is ambiguity in the perinodal area to be selected for its calculation. Cutoff values ranging from 2.47 to 32.07 are described, yielding variable sensitivity, specificity, and diagnostic accuracy. In our meta-analysis, this method had the least AUC among the most commonly used methods. The method of selection of areas for SR is not standardized; therefore, this is subject to heavy operator bias. Although operators have attempted to minimize the error by taking a mean of multiple readings for the SR, this still does not take care of the area of selection. The second most frequently described method (3 studies) is the SAR [stiff areas as blue pixels (145 to 180 pixel area)/ lymph node area as ROI pixels].[8,26,34] However, this requires another image analysis software (Image J) to calculate the stiff (blue) areas. It requires obtaining JPEG images or video clips for the software. Addition of another software for image analysis increases the procedure complexity, increasing the reporting times, and this impacts the real-life clinical utility of this method.[8] One study used a BCP based on a similar principle, but the software (Photoshop CS5) for the purpose was different. A multicenter study and a previous publication by 1 group explored the strain histogram method (2 studies) based on the mean strain.[15,32] However, the cutoffs of the mean strain in the 2 studies were different. A combination of mean strain, node size, and PET-CT findings improved accuracy. In this method, examined lymph node showed elastography color dispersion in the ROI and provided the mean tissue elasticity. The blue color corresponded to a value of 0 and red color corresponded to a value of 255. Lymph nodes with more strain were suggestive of benignity and showed histograms with higher mean strain values.

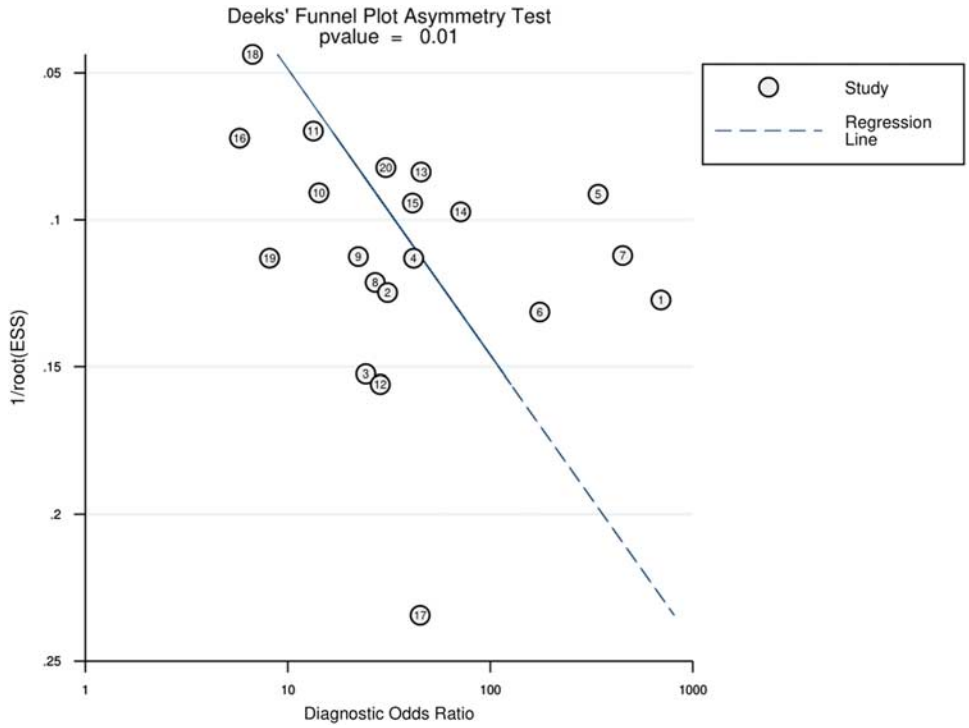

FIGURE 4. Deek funnel plot for publication bias. ESS indicates effective sample size.

However, this method showed low diagnostic accuracy as compared with the other methods. The frequency histograms and blue proportion are less variable (< 10%) than the SR (30.8%).[31] Qualitative versus quantitative method did not influence the heterogeneity in sensitivity in our meta-analysis. Both methods have been found to be comparable in some studies where both techniques were used.[23]

All the described methods of elastography have significant limitations. As has been reported by various authors, the high negative and positive predictive values of elastography do not underscore the need to obtain tissue for a definitive diagnosis. The technology may aid in choosing a node for sampling if multiple nodes are involved, for selecting a specific area for sampling, and to reduce the number of passes.[21] Despite these limitations, data indicate that elastographic features are more sensitive than B mode ultrasound features alone. Ideally, a combination of elastography with B mode features gives a superior diagnostic accuracy.[7,21,26] Lin et al[28] also observed that B mode features such as central necrosis influence the accuracy of elastography for malignancy. Increased specificity and PPV for malignancy have also been reported when elastography is combined with PET-CT.[30]

Overall, the analysis found an NLR of 0.12, which indicates that the test could reasonably exclude malignancy when it is negative. However, the PLR is 4.3 (usually an LR+ > 10 is associated with a large and significant increase in disease probability with a positive test result), thereby indicating the possibility of FP results. Hence, the pooled estimates are not strong enough to replace the actual sampling of the lymph nodes. Even with relatively high specificity and sensitivity, the PLR is low, making this test prone to FP results. In the common scenario where EBUS-TBNA is being performed to diagnose or stage a lung cancer, the information that this test provides will not change the bronchoscopists' choice of which lymph nodes to biopsy. There are certain limitations in this meta-analysis. Only 1 parameter was included per study for pooled analysis. Second, the pooled data have significant heterogeneity in terms of the diagnostic cutoffs and the gold standard. The elastography procedure itself has inherent limitations such as the amount of pressure used while generating the images, the selection of the perinodal area for estimation of SR, and multiple components of subjective interpretation. We did not publish the meta-analysis protocol in advance. In systematic reviews and meta-analysis, it may be useful to compare the outcomes reported in the manuscript against those in the protocol to check for outcome reporting bias. However, we did not observe deviations from the preplanned analyses.

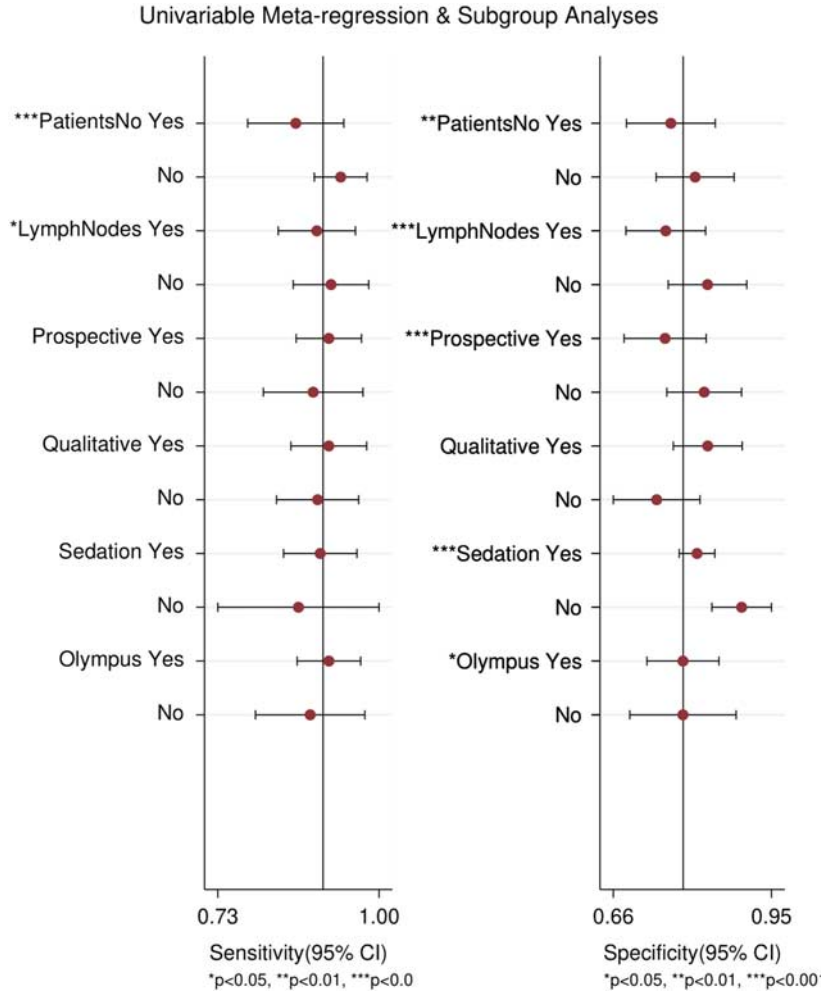

FIGURE 5. Results of the meta-regression analysis of the influence of various subgroups on heterogeneity in sensitivity and specificity. *a+*

Limitations of Existing Elastography Technology and Implications for Future Research

Although the results of the meta-analysis support the utility of elastography during EBUS-TBNA, the current technology has many limitations. Future research should focus on the refinements in this technology. Ideally, such a modality to assist in the prediction of a possible intranodal pathology should be operator independent. This bias is one of the most critical limitations of current technology. The

TABLE 5. Subgroup Analysis Showing the Influence of Baseline Characteristics on the Sensitivity and Specificity

Parameters	Category	No. Studies	Sensitivity	*P*	Specificity	*P*
No. patients	< 65	11	0.93 (0.89-0.98)	< 0.01	0.81 (0.74-0.88)	< 0.01
	≥ 65	9	0.86 (0.78-0.94)		0.76 (0.68-0.85)	
No. lymph nodes	< 100	9	0.92 (0.85-0.98)	0.03	0.83 (0.76-0.91)	< 0.01
	≥ 100	11	0.89 (0.83-0.96)		0.76 (0.68-0.83)	
Study design	Prospective	12	0.91 (0.86-0.97)	0.18	0.75 (0.68-0.83)	< 0.01
	Retrospective	8	0.89 (0.80-0.97)		0.83 (0.76-0.90)	
Primary elastography method	Qualitative	10	0.91 (0.85-0.98)	0.14	0.83 (0.77-0.90)	0.11
	Quantitative	10	0.89 (0.83-0.96)		0.74 (0.66-0.82)	
Use of sedation vs. general anesthesia	Sedation	11	0.90 (0.84-0.96)	0.61	0.81 (0.78-0.85)	< 0.01
	General anesthesia	4	0.86 (0.73-1.00)		0.90 (0.84-0.95)	
Type of bronchoscope used	Olympus	13	0.91 (0.86-0.97)	0.24	0.79 (0.72-0.86)	0.03
	Pentax	7	0.88 (0.79-0.97)		0.79 (0.69-0.89)	

algorithms and software of different manufacturers vary, thereby limiting the generalizability of the results. A standard algorithm across manufacturers may be ideal.

As there was a possible effect of the method of sedation on specificity, a standardized protocol should be used for the EBUS-TBNA procedure. Elastography findings are likely to be affected by a coughing or a lightly sedated patient as compared with an immobile comfortable field. The results should be available in real time to the operator without the delay of image processing using additional software. Most of the studies on elastography are single-center studies with a specific patient profile. Many have included only lung cancer and excluded the other conditions. Prospective multicenter studies, including a variety of disease conditions, with large sample sizes are required for validation. None of the studies has evaluated the elastography characteristics during EUS-B-FNA, and future research should also include this. The protocol for selecting an ROI should preferably be automated as this is a significant cause for heterogeneity in calculations. Also, apart from lung cancer, other malignant causes of lymphadenopathy should be validated. The consistency of performance at all lymph node stations needs to be confirmed. Some authors have described difficulty at the 4R station, especially in patients with mediastinal fat. The protocol should work on dynamic images rather than a static protocol so that it is not an individual static image, but a composite of pictures that are interpreted. One of the arguments made in favor of EBUS elastography is the potential to save time by selecting out the likely benign lymph nodes and limiting the number of stations that need to be biopsied. EBUS-TBNA is not necessarily a time-consuming procedure and even a full mediastinal survey can be conducted in a reasonable amount of time.[37]

Finally, the validation against a surgical gold standard will be ideal in nondiagnostic EBUS-TBNA. Many studies included the results of EBUS-TBNA as the gold standard, which is not appropriate for validation of new technology. Prediction models may need to be created incorporating the clinical and imaging data to improve the diagnostic accuracy.

The data presented in the meta-analysis highlight the need for more standardization in terms of technology to improve test discrimination and limit operator dependence. The results do not support any change in standard clinical practice. In the current form, standalone elastography may not be sufficient to exclude malignancy or confirm benignity.

CONCLUSIONS

EBUS elastography is a noninvasive modality with good overall diagnostic accuracy for differentiating benign and malignant intrathoracic lymph nodes. However, the present technology has many limitations and lack of generalizability. Future research should focus on further refinements and creation of novel analytic models of this potentially useful and exciting technology.

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