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CLINICAL RESEARCH

Endoscopic ultrasound: It's accuracy in evaluating mediastinal lymphadenopathy? A meta-analysis and systematic review

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Abstract

AIM: To evaluate the accuracy of endoscopic ultrasound (EUS), EUS-fine needle aspiration (FNA) in evaluating mediastinal lymphadenopathy.

METHODS: Only EUS and EUS-FNA studies confirmed by surgery or with appropriate follow-up were selected. Articles were searched in Medline, Pubmed, and Cochrane control trial registry. Only studies from which a 2 × 2 table could be constructed for true positive, false negative, false positive and true negative values were included. Two reviewers independently searched and extracted data. The differences were resolved by mutual agreement. Meta-analysis for the accuracy of EUS was analyzed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratios. Pooling was conducted by both Mantel-Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model). The heterogeneity of studies was tested using Cochran's *Q* test based upon inverse variance weights.

RESULTS: Data was extracted from 76 studies (n = 9310) which met the inclusion criteria. Of these, 44 studies used EUS alone and 32 studies used EUS-FNA. FNA improved the sensitivity of EUS from 84.7% (95% CI: 82.9-86.4) to 88.0% (95% CI: 85.8-90.0). With FNA, the specificity of EUS improved from 84.6% (95% CI: 83.2-85.9) to 96.4% (95% CI: 95.3-97.4). The P for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10.

CONCLUSION: EUS is highly sensitive and specific for the evaluation of mediastinal lymphadenopathy and FNA substantially improves this. EUS with FNA should be the diagnostic test of choice for evaluating mediastinal lymphadenopathy.

Key words: Endoscopic ultrasound; EUS-fine needle aspiration; Mediastinal lymphadenopathy

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INTRODUCTION

Management of patients with mediastinal lymphadenopathy depends on the etiology of lymphadenopathy. Differentiating inflammatory from neoplastic processes in the mediastinal lymph nodes is not only important from the treatment standpoint, but also vital in predicting survival. Multiple diagnostic modalities are available to evaluate mediastinal lymphadenopathy. Computer tomography (CT) of the chest does not clearly image the aortopulmonary, subcarinal, and paraesophageal areas due to the lowering of image resolution because of the movement and partial volume effect of pulmonary vessels, aortic arch, and left atrium[1]. Also, for lesions smaller than 1 cm, the sensitivity of CT is low[2-5], and the size-based criteria to diagnose metastatic involvement of the lymph nodes have lower accuracy[6]. Therefore, other methods were introduced, including transbronchial biopsy, CT-guided transthoracic fine-needle aspiration (FNA), mediastinoscopy, or thoracoscopic biopsy.

In the transbronchial technique, the FNA needle

is advanced blindly, reducing the yield of diagnosing subcarinal and paraesophageal nodes to approximately 50%[7,8]. Due to the potential danger of inadvertent vascular puncture, transthoracic biopsy is avoided when the mass is close to major vessels. This procedure is also associated with significant complications, including bleeding and pneumothorax in up to 25%-35% of cases[9,10]. Extended cervical mediastinoscopy or anterior mediastinoscopy can be used to access level 5 (aortopulmonary window) mediastinal nodes, which is not inspected by the standard methods[11-13]. Extended cervical mediastinoscopy has a sensitivity of 83% in examining the paraaortic and subaortic lymph node chains, but the subcarinal group is inaccessible[11]. Thoracoscopy can visualize the inferior mediastinum effectively, but it is limited only to accessing the level of major bronchi, leaving the superior mediastinum non-visualized[14]. Both procedures are invasive, require hospitalization and general anesthesia, and both have limitations.

With the introduction of endoscopic ultrasonography (EUS), it is now possible to visualize not only the gastrointestinal tract but also surrounding structures. However, EUS is limited in its ability to distinguish an inflammatory/reactive process from a malignancy, particularly within lymph nodes[15,16]. The accuracy of EUS in diagnosing mediastinal lymphadenopathy has been varied[17-21]. FNA during EUS may be performed safely in a short outpatient procedure setting without general anesthesia. It is not clear to what extent, if any, FNA adds in improving the accuracy of EUS to diagnose mediastinal lymphadenopathy[22-25].

The goal of this meta-analysis was to evaluate the accuracy of EUS alone and EUS with FNA in correctly diagnosing mediastinal lymphadenopathy. Due to multiple studies scattered in the literature and no published meta-analysis in this area, this meta-analysis was performed in an attempt to answer this essential clinical question. This meta-analysis and systematic review was written in accordance with the proposal for reporting by the QUOROM (Quality of Reporting of Meta-analyses) statement[26]. Since this manuscript looks at diagnostic accuracy of a test, the study design for this meta-analysis and systematic review conformed to the guidelines of Standards for Reporting of Diagnostic Accuracy (STARD) initiative[27].

MATERIALS AND METHODS

Study selection criteria

Only EUS-FNA studies confirmed by surgery or appropriate follow-up were selected. From this pool, only studies from which a 2 × 2 table could be constructed for true positive, false negative, false positive and true negative values were included.

Data collection and extraction

Articles were searched in Medline, Pubmed, Ovid journals, Cumulative Index for Nursing & Allied Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old Medline, Medline non-indexed citations, OVID Healthstar, and Cochrane Control Trial Registry. The search terms used were endoscopic ultrasound, EUS, ultrasound, mediastinal lymphadenopathy, nodal invasion, fine needle aspiration, FNA, staging, surgery, sensitivity, specificity, positive predictive value, and negative predictive value. 2 × 2 tables were constructed with the data extracted from each study. To give validity to the data, two authors (SP and JR) independently searched and extracted the data into an abstraction form. Any differences were resolved by mutual agreement.

Quality of studies

Clinical trial with a control arm can be assessed for the quality of the study. A number of criteria have been used to assess this quality of a study (e.g. randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome)[28,29]. There is no consensus on how to assess studies without a control arm. Hence, these criteria do no apply to studies without a control arm[29]. Therefore, for this meta-analysis and systematic review, studies were selected based on completeness of data and inclusion criteria.

Statistical analysis

Meta-analysis for the accuracy of EUS in diagnosing the etiology of mediastinal lymphadenopathy was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratios. EUS studies were grouped into time periods to standardize the change in EUS technology and EUS criteria for lymph node involvement[30]. These time periods were 1988 to 1994, 1995 to 1999, and 2000 to 2006. Pooling was conducted using both Mantel-Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model). The confidence intervals were calculated using the F distribution method[31]. The width of the point estimates in the Forrest plots indicates the assigned weight to that study. For 0 value cells, a 0.5 was added as described by Cox[32]. The heterogeneity of the sensitivities and specificities was tested by applying the likelihood ratio test[33]. The heterogeneity of likelihood ratios and diagnostic odds ratios were tested using Cochran's Q test based upon inverse variance weights[34]. Heterogeneity among studies was also tested by using summary receiver operating characteristic (SROC) curves. SROC curves were used to calculate the area under the curve (AUC). The effect of publication and selection bias on the summary estimates was tested by Harbord-Egger bias indicator[35] and Begg-Mazumdar indicator[36]. Also, funnel plots were constructed to evaluate potential publication bias using the standard error and diagnostic odds ratio[37,38].

RESULTS

The initial search using the search terms identified 4310 reference articles. Among these, 460 relevant articles were selected and reviewed by two authors independently. Data was extracted from 76 studies (n = 9310) which met the inclusion criteria. Of these, 44 studies used EUS alone[17,18,39-80] and 32 studies used EUS-FNA[19-25,81-107]. Figure 1 shows the search results. Table 1 shows the characteristics for EUS studies without FNA and Table 2

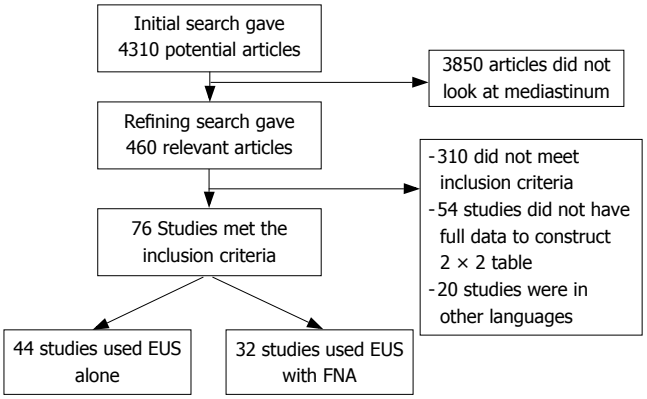

Figure 1 The search results.

Table 1 Characteristics of studies included in this meta-analysis for EUS without FNA

Author	Year of publication	No. of patients	Type of recruitment	Confirmatory procedure
Tio *et al*[71]	1986	26	Prospective	Surgery
Murata *et al*[57]	1988	173	Consecutive	Surgery
Tio *et al*[69]	1989	75	Prospective	Surgery
Vilgrain *et al*[75]	1990	51	Consecutive	Surgery
Tio *et al*[68]	1990	102	Consecutive	Surgery
Rice *et al*[63]	1991	22	Consecutive	Surgery
Heintz *et al*[52]	1991	40	Consecutive	Surgery
Botet *et al*[40]	1991	50	Consecutive	Surgery
Tio *et al*[70]	1989	74	Prospective	Surgery
Ziegler *et al*[80]	1991	52	Consecutive	Surgery
Rosch *et al*[64]	1992	44	Consecutive	Surgery
Fok *et al*[46]	1992	54	Consecutive	Surgery
Yoshikane *et al*[79]	1993	28	Consecutive	Surgery
Grimm *et al*[49]	1993	63	Prospective	Surgery
Dittler *et al*[45]	1993	167	Consecutive	Surgery
Peters *et al*[61]	1994	42	Consecutive	Surgery
Catalano *et al*[43]	1994	100	Consecutive	Surgery
McLoughlin *et al*[18]	1995	15	Consecutive	Surgery
Binmoeller *et al*[39]	1995	87	Prospective	Surgery
HunerBein *et al*[53]	1996	19	Consecutive	Surgery
Hasegawa *et al*[50]	1996	22	Consecutive	Surgery
Francois *et al*[47]	1996	29	Consecutive	Surgery
Natsugoe *et al*[58]	1996	37	Consecutive	Surgery
Milena *et al*[54]	1997	40	Prospective	Surgery
Vikers *et al*[73]	1997	50	Consecutive	Surgery
Shimizu *et al*[67]	1997	431	Consecutive	Surgery
Pham *et al*[62]	1998	28	Consecutive	Surgery
Vikers *et al*[74]	1998	50	Prospective	Surgery
Salminen *et al*[65]	1999	32	Consecutive	Surgery
Krasna *et al*[56]	1999	88	Consecutive	Surgery
Browrey *et al*[41]	1999	98	Prospective	Surgery
Catalano *et al*[42]	1999	149	Prospective	Surgery
Giovannini *et al*[48]	1999	198	Prospective	Surgery
Nishimaki *et al*[60]	1999	224	Consecutive	Surgery
Heidemann *et al*[51]	2000	68	Consecutive	Surgery
Nesje *et al*[59]	2000	68	Prospective	Surgery
Vazquez-Sequeiros *et al*[105]	2001	37	Consecutive	Surgery
Wiersema *et al*[77]	2001	82	Prospective	Surgery
Wakelin *et al*[76]	2002	36	Consecutive	Surgery
Kienle *et al*[55]	2002	117	Prospective	Surgery
Schwartz *et al*[66]	2002	188	Consecutive	Surgery
Wu *et al*[78]	2003	31	Prospective	Surgery
Arima *et al*[17]	2003	58	Consecutive	Surgery
DeWitt *et al*[44]	2005	102	Prospective	Surgery

depicts characteristics of EUS studies with FNA. All the

Table 2 Characteristics of studies included in this meta-analysis for EUS with FNA

Author	Year of publication	No. of patients	Type of recruitment	Confirmatory procedure
Kondo *et al*[6]	1990	503	Consecutive	Surgery
Schuder *et al*[25]	1991	32	Consecutive	Surgery
Silvestri *et al*[83]	1995	27	Prospective	Surgery
Giovannini *et al*[82]	1995	141	Prospective	Surgery or appropriate follow-up
Pedersen *et al*[21]	1996	9	Consecutive	FNA and appropriate follow-up
HunerBein *et al*[90]	1996	19	Consecutive	Surgery
Gress *et al*[19]	1997	52	Prospective	Surgery
Wiersema *et al*[104]	1997	60	Consecutive	FNA and appropriate follow-up
HunerBein *et al*[91]	1998	15	Consecutive	Surgery
HunerBein *et al*[98]	1998	16	Consecutive	Surgery
Fritscher-Ravens *et al*[101]	1999	16	Consecutive	FNA and appropriate follow-up
Mishra *et al*[102]	1999	111	Consecutive	FNA and appropriate follow-up
Giovannini *et al*[81]	1999	198	Prospective	Surgery or appropriate follow-up
Williams *et al*[89]	1999	333	Prospective	Surgery or appropriate follow-up
Fritscher-Ravens *et al*[84]	2000	35	Prospective	Surgery
Fritscher-Ravens *et al*[98]	2000	35	Consecutive	FNA and appropriate follow-up
Savides *et al*[100]	2000	54	Consecutive	FNA and appropriate follow-up
Fritscher-Ravens *et al*[103]	2000	153	Consecutive	FNA and appropriate follow-up
Vazquez-Sequeiros *et al*[105]	2001	37	Consecutive	Surgery
Wallace *et al*[91]	2001	43	Consecutive	FNA and appropriate follow-up
Wiersema *et al*[85]	2001	82	Prospective	Surgery
Chhieng *et al*[96]	2001	103	Consecutive	Surgery
Devereaux *et al*[22]	2002	49	Consecutive	Surgery
Catalano *et al*[92]	2002	62	Consecutive	Surgery
Schwartz *et al*[66]	2002	188	Consecutive	Surgery
Arima *et al*[95]	2003	58	Consecutive	Surgery
Pellise *et al*[23]	2004	11	Consecutive	Surgery
Kramer *et al*[86]	2004	81	Prospective	Surgery
Walsh *et al*[97]	2005	27	Consecutive	Surgery or appropriate follow-up
Tournoy *et al*[88]	2005	67	Prospective	Surgery
Khoo *et al*[93]	2006	20	Prospective	Surgery
Beek *et al*[87]	2006	43	Prospective	Surgery

76 selected studies were published as full-text articles in peer review journals. The pooled estimates given are estimates calculated by the fixed effect model.

Accuracy of EUS with and without FNA

Pooled sensitivity to diagnose the cause for mediastinal lymphadenopathy was 84.7% (95% CI: 82.9-86.4) for

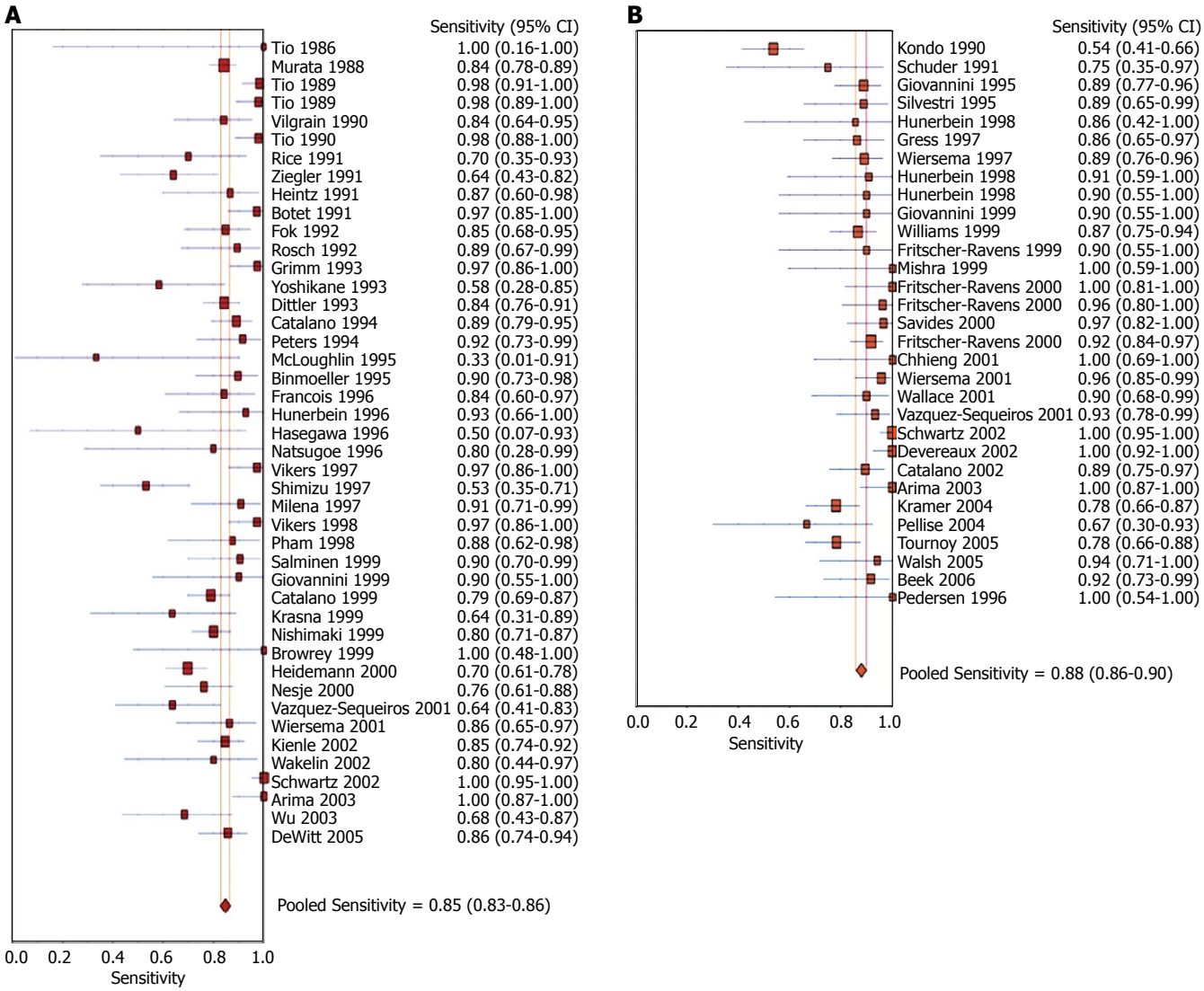

Figure 2 Forrest plots. **A**: Sensitivity of EUS alone in diagnosing mediastinal lymphadenopathy; **B**: Sensitivity of EUS-FNA in diagnosing mediastinal lymphadenopathy.

EUS alone *versus* 88.0% (95% CI: 85.8-90.0) for EUS with FNA. The Forrest plot showing the sensitivity of EUS with and without FNA in various studies is shown in Figure 2A and B, respectively. EUS without FNA had a pooled specificity of 84.6% (95% CI: 83.2-85.9) and with FNA was 96.4% (95% CI: 95.3-97.4). Forrest plots showing specificity from various studies with and without FNA is depicted in Figure 3A and B, respectively.

The pooled positive likelihood ratio of EUS without FNA was 3.3 (95% CI: 2.6-4.3) and with FNA was 11.2 (95% CI: 5.9-21.2). The pooled negative likelihood ratio was 0.24 (95% CI: 0.1-0.3) for EUS without FNA and 0.13 (95% CI: 0.1-0.2) for EUS with FNA. The diagnostic odds ratio, the odds of having nodal metastasis in positive as compared to negative EUS studies, was 19.1 (95% CI: 12.7-28.5) for EUS without FNA and 106.9 (95% CI: 54.4-210.3) for EUS with FNA. Figure 4 shows a Forrest plot of various studies with FNA and their DOR. All the pooled estimates calculated by random effect models were similar to the estimates of fixed effect model.

SROC curves for EUS without FNA showed an area under the curve (AUC) of 0.91. EUS with FNA showed an AUC of 0.97. Figure 5 shows the SROC curve. The *P* for Chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10. Table 3 shows the accuracy estimates of EUS alone and EUS-FNA.

Effect of technology over time

To standardize the criteria for lymph node involvement and change in technology, the studies were grouped into three time periods[30]. These time periods were 1988 to 1994, 1995 to 1999, and 2000 to 2006. During these time periods, the number of studies that met the inclusion criteria for EUS alone were 17, 17, and 10, respectively. Studies that met inclusion criteria for EUS-FNA were 4, 10, and 18, respectively. For the most recent time period, EUS alone had a sensitivity of 81.6% (95% CI: 77.8-85.1) and specificity of 82.4% (95% CI: 78.2-86.1). During the same time period, EUS-FNA had a sensitivity of 91.7% (95% CI: 89.3-93.7) and specificity of 96.8% (95% CI: 94.9-98.2). All pooled estimates during the three time periods are given in Table 4. The *P* for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.1.

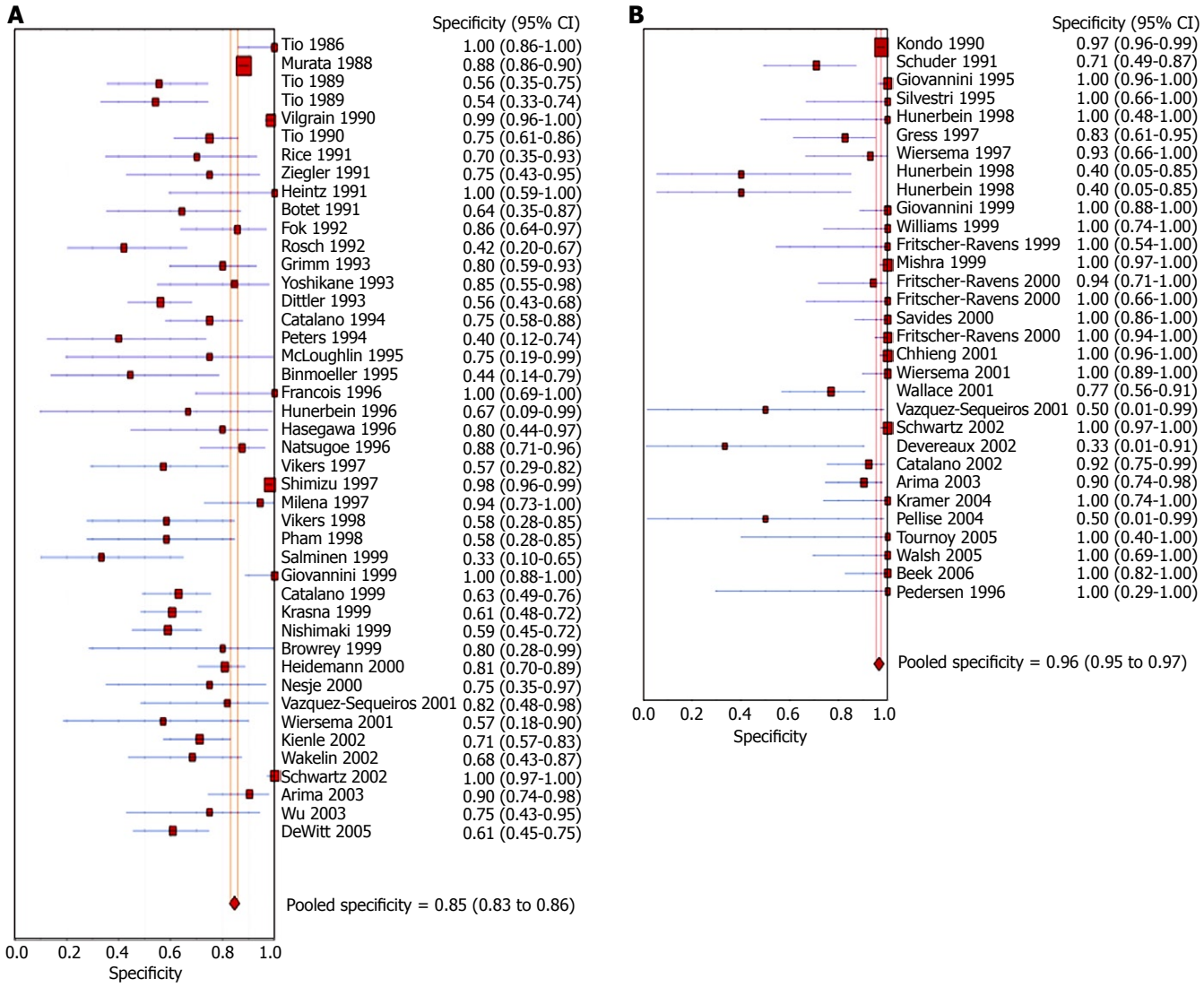

Figure 3 Forrest plots. **A**: Specificity of EUS alone in diagnosing mediastinal lymphadenopathy. **B**: Specificity of EUS-FNA alone in diagnosing mediastinal lymphadenopathy.

Bias estimates

The bias calculations using Harbord-Egger bias indicator gave a value of 1.08 (95% CI: -0.79-2.95, $P = 0.29$) for EUS studies without FNA and 2.02 (95% CI: 0.29-3.74, $P = 0.04$) for studies with FNA. The Begg-Mazumdar indicator for bias gave a Kendall's tau b value of 0.13 ($P = 0.36$) for studies without FNA and -0.19 ($P = 0.07$) for studies with FNA. The funnel plots for the studies without and with FNA are shown in Figure 6A and B.

DISCUSSION

Diagnosing the correct etiology for mediastinal lymphadenopathy helps direct precise therapy and prognosis. Thoracoscopic procedures for tissue biopsy carry a risk of complications in 25%-35% of cases[9,10]. The advantage of EUS is the ability to perform FNA during the procedure for tissue diagnosis. The procedure is, in comparison with other alternative options, safe, less invasive, and does not require general anesthesia or hospitalization[107]. The complication rate is extremely low (0.5%-2.3%) with several studies reporting no complications[48,77,83,107]. Modalities using FNA, such as transbronchial, computed tomography, or thoracoscopic procedure, cannot be used for the entire mediastinum[2-13]. EUS has the ability to image the aortopulmonary window, the subcarinal nodes, inferior mediastinum, and entire posterior part of the mediastinum.

This meta-analysis and systematic review was written in accordance with the proposal for reporting by the QUOROM (Quality of Reporting of Meta-analyses) statement[7]. This meta-analysis and systematic review shows that the pooled sensitivity of EUS for mediastinal lymphadenopathy is high and use of FNA during the procedure, further increases such sensitivity. The pooled specificity for diagnosing mediastinal lymphadenopathy is also high with substantial improvement if FNA is performed during the procedure (from 84.6% to 96.4%). Diagnostic odds ratio is defined as the odds of having a positive test in patients with true anatomic disease when compared to patients who do not have the disease. EUS has a very high diagnostic odds ratio for mediastinal lymphadenopathy. For example, if EUS indicates mediastinal lymphadenopathy and if FNA is performed on the enlarged nodes, the patient has odds of 106 times to have the correct etiology for lymph node enlargement. If EUS shows mediastinal lymphadenopathy, then the nodes

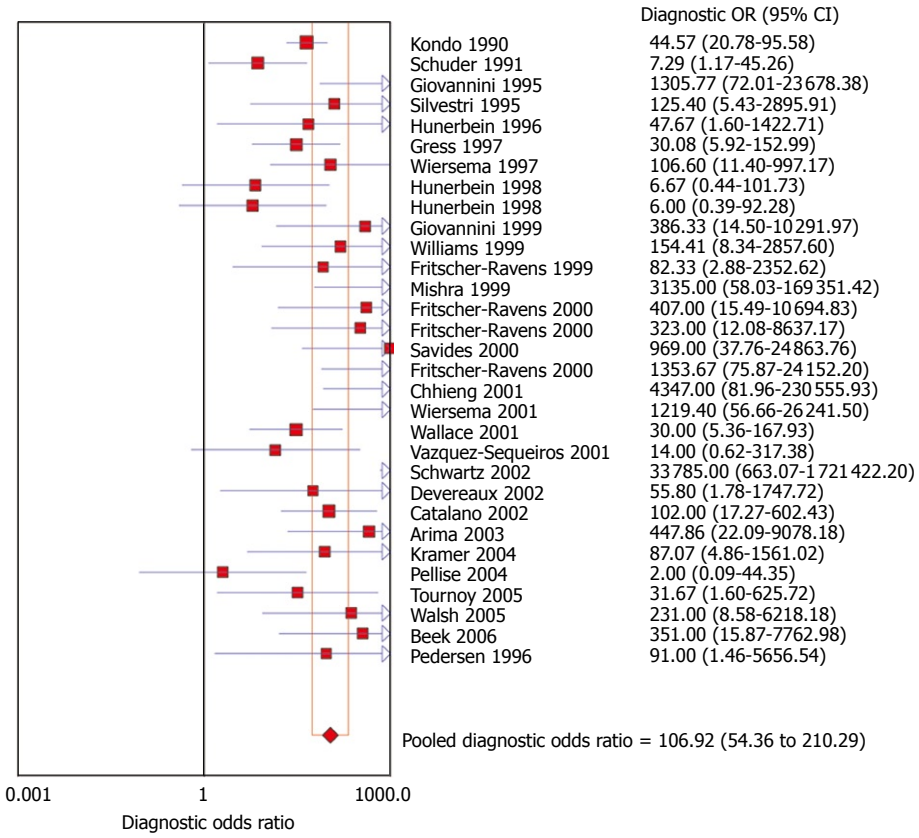

Figure 4 Forrest plot showing diagnostic odds ratio of EUS-FNA in identifying mediastinal lymphadenopathy.

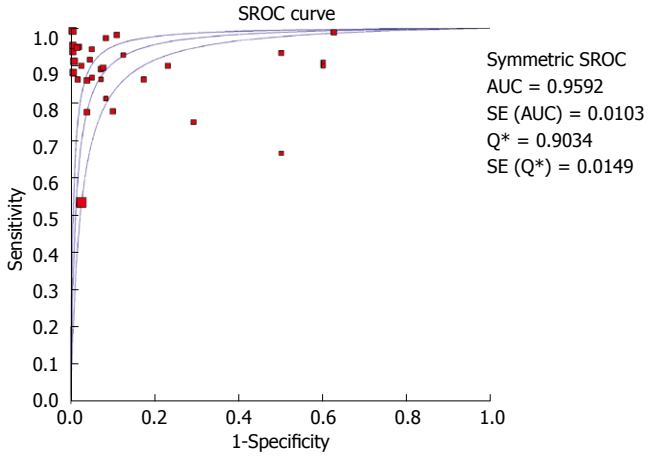

Figure 5 SROC for EUS to diagnose mediastinal lymphadenopathy.

Table 3 Pooled diagnostic accuracy estimates of EUS alone and EUS-FNA

	EUS	EUS-FNA
Studies	44	32
Pooled sensitivity	84.7% (82.9-86.4)	88.0% (85.8-90.0)
Pooled specificity	84.6% (83.2-85.9)	96.4% (95.3-97.4)
Positive likelihood ratio	3.3 (2.6-4.3)	11.2 (5.9-21.2)
Negative likelihood ratio	0.24 (0.1-0.3)	0.13 (0.1-0.2)
Diagnostic odds ratio	19.1 (12.7-28.5)	106.9 (54.4-210.3)
Area under the curve	0.91	0.97

should be biopsied by FNA to improve the diagnostic accuracy.

The positive likelihood ratio measures how well a test identifies a disease state. The higher the positive likelihood ratio, the better the test performs in identifying the correct disease state. The negative likelihood ratio of the same test measures how well the test performs in excluding a disease state. The lower the negative likelihood ratio, the better the test performs in excluding a disease. For mediastinal lymphadenopathy, EUS has a high positive likelihood ratio and low negative likelihood ratio. This indicates that EUS performs better in diagnosing and excluding mediastinal lymphadenopathy. For mediastinal lymphadenopathy, all the pooled accuracy estimates of EUS are higher if FNA is performed during the procedure. Also, these pooled estimates give a baseline for future study comparisons.

The EUS studies with FNA were grouped into time periods and analyzed to standardize the criteria and the technology of EUS over the past two decades. Over the last two decades, the sensitivity and specificity of EUS with FNA has substantially improved.

Due to the possibility of different studies using slightly different criteria for diagnosis, heterogeneity among the studies was tested by drawing SROC curves and finding the AUC. An AUC of 1 for any test indicates that the test is excellent. SROC curves for EUS showed that the value for AUC was very close to 1, indicating that EUS is an excellent test to diagnose mediastinal lymphadenopathy. Publication bias and selection bias may affect the summary estimates. Studies with statistically significant results tend to be published and cited. Smaller studies may show larger treatment effects due to fewer case-mix differences (e.g. patients with only early or late disease) than larger trials. This bias can be estimated by bias indicators and construction of

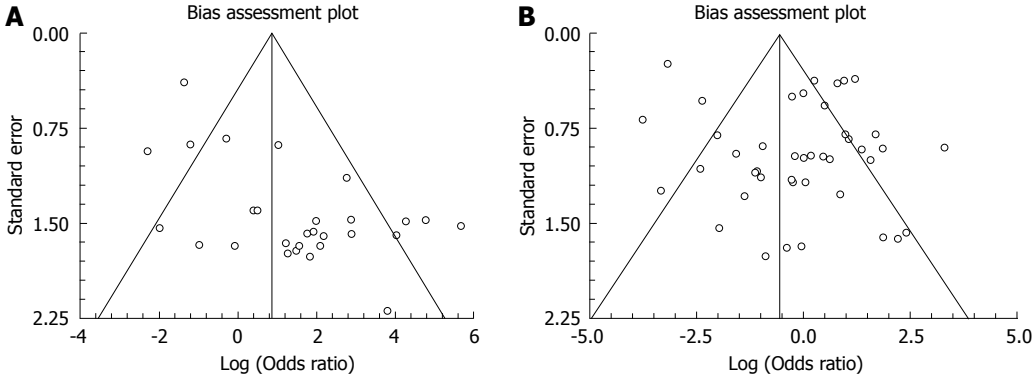

Figure 6 Funnel plots. **A**: Bias assessment for EUS studies without FNA in examining mediastinal lymphadenopathy; **B**: Bias assessment for EUS-FNA studies in examining mediastinal lymphadenopathy.

Table 4 Pooled diagnostic accuracy estimates of EUS alone and EUS-FNA for different time periods with 95% CI

Time period	No. of studies	Pooled sensitivity	Pooled specificity	Pooled LR+ 1	Pooled LR-2	Pooled DOR3
EUS without FNA						
1988 to 1994	17	88.0% (85.4-90.2)	85.2% (83.4-86.9)	3.6 (2.4-5.4)	0.2 (0.1-0.3)	27.5 (14.5-52.4)
1995 to 1999	17	82.6% (78.8-85.9)	84.4% (81.6-86.9)	3.0 (2.0-4.5)	0.3 (0.2-0.4)	14.8 (7.5-29.3)
2000 to 2005	10	81.6% (77.8-85.1)	82.4% (78.2-86.1)	3.4 (2.2-5.3)	0.3 (0.2-0.4)	14.9 (6.7-33.1)
EUS-FNA						
1988 to 1994	4	71.8% (63.9-78.9)	96.8% (94.9-98.1)	15.5 (2.4-101.2)	0.3 (0.1-0.6)	61.8 (10.5-63.8)
1995 to 1999	10	88.9% (83.5-93.0)	94.7% (90.7-97.3)	8.1 (2.8-23.3)	0.1 (0.1-0.2)	57.0 (20.7-57.1)
2000 to 2005	18	91.7% (89.3-93.7)	96.8% (94.9-98.2)	12.5 (5.2-29.8)	0.1 (0.1-0.2)	17.7 (5.0-62.8)

[1]LR+: Positive likelihood ratio; [2]LR-: Negative likelihood ratio; [3]DOR: Diagnostic odds ratio.

funnel plots. Bias among studies can affect the shape of the funnel plot. In this meta-analysis and systematic review, bias calculations using Harbord-Egger indicator[36] and Begg-Mazumdar indicator[37] showed no statistically significant bias for EUS studies without FNA. Furthermore, funnel plot analyses showed no significant bias for EUS without FNA and EUS-FNA studies (Figure 6B).

In conclusion, EUS has high sensitivity and specificity to evaluate mediastinal lymphadenopathy. This meta-analysis demonstrates that FNA substantially improves the specificity of EUS in evaluating mediastinal lymphadenopathy. EUS with FNA should be the diagnostic test of choice for evaluating mediastinal lymphadenopathy.

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