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Staging accuracy of esophageal cancer by endoscopic ultrasound: A meta-analysis and systematic review

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Abstract

AIM: To evaluate the accuracy of endoscopic ultrasound (EUS) in the staging of esophageal cancer.

METHODS: Only EUS studies confirmed by surgery were selected. Articles were searched in Medline and Pubmed. Two reviewers independently searched and extracted data. Meta-analysis of the accuracy of EUS was analyzed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio. Pooling was conducted by both the 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: Forty-nine studies (n = 2558) which met the inclusion criteria were included in this analysis. Pooled sensitivity and specificity of EUS to diagnose T1 was 81.6% (95% CI: 77.8-84.9) and 99.4% (95% CI: 99.0-99.7), respectively. To diagnose T4, EUS had a pooled sensitivity of 92.4% (95% CI: 89.2-95.0) and specificity of 97.4% (95% CI: 96.6-98.0). With Fine Needle Aspiration (FNA), sensitivity of EUS to diagnose N stage improved from 84.7% (95% CI: 82.9-86.4) to 96.7% (95% CI: 92.4-98.9). The P value for the χ^2 test of heterogeneity for all pooled estimates was > 0.10.

CONCLUSION: EUS has excellent sensitivity and specificity in accurately diagnosing the TN stage of esophageal cancer. EUS performs better with advanced (T4) than early (T1) disease. FNA substantially improves the sensitivity and specificity of EUS in evaluating N stage disease. EUS should be strongly considered for staging esophageal cancer.

Key words: Esophageal cancer; Cancer staging; Endoscopic ultrasound; TNM staging; Diagnostic accuracy

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INTRODUCTION

Esophageal cancer is a devastating disease with a significant impact on patients' lives and health-care systems world-wide. Esophageal cancer affects 1%-2% of people in the United States and up to 15% of people undergoing endoscopy for gastroesophageal reflux disease (GERD)[1]. The incidence of esophageal cancer is increasing in the USA, approximately 20.6% on average annually, despite a decrease in esophageal squamous cell cancer[2,3]. This increase is mostly due to a dramatic rise in esophageal adenocarcinoma, from 1.8 cases per 100 000 during 1987-1992 to 2.5 cases per 100 000 during 1992-1996[4]. From 1973 to 2002, esophageal adenocarcinoma has increased fourfold[5]. The impact of this disease is significant throughout the world due to its increasing incidence and significant mortality (5-year mortality rate > 80%)[6].

Based upon the increasing incidence and devastating consequences of esophageal adenocarcinoma, an increasing amount of resources has been evaluated and implemented in an effort to stage and treat this disease. Based upon the 1996 US national cancer database, the 5-year survival rate for esophageal cancer is as follows: stage 0 (TisN0M0) is 52%, stage I (T1N0M0) is 42%, stage Ⅱ (T2N0M0 or T3N0M0) or (T1N1M0 or T2N1M0) is 29%, stage Ⅲ (T3N1MO or T4NxM0) is 15%, and stage Ⅳ (TxNxM1) is 3%[7].

Staging of esophageal cancer is extremely important since it helps differentiate treatment options. To improve survival, many treatment modalities have been utilized for esophageal cancer, including surgery, radiotherapy, chemotherapy, and combinations of the aforementioned options[7]. For early disease, recent studies that have investigated endoscopic mucosal resection have shown a 5-year survival of 98%[8] and a low recurrence rate[9]. Although multiple treatment regimens exist and they overlap

for each stage, the stage of disease is very important in guiding treatment and predicting outcomes.

Many staging modalities have been utilized for esophageal cancer, including chest CT, MRI, positron emission tomography (PET), and endoscopic ultrasound (EUS). CT and MRI lack the ability to differentiate layers of the esophageal mucosa. Thus, these modalities cannot accurately discern T stage of esophageal cancer. Chest CT provides important information regarding tumor size, lymph node involvement, and potential metastatic lesions. However, chest CT alone has a sensitivity of only 48% for mediastinal lymph node involvement[10]. MRI has been shown to be useful in preoperative evaluation and equally as accurate as CT in staging esophageal cancer; however, studies do vary[11]. MRI staging has been shown to have an accuracy of 40% with very low sensitivity and specificity[12,13]. For mediastinal lymph node involvement, thoracoscopic procedures for tissue biopsy carry a risk of complications in 25%-35% of cases[14,15]. An alternative to CT or MRI is PET. PET is a non-invasive test which has been shown to be beneficial in detection of metastatic disease (stage IV); however, detection of locoregional metastases is limited[13]. Due to limitations of CT, MRI, and PET, other modalities, such as EUS, have been initiated and reviewed.

EUS utilizes an echoendoscope that is passed directly into the esophagus, with the ability to visualize the individual histological layers of the esophagus[16]. This approach is particularly useful in evaluating invasion of local disease, especially esophageal cancer. EUS has been shown to detect more locoregional node involvement than CT or PET, with a higher sensitivity[17,18]. The accuracy of EUS to determine tumor depth has also been estimated to be quite accurate[18-20]. However, studies vary as to the accuracy of EUS in both the depth of local disease, nodal involvement, and the detection of distant metastases[21-24].

With EUS emerging as a very useful staging tool, its role in staging esophageal cancer continues to be addressed. Several studies have identified the potential benefits of EUS with esophageal cancer staging; however, results regarding the extent of its benefits have been inconsistent[52,72,82]. We conducted a meta-analysis to examine the role of EUS in the staging of esophageal cancer for loco-regional spread.

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[25]. Since this study investigated diagnostic accuracy of a test, the study design for this meta-analysis and systematic review conformed to the guidelines of the Standards for Reporting of Diagnostic Accuracy (STARD) initiative[26].

MATERIALS AND METHODS

Study selection criteria

Only EUS studies confirmed by surgery or appropriate follow-up were selected. EUS criteria used for T staging were: T1, tumor invades the lamina propria or submucosa but not the muscularis propria; T2, tumor invades but does not extend beyond the muscularis propria; T3, tumor invades the peri-esophageal tissues but not adjacent organs; and T4, tumor invades adjacent structures. Nodal invasion was defined as invasion of mediastinal lymph nodes. 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, CINAHL, ACP Journal Club, DARE, International Pharmaceutical Abstracts, Old Medline, Medline Non-indexed Citations, OVID Healthstar, and Cochrane Controlled Trials Registry. The search terms used were endoscopic ultrasound, EUS, ultrasound, endosonography, esophageal cancer, esophageal cancer, tumor staging, nodal invasion, staging, surgery, sensitivity, specificity, positive predictive value, and negative predictive value. 2 × 2 tables were constructed with the data extracted from each study. Two authors (SP and JR) independently searched and extracted the data. 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)[27,28]. 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[28]. 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 periods of time to standardize the change in EUS technology and EUS criteria for lymph node involvement[29]. These periods of time were 1986-1994, 1995-1999 and 2000-2006. Pooling was conducted using the Mantel-Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model). The confidence intervals (CIs) were calculated using the F distribution method[30]. Forrest plots were drawn to show the point estimates in each study, in relation to the summary pooled estimate. The width of the point estimates in the Forrest plots indicated the assigned weight for that study. For 0 values, 0.5 was added, as described by Cox[31]. The heterogeneity of the sensitivities and specificities was tested by applying the likelihood ratio test[32]. The heterogeneity of likelihood ratios and diagnostic odds ratios were tested using Cochran's Q test, based upon inverse variance weights[33]. 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 the Egger[34] and

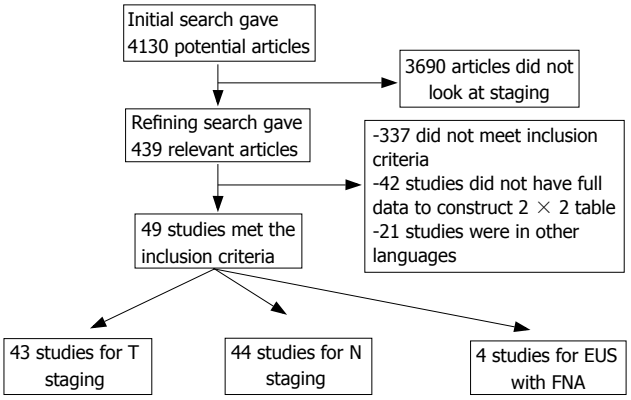


Figure 1 Search results.

Begg-Mazumdar[35] bias indicators. Also, funnel plots were constructed to evaluate potential publication bias using the standard error and diagnostic odds ratio[36,37].

RESULTS

An initial search identified 4130 reference articles, of these, 439 relevant articles were selected and reviewed. Forty-nine studies (n = 2558) which met the inclusion criteria were included in this analysis[10,18,20-24,38-40]. For T staging, there were 43 studies[10,18,20-24,39-72]. There were 44 studies for nodal staging[10,18,20-24,38-46,48-50,53,54,56-63,66-80], and of these, 4 used FNA for nodal staging[23,38,76,77]. Figure 1 shows the search results and Table 1 the characteristics for EUS studies included in this meta-analysis. All of the 49 studies included were published as full-text articles in peer-review journals. Not all studies had data for all the stages; we only used data for the available stage of esophageal cancer in a given paper. All the studies included used dedicated EUS machines. The calculated pooled estimates given are estimates calculated by the fixed effect model.

Accuracy of EUS for T staging

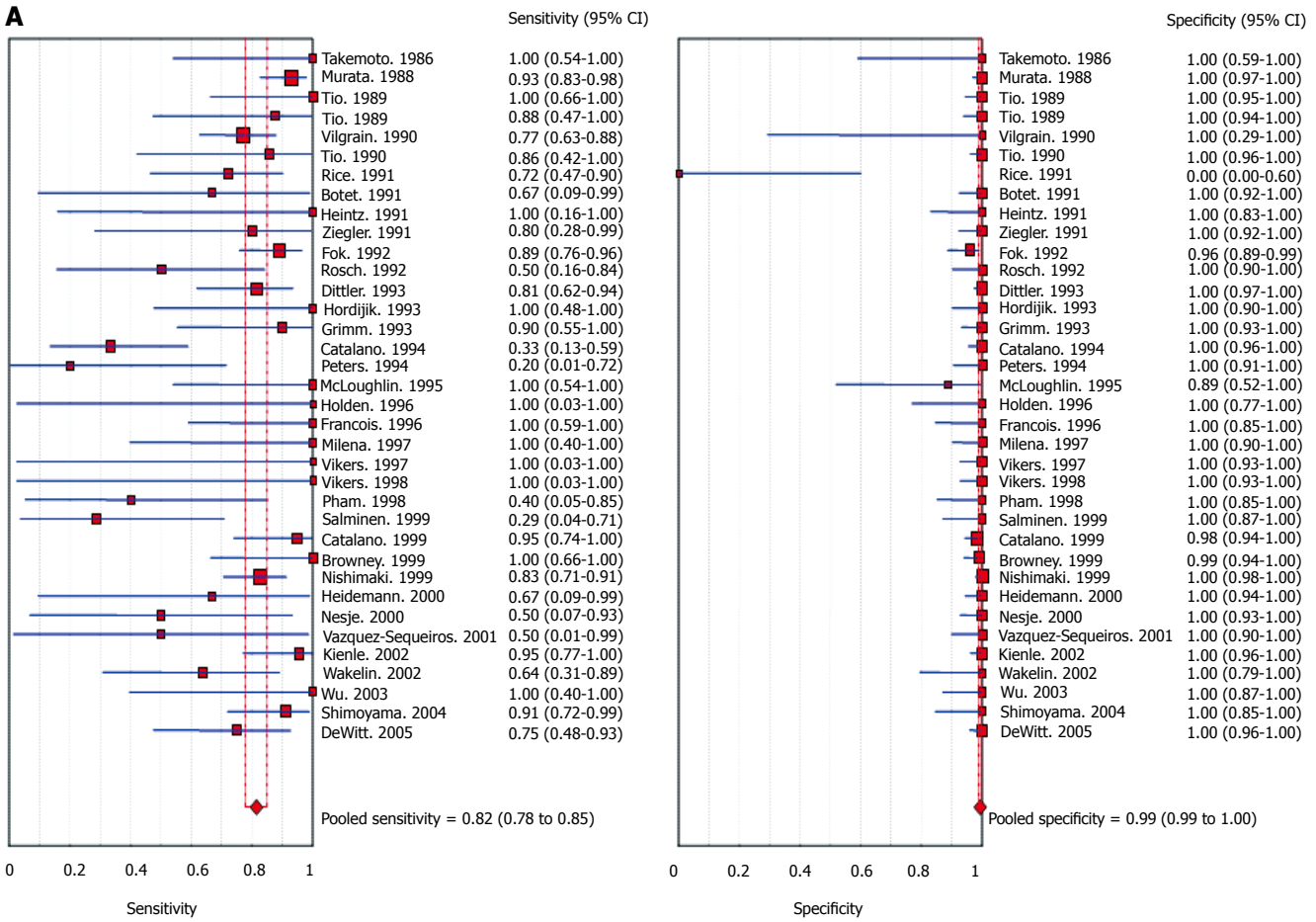
The pooled sensitivity and specificity of EUS to diagnose T1 stage cancer was 81.6% (95% CI: 77.8-84.9) and 99.4% (95% CI: 99.0-99.7), respectively. Figure 2A shows the sensitivity and specificity to diagnose T1 stage cancer in a Forrest plot. For T2 stage, EUS had a pooled sensitivity and specificity of 81.4% (95% CI: 77.5-84.8) and 96.3% (95% CI: 95.4-97.1), respectively. The Forrest plot in Figure 2B shows the sensitivity and specificity of EUS to diagnose T2 stage cancer. For T3 stage, EUS had a pooled sensitivity and specificity of 91.4% (95% CI: 89.5-93.0) and 94.4% (95% CI: 93.1-95.5), respectively. Figure 2C shows the ability of EUS to diagnose stage T3. To diagnose T4 stage cancer, EUS had a pooled sensitivity of 92.4% (95% CI: 89.2-95.0) and specificity of 97.4% (95% CI: 96.6-98.0). The sensitivity and specificity of EUS to diagnose T4 stage cancer from individual studies are shown as a Forrest plot in Figure 2D. A test of heterogeneity for all the pooled estimates for T stages had a P value > 0.10. All the pooled estimates calculated by fixed and random effect models were similar. Table 2 shows the pooled accuracy estimates of EUS for T stage esophageal cancer.

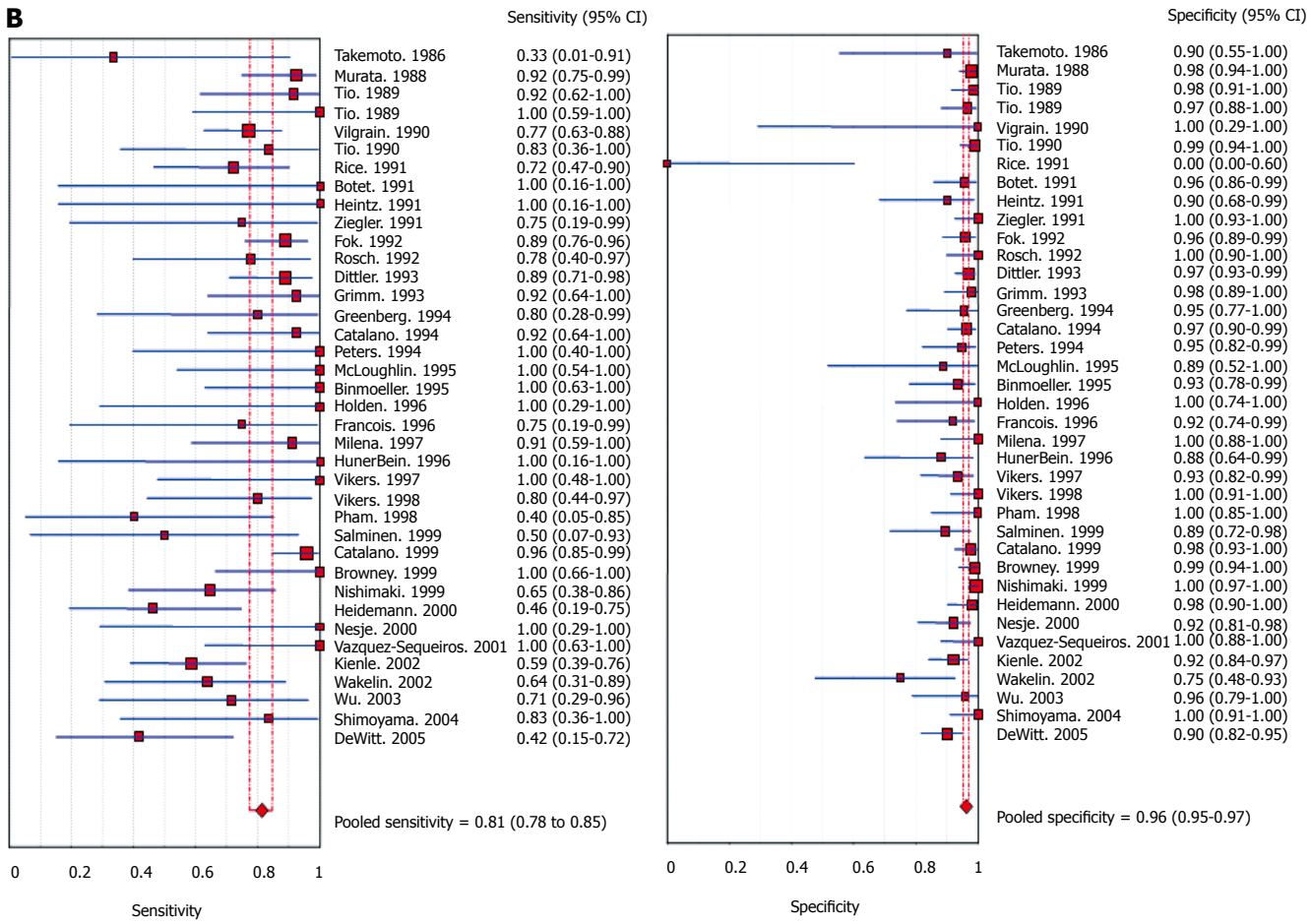
Table 1 Characteristics of studies included in this analysis

	Author	Year of publication	Type of enrolment	Confirmatory test
1	Takemoto *et al*	1986	Consecutive	Surgery
2	Tio *et al*	1986	Prospective	Surgery
3	Murata *et al*	1988	Consecutive	Surgery
4	Tio *et al*	1989	Prospective	Surgery
5	Vilgrain *et al*	1990	Consecutive	Surgery
6	Botet *et al*	1991	Consecutive	Surgery
7	Tio *et al*	1989	Prospective	Surgery
8	Heintz *et al*	1991	Consecutive	Surgery
9	Rice *et al*	1991	Consecutive	Surgery
10	Ziegler *et al*	1991	Consecutive	Surgery
11	Tio *et al*	1990	Consecutive	Surgery
12	Fok *et al*	1992	Consecutive	Surgery
13	Rosch *et al*	1992	Consecutive	Surgery
14	Dittler *et al*	1993	Consecutive	Surgery
15	Grimm *et al*	1993	Prospective	Surgery
16	Hordijik *et al*	1993	Consecutive	Surgery
17	Yoshikane *et al*	1993	Consecutive	Surgery
18	Catalano *et al*	1994	Consecutive	Surgery
19	Greenberg *et al*	1994	Prospective	Surgery
20	Peters *et al*	1994	Consecutive	Surgery
21	Binmoeller *et al*	1995	Prospective	Surgery
22	Kallimanis *et al*	1995	Consecutive	Surgery
23	McLoughlin *et al*	1995	Consecutive	Surgery
24	Francois *et al*	1996	Consecutive	Surgery
25	Hasegawa *et al*	1996	Consecutive	Surgery
26	Holden *et al*	1996	Consecutive	Surgery
27	Hunerbein *et al*	1996	Consecutive	Surgery
28	Massari *et al*	1996	Prospective	Surgery
29	Natsugoe *et al*	1996	Consecutive	Surgery
30	Vikers *et al*	1997	Consecutive	Surgery
31	Shimizu *et al*	1997	Consecutive	Surgery
32	Pham *et al*	1998	Consecutive	Surgery
33	Vikers *et al*	1998	Prospective	Surgery
34	Browney *et al*	1999	Prospective	Surgery
35	Catalano *et al*	1999	Prospective	Surgery
36	Nishimaki *et al*	1999	Consecutive	Surgery
37	Salminen *et al*	1999	Consecutive	Surgery
38	Giovannini *et al*	1999	Prospective	Surgery
39	Krasna *et al*	1999	Consecutive	Surgery
40	Heidemann *et al*	2000	Consecutive	Surgery
41	Nesje *et al*	2000	Prospective	Surgery
42	Vazquez-Sequeiros *et al*	2001	Consecutive	Surgery
43	Wiersema *et al*	2001	Prospective	Surgery
44	Kienle *et al*	2002	Prospective	Surgery
45	Wakelin *et al*	2002	Consecutive	Surgery
46	Schwartz *et al*	2002	Consecutive	Surgery
47	Wu *et al*	2003	Prospective	Surgery
48	Shimoyama *et al*	2004	Consecutive	Surgery
49	DeWitt *et al*	2005	Prospective	Surgery

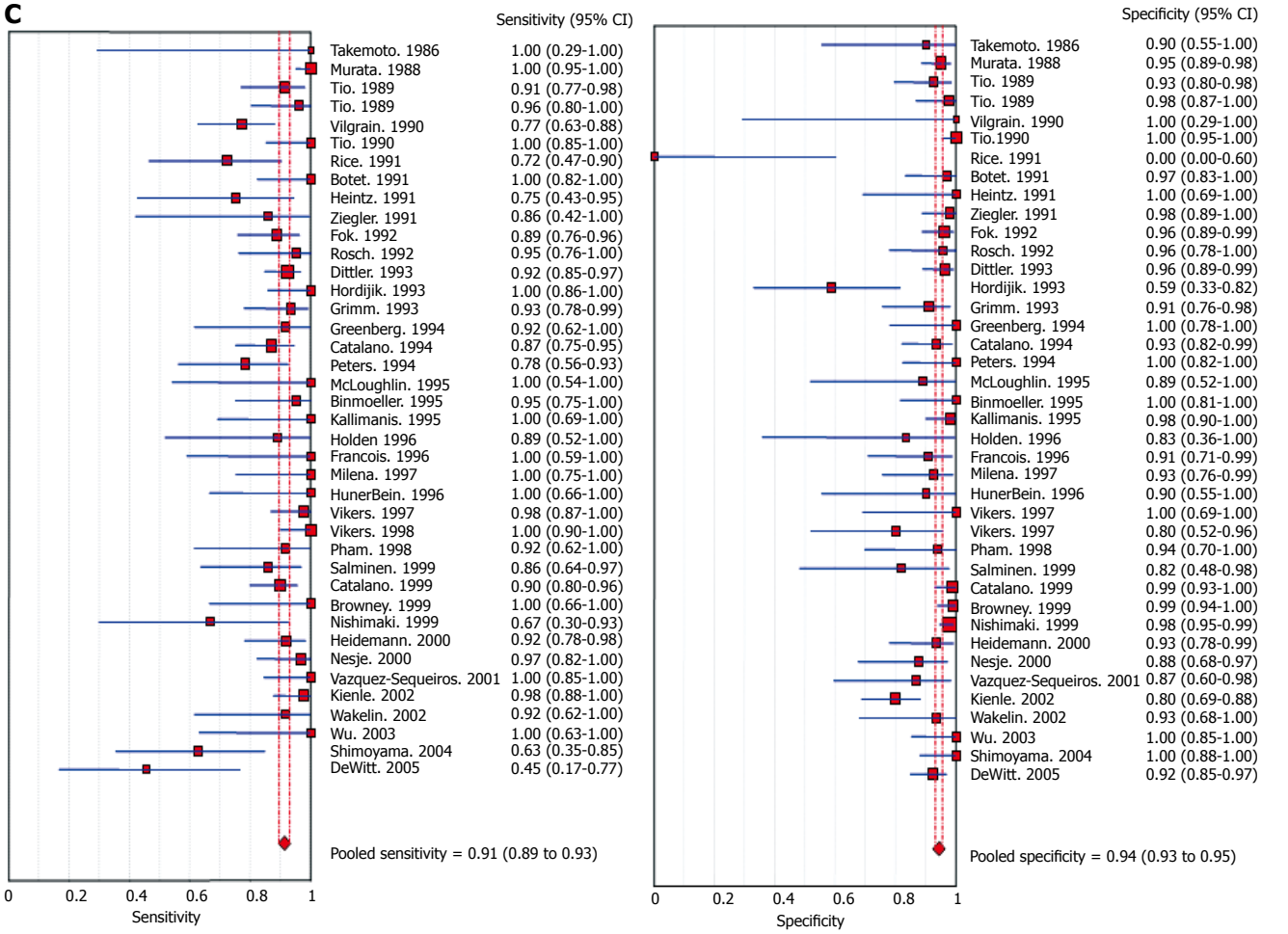
Accuracy of EUS for N staging

With FNA, the sensitivity of EUS to diagnose N stage cancer improved from 84.7% (95% CI: 82.9-86.4) to 96.7% (95% CI: 92.4-98.9). Figure 2E depicts the sensitivity of EUS alone and EUS with FNA in diagnosing N stage cancer. The specificity of EUS improved from 84.6% (95% CI: 83.2-85.9) to 95.5% (95% CI: 91.0-98.2) with FNA. The Forrest plot in Figure 2F shows the specificity of EUS alone and EUS with FNA in diagnosing nodal invasion by esophageal cancer. The accuracy estimates of EUS alone and EUS with FNA are shown in Table 3. All the pooled estimates calculated by fixed and random effect models were similar. The P values for χ^2 heterogeneity for all the pooled accuracy estimates were > 0.10.

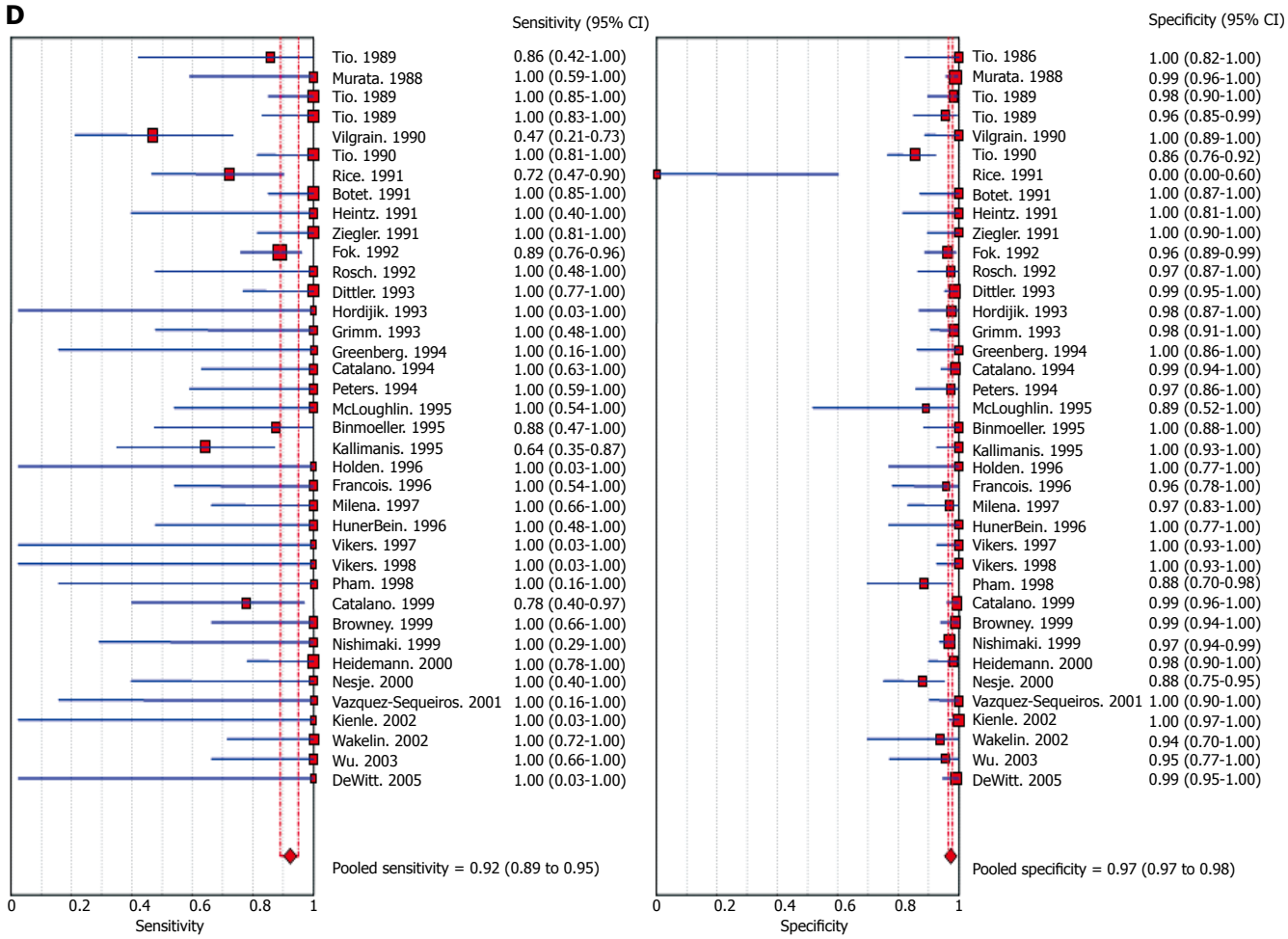

A
Sensitivity (95% CI)
Takemoto. 1986 1.00 (0.54-1.00)
Murata. 1988 0.93 (0.83-0.98)
Tio. 1989 1.00 (0.66-1.00)
Tio. 1989 0.88 (0.47-1.00)
Vilgrain. 1990 0.77 (0.63-0.88)
Tio. 1990 0.86 (0.42-1.00)
Rice. 1991 0.72 (0.47-0.90)
Botet. 1991 0.67 (0.09-0.99)
Heintz. 1991 1.00 (0.16-1.00)
Ziegler. 1991 0.80 (0.28-0.99)
Fok. 1992 0.89 (0.76-0.96)
Rosch. 1992 0.50 (0.16-0.84)
Dittler. 1993 0.81 (0.62-0.94)
Hordijik. 1993 1.00 (0.48-1.00)
Grimm. 1993 0.90 (0.55-1.00)
Catalano. 1994 0.33 (0.13-0.59)
Peters. 1994 0.20 (0.01-0.72)
McLoughlin. 1995 1.00 (0.54-1.00)
Holden. 1996 1.00 (0.03-1.00)
Francois. 1996 1.00 (0.59-1.00)
Milena. 1997 1.00 (0.40-1.00)
Vikers. 1997 1.00 (0.03-1.00)
Vikers. 1998 1.00 (0.03-1.00)
Pham. 1998 0.40 (0.05-0.85)
Salminen. 1999 0.29 (0.04-0.71)
Catalano. 1999 0.95 (0.74-1.00)
Browney. 1999 1.00 (0.66-1.00)
Nishimaki. 1999 0.83 (0.71-0.91)
Heidemann. 2000 0.67 (0.09-0.99)
Nesje. 2000 0.50 (0.07-0.93)
Vazquez-Sequeiros. 2001 0.50 (0.01-0.99)
Kienle. 2002 0.95 (0.77-1.00)
Wakelin. 2002 0.64 (0.31-0.89)
Wu. 2003 1.00 (0.40-1.00)
Shimoyama. 2004 0.91 (0.72-0.99)
DeWitt. 2005 0.75 (0.48-0.93)
Pooled sensitivity = 0.82 (0.78 to 0.85)
0 0.2 0.4 0.6 0.8 1
Sensitivity
Specificity (95% CI)
Takemoto. 1986 1.00 (0.59-1.00)
Murata. 1988 1.00 (0.97-1.00)
Tio. 1989 1.00 (0.95-1.00)
Tio. 1989 1.00 (0.94-1.00)
Vilgrain. 1990 1.00 (0.29-1.00)
Tio. 1990 1.00 (0.96-1.00)
Rice. 1991 0.00 (0.00-0.60)
Botet. 1991 1.00 (0.92-1.00)
Heintz. 1991 1.00 (0.83-1.00)
Ziegler. 1991 1.00 (0.92-1.00)
Fok. 1992 0.96 (0.89-0.99)
Rosch. 1992 1.00 (0.90-1.00)
Dittler. 1993 1.00 (0.97-1.00)
Hordijik. 1993 1.00 (0.90-1.00)
Grimm. 1993 1.00 (0.93-1.00)
Catalano. 1994 1.00 (0.96-1.00)
Peters. 1994 1.00 (0.91-1.00)
McLoughlin. 1995 0.89 (0.52-1.00)
Holden. 1996 1.00 (0.77-1.00)
Francois. 1996 1.00 (0.85-1.00)
Milena. 1997 1.00 (0.90-1.00)
Vikers. 1997 1.00 (0.93-1.00)
Vikers. 1998 1.00 (0.93-1.00)
Pham. 1998 1.00 (0.85-1.00)
Salminen. 1999 1.00 (0.87-1.00)
Catalano. 1999 0.98 (0.94-1.00)
Browney. 1999 0.99 (0.94-1.00)
Nishimaki. 1999 1.00 (0.98-1.00)
Heidemann. 2000 1.00 (0.94-1.00)
Nesje. 2000 1.00 (0.93-1.00)
Vazquez-Sequeiros. 2001 1.00 (0.90-1.00)
Kienle. 2002 1.00 (0.96-1.00)
Wakelin. 2002 1.00 (0.79-1.00)
Wu. 2003 1.00 (0.87-1.00)
Shimoyama. 2004 1.00 (0.85-1.00)
DeWitt. 2005 1.00 (0.96-1.00)
Pooled specificity = 0.99 (0.99 to 1.00)
0 0.2 0.4 0.6 0.8 1
Specificity


B
Sensitivity (95% CI)
Takemoto. 1986 0.33 (0.01-0.91)
Murata. 1988 0.92 (0.75-0.99)
Tio. 1989 0.92 (0.62-1.00)
Tio. 1989 1.00 (0.59-1.00)
Vilgrain. 1990 0.77 (0.63-0.88)
Tio. 1990 0.83 (0.36-1.00)
Rice. 1991 0.72 (0.47-0.90)
Botet. 1991 1.00 (0.16-1.00)
Heintz. 1991 1.00 (0.16-1.00)
Ziegler. 1991 0.75 (0.19-0.99)
Fok. 1992 0.89 (0.76-0.96)
Rosch. 1992 0.78 (0.40-0.97)
Dittler. 1993 0.89 (0.71-0.98)
Grimm. 1993 0.92 (0.64-1.00)
Greenberg. 1994 0.80 (0.28-0.99)
Catalano. 1994 0.92 (0.64-1.00)
Peters. 1994 1.00 (0.40-1.00)
McLoughlin. 1995 1.00 (0.54-1.00)
Binmoeller. 1995 1.00 (0.63-1.00)
Holden. 1996 1.00 (0.29-1.00)
Francois. 1996 0.75 (0.19-0.99)
Milena. 1997 0.91 (0.59-1.00)
HunerBein. 1996 1.00 (0.16-1.00)
Vikers. 1997 1.00 (0.48-1.00)
Vikers. 1998 0.80 (0.44-0.97)
Pham. 1998 0.40 (0.05-0.85)
Salminen. 1999 0.50 (0.07-0.93)
Catalano. 1999 0.96 (0.85-0.99)
Browney. 1999 1.00 (0.66-1.00)
Nishimaki. 1999 0.65 (0.38-0.86)
Heidemann. 2000 0.46 (0.19-0.75)
Nesje. 2000 1.00 (0.29-1.00)
Vazquez-Sequeiros. 2001 1.00 (0.63-1.00)
Kienle. 2002 0.59 (0.39-0.76)
Wakelin. 2002 0.64 (0.31-0.89)
Wu. 2003 0.71 (0.29-0.96)
Shimoyama. 2004 0.83 (0.36-1.00)
DeWitt. 2005 0.42 (0.15-0.72)
Pooled sensitivity = 0.81 (0.78 to 0.85)
0 0.2 0.4 0.6 0.8 1
Sensitivity
Specificity (95% CI)
Takemoto. 1986 0.90 (0.55-1.00)
Murata. 1988 0.98 (0.94-1.00)
Tio. 1989 0.98 (0.91-1.00)
Tio. 1989 0.97 (0.88-1.00)
Vigrain. 1990 1.00 (0.29-1.00)
Tio. 1990 0.99 (0.94-1.00)
Rice. 1991 0.00 (0.00-0.60)
Botet. 1991 0.96 (0.86-0.99)
Heintz. 1991 0.90 (0.68-0.99)
Ziegler. 1991 1.00 (0.93-1.00)
Fok. 1992 0.96 (0.89-0.99)
Rosch. 1992 1.00 (0.90-1.00)
Dittler. 1993 0.97 (0.93-0.99)
Grimm. 1993 0.98 (0.89-1.00)
Greenberg. 1994 0.95 (0.77-1.00)
Catalano. 1994 0.97 (0.90-0.99)
Peters. 1994 0.95 (0.82-0.99)
McLoughlin. 1995 0.89 (0.52-1.00)
Binmoeller. 1995 0.93 (0.78-0.99)
Holden. 1996 1.00 (0.74-1.00)
Francois. 1996 0.92 (0.74-0.99)
Milena. 1997 1.00 (0.88-1.00)
HunerBein. 1996 0.88 (0.64-0.99)
Vikers. 1997 0.93 (0.82-0.99)
Vikers. 1998 1.00 (0.91-1.00)
Pham. 1998 1.00 (0.85-1.00)
Salminen. 1999 0.89 (0.72-0.98)
Catalano. 1999 0.98 (0.93-1.00)
Browney. 1999 0.99 (0.94-1.00)
Nishimaki. 1999 1.00 (0.97-1.00)
Heidemann. 2000 0.98 (0.90-1.00)
Nesje. 2000 0.92 (0.81-0.98)
Vazquez-Sequeiros. 2001 1.00 (0.88-1.00)
Kienle. 2002 0.92 (0.84-0.97)
Wakelin. 2002 0.75 (0.48-0.93)
Wu. 2003 0.96 (0.79-1.00)
Shimoyama. 2004 1.00 (0.91-1.00)
DeWitt. 2005 0.90 (0.82-0.95)
Pooled specificity = 0.96 (0.95-0.97)
0 0.2 0.4 0.6 0.8 1
Specificity

C


Sensitivity (95% CI)
Takemoto. 1986 1.00 (0.29-1.00)
Murata. 1988 1.00 (0.95-1.00)
Tio. 1989 0.91 (0.77-0.98)
Tio. 1989 0.96 (0.80-1.00)
Vilgrain. 1990 0.77 (0.63-0.88)
Tio. 1990 1.00 (0.85-1.00)
Rice. 1991 0.72 (0.47-0.90)
Botet. 1991 1.00 (0.82-1.00)
Heintz. 1991 0.75 (0.43-0.95)
Ziegler. 1991 0.86 (0.42-1.00)
Fok. 1992 0.89 (0.76-0.96)
Rosch. 1992 0.95 (0.76-1.00)
Dittler. 1993 0.92 (0.85-0.97)
Hordijik. 1993 1.00 (0.86-1.00)
Grimm. 1993 0.93 (0.78-0.99)
Greenberg. 1994 0.92 (0.62-1.00)
Catalano. 1994 0.87 (0.75-0.95)
Peters. 1994 0.78 (0.56-0.93)
McLoughlin. 1995 1.00 (0.54-1.00)
Binmoeller. 1995 0.95 (0.75-1.00)
Kallimanis. 1995 1.00 (0.69-1.00)
Holden 1996 0.89 (0.52-1.00)
Francois. 1996 1.00 (0.59-1.00)
Milena. 1997 1.00 (0.75-1.00)
HunerBein. 1996 1.00 (0.66-1.00)
Vikers. 1997 0.98 (0.87-1.00)
Vikers. 1998 1.00 (0.90-1.00)
Pham. 1998 0.92 (0.62-1.00)
Salminen. 1999 0.86 (0.64-0.97)
Catalano. 1999 0.90 (0.80-0.96)
Browney. 1999 1.00 (0.66-1.00)
Nishimaki. 1999 0.67 (0.30-0.93)
Heidemann. 2000 0.92 (0.78-0.98)
Nesje. 2000 0.97 (0.82-1.00)
Vazquez-Sequeiros. 2001 1.00 (0.85-1.00)
Kienle. 2002 0.98 (0.88-1.00)
Wakelin. 2002 0.92 (0.62-1.00)
Wu. 2003 1.00 (0.63-1.00)
Shimoyama. 2004 0.63 (0.35-0.85)
DeWitt. 2005 0.45 (0.17-0.77)
Pooled sensitivity = 0.91 (0.89 to 0.93)
0 0.2 0.4 0.6 0.8 1
Sensitivity
Specificity (95% CI)
Takemoto. 1986 0.90 (0.55-1.00)
Murata. 1988 0.95 (0.89-0.98)
Tio. 1989 0.93 (0.80-0.98)
Tio. 1989 0.98 (0.87-1.00)
Vilgrain. 1990 1.00 (0.29-1.00)
Tio.1990 1.00 (0.95-1.00)
Rice. 1991 0.00 (0.00-0.60)
Botet. 1991 0.97 (0.83-1.00)
Heintz. 1991 1.00 (0.69-1.00)
Ziegler. 1991 0.98 (0.89-1.00)
Fok. 1992 0.96 (0.89-0.99)
Rosch. 1992 0.96 (0.78-1.00)
Dittler. 1993 0.96 (0.89-0.99)
Hordijik. 1993 0.59 (0.33-0.82)
Grimm. 1993 0.91 (0.76-0.98)
Greenberg. 1994 1.00 (0.78-1.00)
Catalano. 1994 0.93 (0.82-0.99)
Peters. 1994 1.00 (0.82-1.00)
McLoughlin. 1995 0.89 (0.52-1.00)
Binmoeller. 1995 1.00 (0.81-1.00)
Kallimanis. 1995 0.98 (0.90-1.00)
Holden. 1996 0.83 (0.36-1.00)
Francois. 1996 0.91 (0.71-0.99)
Milena. 1997 0.93 (0.76-0.99)
HunerBein. 1996 0.90 (0.55-1.00)
Vikers. 1997 1.00 (0.69-1.00)
Vikers. 1997 0.80 (0.52-0.96)
Pham. 1998 0.94 (0.70-1.00)
Salminen. 1999 0.82 (0.48-0.98)
Catalano. 1999 0.99 (0.93-1.00)
Browney. 1999 0.99 (0.94-1.00)
Nishimaki. 1999 0.98 (0.95-0.99)
Heidemann. 2000 0.93 (0.78-0.99)
Nesje. 2000 0.88 (0.68-0.97)
Vazquez-Sequeiros. 2001 0.87 (0.60-0.98)
Kienle. 2002 0.80 (0.69-0.88)
Wakelin. 2002 0.93 (0.68-1.00)
Wu. 2003 1.00 (0.85-1.00)
Shimoyama. 2004 1.00 (0.88-1.00)
DeWitt. 2005 0.92 (0.85-0.97)
Pooled specificity = 0.94 (0.93 to 0.95)
0 0.2 0.4 0.6 0.8 1
Specificity

D


Sensitivity (95% CI)
Tio. 1989 0.86 (0.42-1.00)
Murata. 1988 1.00 (0.59-1.00)
Tio. 1989 1.00 (0.85-1.00)
Tio. 1989 1.00 (0.83-1.00)
Vilgrain. 1990 0.47 (0.21-0.73)
Tio. 1990 1.00 (0.81-1.00)
Rice. 1991 0.72 (0.47-0.90)
Botet. 1991 1.00 (0.85-1.00)
Heintz. 1991 1.00 (0.40-1.00)
Ziegler. 1991 1.00 (0.81-1.00)
Fok. 1992 0.89 (0.76-0.96)
Rosch. 1992 1.00 (0.48-1.00)
Dittler. 1993 1.00 (0.77-1.00)
Hordijik. 1993 1.00 (0.03-1.00)
Grimm. 1993 1.00 (0.48-1.00)
Greenberg. 1994 1.00 (0.16-1.00)
Catalano. 1994 1.00 (0.63-1.00)
Peters. 1994 1.00 (0.59-1.00)
McLoughlin. 1995 1.00 (0.54-1.00)
Binmoeller. 1995 0.88 (0.47-1.00)
Kallimanis. 1995 0.64 (0.35-0.87)
Holden. 1996 1.00 (0.03-1.00)
Francois. 1996 1.00 (0.54-1.00)
Milena. 1997 1.00 (0.66-1.00)
HunerBein. 1996 1.00 (0.48-1.00)
Vikers. 1997 1.00 (0.03-1.00)
Vikers. 1998 1.00 (0.03-1.00)
Pham. 1998 1.00 (0.16-1.00)
Catalano. 1999 0.78 (0.40-0.97)
Browney. 1999 1.00 (0.66-1.00)
Nishimaki. 1999 1.00 (0.29-1.00)
Heidemann. 2000 1.00 (0.78-1.00)
Nesje. 2000 1.00 (0.40-1.00)
Vazquez-Sequeiros. 2001 1.00 (0.16-1.00)
Kienle. 2002 1.00 (0.03-1.00)
Wakelin. 2002 1.00 (0.72-1.00)
Wu. 2003 1.00 (0.66-1.00)
DeWitt. 2005 1.00 (0.03-1.00)
Pooled sensitivity = 0.92 (0.89 to 0.95)
0 0.2 0.4 0.6 0.8 1
Sensitivity
Specificity (95% CI)
Tio. 1986 1.00 (0.82-1.00)
Murata. 1988 0.99 (0.96-1.00)
Tio. 1989 0.98 (0.90-1.00)
Tio. 1989 0.96 (0.85-0.99)
Vilgrain. 1990 1.00 (0.89-1.00)
Tio. 1990 0.86 (0.76-0.92)
Rice. 1991 0.00 (0.00-0.60)
Botet. 1991 1.00 (0.87-1.00)
Heintz. 1991 1.00 (0.81-1.00)
Ziegler. 1991 1.00 (0.90-1.00)
Fok. 1992 0.96 (0.89-0.99)
Rosch. 1992 0.97 (0.87-1.00)
Dittler. 1993 0.99 (0.95-1.00)
Hordijik. 1993 0.98 (0.87-1.00)
Grimm. 1993 0.98 (0.91-1.00)
Greenberg. 1994 1.00 (0.86-1.00)
Catalano. 1994 0.99 (0.94-1.00)
Peters. 1994 0.97 (0.86-1.00)
McLoughlin. 1995 0.89 (0.52-1.00)
Binmoeller. 1995 1.00 (0.88-1.00)
Kallimanis. 1995 1.00 (0.93-1.00)
Holden. 1996 1.00 (0.77-1.00)
Francois. 1996 0.96 (0.78-1.00)
Milena. 1997 0.97 (0.83-1.00)
HunerBein. 1996 1.00 (0.77-1.00)
Vikers. 1997 1.00 (0.93-1.00)
Vikers. 1998 1.00 (0.93-1.00)
Pham. 1998 0.88 (0.70-0.98)
Catalano. 1999 0.99 (0.96-1.00)
Browney. 1999 0.99 (0.94-1.00)
Nishimaki. 1999 0.97 (0.94-0.99)
Heidemann. 2000 0.98 (0.90-1.00)
Nesje. 2000 0.88 (0.75-0.95)
Vazquez-Sequeiros. 2001 1.00 (0.90-1.00)
Kienle. 2002 1.00 (0.97-1.00)
Wakelin. 2002 0.94 (0.70-1.00)
Wu. 2003 0.95 (0.77-1.00)
DeWitt. 2005 0.99 (0.95-1.00)
Pooled specificity = 0.97 (0.97 to 0.98)
0 0.2 0.4 0.6 0.8 1
Specificity

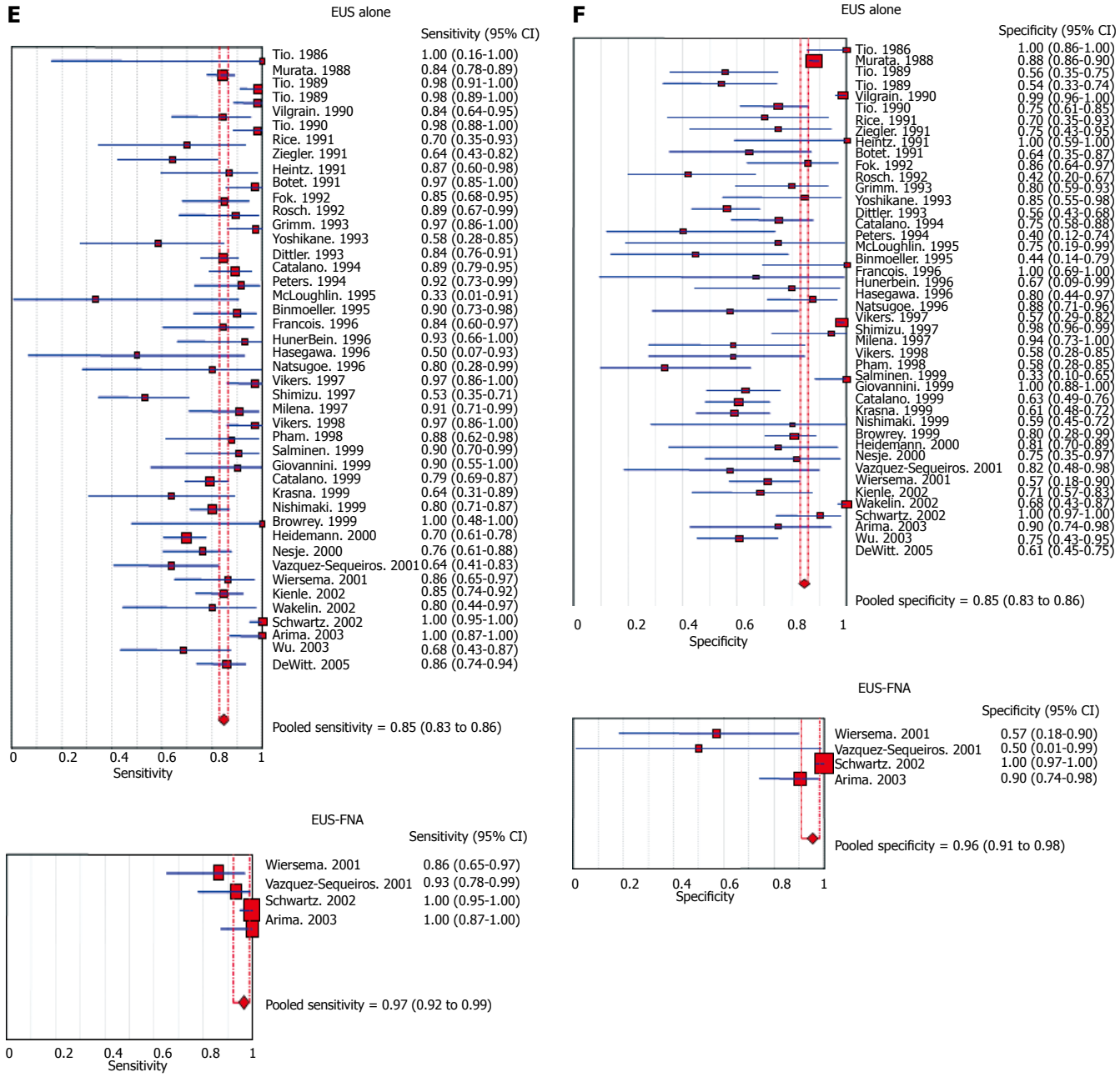


Figure 2 **A**: Forrest plot showing sensitivity and specificity of EUS to diagnose T1 stage of esophageal cancer; **B**: Forrest plot showing sensitivity and specificity of EUS to diagnose T2 stage of esophageal cancer; **C**: Forrest plot showing sensitivity and specificity of EUS to diagnose T3 stage of esophageal cancer; **D**: Forrest plot showing sensitivity and specificity of EUS to diagnose T4 stage of esophageal cancer; **E**: Forrest plot showing sensitivity of EUS alone and EUS with FNA for N staging of esophageal cancer; **F**: Forrest plot showing specificity of EUS alone and EUS with FNA for N staging of esophageal cancer.

Table 2 Accuracy of EUS with CIs to diagnose T stage in esophageal cancer

	Pooled sensitivity (%)	Pooled specificity (%)	Pooled LR+	Pooled LR-	Pooled DOR
T1	81.6	99.4	44.4	0.2	221.5
	(77.8-84.9)	(99.0-99.7)	(15.5-127.4)	(0.2-0.4)	(118.5-413.9)
T2	81.4	96.3	16.6	0.2	90.7
	(77.5-84.8)	(95.4-97.1)	(9.3-29.7)	(0.2-0.3)	(48.3-170.5)
T3	91.4	94.4	12.5	0.1	145.2
	(89.5-93.0)	(93.1-95.5)	(7.7-20.3)	(0.1-0.2)	(90.3-233.4)
T4	92.4	97.4	25.4	0.1	250.0
	(89.2-95.0)	(96.6-98.0)	(13.7-47.0)	(0.1-0.2)	(145.2-430.5)

LR+: Positive likelihood ratio; LR-: Negative likelihood ratio; DOR: Diagnostic odds ratio.

Table 3 Pooled estimate of accuracy of EUS alone and EUS-FNA in nodal staging of esophageal cancer with 95% CIs

	EUS	EUS-FNA
Studies	44	4
Pooled sensitivity (%)	84.7 (82.9-86.4)	96.7 (92.4-98.9)
Pooled specificity (%)	84.6 (83.2-85.9)	95.5 (91.0-98.2)
Positive likelihood ratio	3.3 (2.6-4.3)	7.3 (0.9-54.3)
Negative likelihood ratio	0.24 (0.9-0.3)	0.05 (0.01-0.64)
Diagnostic odds ratio	19.1 (12.7-28.5)	164.5 (4.5-6027.7)

Effect of technology

EUS studies were grouped into three periods of time

Table 4 Accuracy of EUS with CIs to stage esophageal cancer over the past two decades

	Year	No. of studies	Pooled sensitivity (%)	Pooled specificity (%)	Pooled LR+	Pooled LR-	Pooled DOR
T1	1986-1944	17	80.4 (75.2-84.8)	99.2 (98.4-99.7)	41.5 (6.1-283.3)	0.25 (0.14-0.43)	181.9 (60.7-545.7)
	1995-1999	11	83.9 (76.0-90.0)	99.4 (98.4-99.8)	36.4 (18.5-71.6)	0.21 (0.09-0.47)	299.9 (107.8-834.1)
	2000-2006	8	82.4 (72.6-89.8)	100.0 (99.1-100.0)	59.5 (22.0-161.1)	0.27 (0.16-0.47)	261.2 (81.4-838.0)
T2	1986-1994	17	85.2 (80.2-89.4)	96.8 (95.5-97.8)	18.6 (5.9-58.6)	0.19 (0.12-0.30)	123.9 (47.7-322.0)
	1995-1999	13	86.8 (79.7-92.1)	97.4 (95.8-98.5)	16.9 (9.1-31.1)	0.20 (0.11-0.38)	139.5 (56.6-343.8)
	2000-2006	8	62.9 (52.0-72.9)	93.4 (90.4-95.6)	8.3 (4.3-15.9)	0.47 (0.34-0.64)	24.7 (9.1-67.4)
T3	1986-1994	18	90.8 (88.1-93.0)	94.6 (92.6-96.2)	13.9 (5.2-36.9)	0.12 (0.07-0.19)	157.7 (70.9-351.1)
	1995-1999	14	93.7 (90.0-96.3)	96.4 (94.5-97.7)	12.6 (7.6-20.9)	0.11 (0.08-0.17)	159.4 (77.9-326.2)
	2000-2006	8	89.9 (84.5-93.9)	90.0 (86.1-93.2)	7.0 (4.6-10.8)	0.11 (0.04-0.32)	100.9 (33.5-303.9)
T4	1986-1994	18	92.1 (87.9-95.2)	96.9 (95.6-97.9)	24.7 (8.4-72.7)	0.09 (0.04-0.23)	278.8 (97.2-799.9)
	1995-1999	14	89.2 (79.8-95.2)	98.0 (96.7-98.96)	22.2 (13.2-37.3)	0.23 (0.15-0.36)	227.1 (89.7-575.0)
	2000-2006	8	100.0 (91.8-100.0)	97.5 (95.4-98.8)	20.2 (8.8-46.3)	0.11 (0.04-0.29)	272.6 (73.4-1013.2)
N	1986-1994	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)	27.6 (14.6-52.4)
	1995-1999	17	82.6 (78.0-85.9)	84.4 (81.6-86.9)	3.0 (2.1-4.5)	0.3 (0.2-0.4)	14.8 (7.5-29.3)
	2000-2005	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)

Table 5 Bias indicators and AUC with the corresponding Q values for various cancer stages

	Begg-Mazumdar bias (Kendall's tau value, *P*)	Egger bias (95% CI, *P*)	AUC (SE)	Q (SE)
T1	-0.51, *P* = 0.01	-0.48 (95% CI = -2.84 to 1.88, *P* = 0.68)	0.97 (0.02)	0.91 (0.02)
T2	-0.14, *P* = 0.24	-0.32 (95% CI = -1.74 to 1.10, *P* = 0.65)	0.95 (0.02)	0.89 (0.02)
T3	-0.11, *P* = 0.32	0.33 (95% CI = -1.43 to 2.09, *P* = 0.70)	0.97 (0.01)	0.92 (0.01)
T4	-0.07, *P* = 0.56	-2.89 (95% CI = -5.35 to -0.44, *P* = 0.02)	0.98 (0.01)	0.93 (0.01)
N	-0.26, *P* = 0.01	0.29 (95% CI = -1.58 to 1.00, *P* = 0.69)	0.91 (0.02)	0.99 (0.02)

to standardize the change in EUS technology and the change in EUS criteria for tumor staging. These periods were 1986-1994, 1995-1999 and 2000-2006. The pooled estimates of studies during these periods of time are shown in Table 4. The *P* value for χ^2 heterogeneity for all the pooled accuracy estimates was > 0.10.

Bias estimates

The publication bias calculated by the Begg-Mazumdar and Egger bias indicators for each stage of esophageal cancer invasion is shown in Table 5. The funnel plots to investigate the effect of publication bias on T stage is shown in Figure 3A. The effect of publication bias on N stage is shown in Figure 3B.

SROC curves were drawn for AUC and *Q* values. The AUC and *Q* values of EUS to diagnose various stages of esophageal cancer are shown in Table 5. SROC curves for T and N staging are shown in Figure 4A and B, respectively.

A subgroup analysis was performed by removing the studies in which the last or the first author was the same (e.g. Tio *et al*). This was done to make sure that the same data were not used by the studies, i.e. to avoid duplication. In the subgroup analysis, there was no significant change in the pooled estimates. Separate accuracy estimated for radial *versus* linear EUS technology could not be performed as the majority of the studies did not make a distinction or give separate accuracy values for radial or linear EUS technology.

DISCUSSION

This meta-analysis and systematic review shows that the pooled sensitivity of EUS for tumor invasion (T stage) is high (about 81%-90%), with it being higher for advanced disease than early disease. For all the T stages, the pooled specificity of EUS to diagnose depth of tumor invasion is very high (about 99%). Diagnostic odds ratio is defined as the odds of having a positive test in patients with a true anatomic stage of the disease when compared to patients who do not have the disease. EUS as a diagnostic test has a very high diagnostic odds ratio for T staging (about 250 times). For example, if EUS demonstrates that a patient has T1 stage disease, the odds of having the correct anatomic stage of T1 disease is 221 to 1. This helps physicians offer endoscopic treatment with confidence to patients with early disease[81-87]. Another way of looking at this is: if a small lesion is found to be esophageal cancer, then EUS is an excellent diagnostic test to examine the depth of tumor invasion, because of its very high sensitivity and specificity. The depth of tumor invasion can help decide if curative surgical or curative endoscopic mucosal resection or submucosal dissection can be offered to resect the lesion en bloc[81-87].

The positive likelihood ratio of a test is a gauge of how well it identifies a disease state. The higher the positive likelihood ratio, the better the test performs in identifying the true disease status. On the other hand, a negative likelihood ratio is a gauge of 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 T staging, EUS has a high positive likelihood ratio for all T stages and a low negative likelihood ratio for T4 disease when compared to T1 disease. This indicates that EUS performs better in excluding T4 than T1 disease. Clinically, another viewpoint is: if EUS diagnoses T2 disease then the patient might still have anatomic T1 disease, but if EUS diagnoses T1 disease then the patient probably truly has

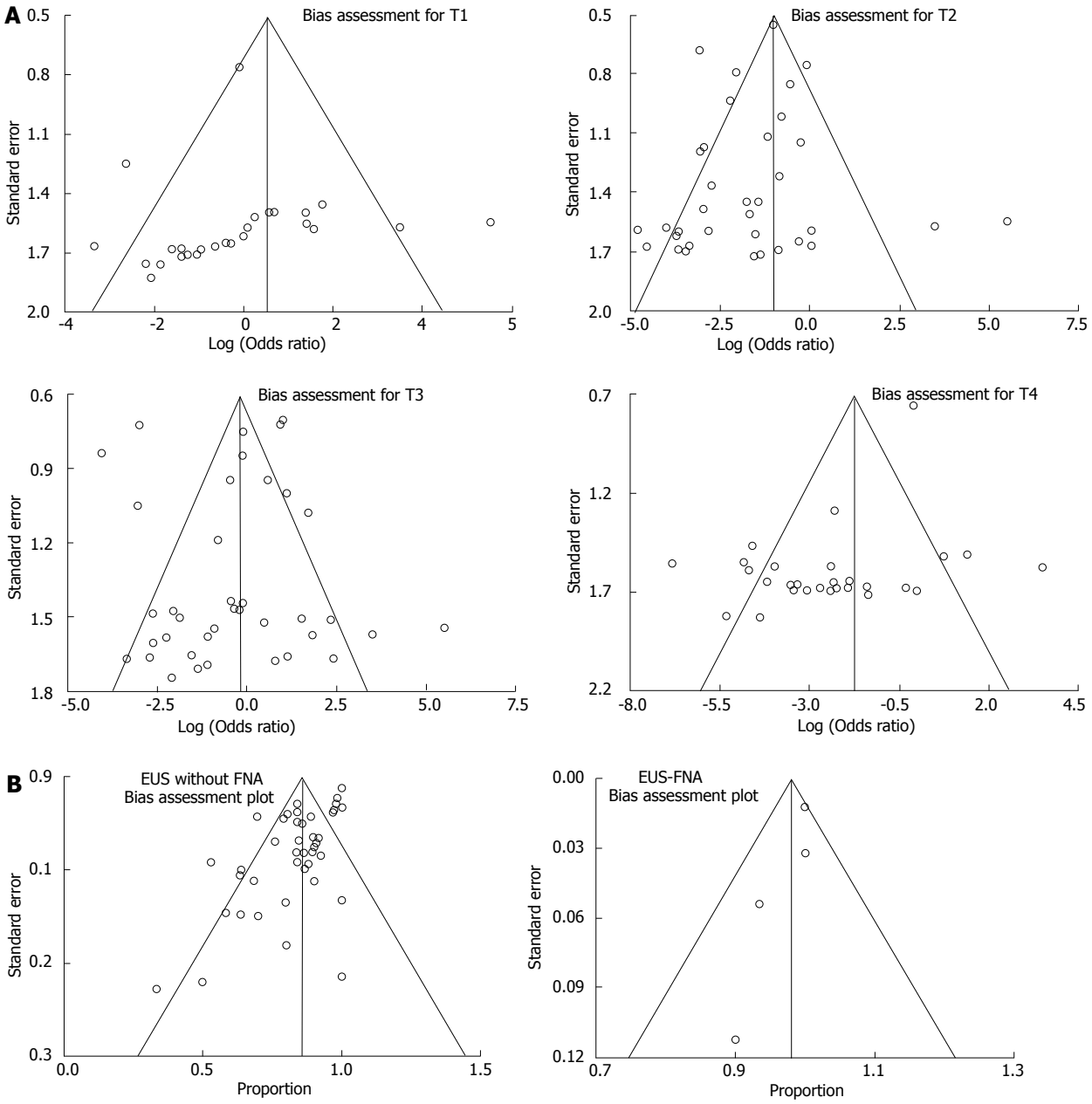


Figure 3 **A:** Funnel plots assessing bias for T staging; **B**: Funnel plots assessing bias for N staging.

anatomic T1 disease. This helps physicians offer surgical or endoscopic treatments with confidence if EUS diagnoses a patient with T1 esophageal cancer[81-87].

The major 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[88]. The complication rate is extremely low (0.5%-2.3%), with several studies reporting no com plications[75,76,88,89]. Other modalities using FNA, such as transbronchial CT or thoracoscopic procedures, cannot be used for the entire mediastinum[14,15,92-101]. EUS has the ability to image the aortopulmonary window, the subcarinal nodes, inferior mediastinum, and the entire posterior part of the mediastinum.

EUS as an imaging modality has high sensitivity and specificity to diagnose N stage esophageal cancer. This meta-analysis shows that FNA substantially improves the sensitivity (85% to 97%) and specificity (85% to 96%) of EUS in evaluating N stage esophageal cancer, therefore, EUS with FNA should be the diagnostic test of choice.

Over the last two decades, the specificity of EUS to diagnose T stage cancer has remained high. In addition, the sensitivity of EUS for T staging has improved, especially for early disease (T1), over the past two decades, which may represent improvement in imaging technology or training. For nodal staging, all the studies in which FNA was performed were from the most recent periods. The sensitivity and specificity of EUS alone to diagnose N stage cancer has not improved in the past two decades. Our meta-analysis demonstrates that the sensitivity and specificity of EUS markedly improved with FNA.

EUS as a diagnostic tool is not designed to detect distant metastasis, so this was not evaluated in this analysis.

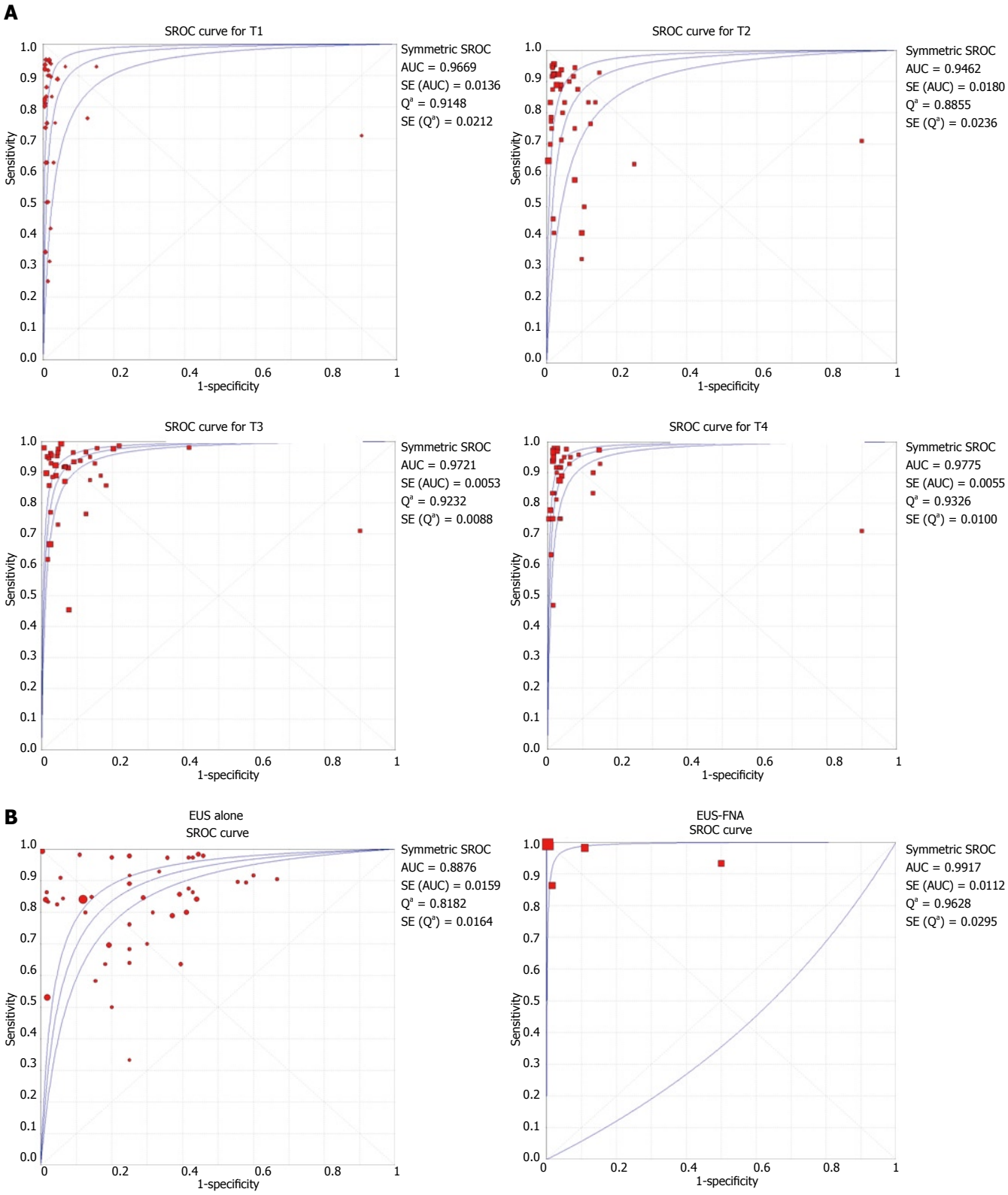


Figure 4 **A**: SROC curves for various T stages of esophageal cancer; **B**: SROC curves for various N stages of esophageal cancer.

Heterogeneity among different studies was determined by drawing SROC curves and finding the AUC, since different studies might use slightly different criteria for staging. An AUC of 1 for any test indicates that the test is excellent. SROC curves for EUS showed that AUC was very close to 1, which indicates that EUS is an excellent diagnostic test for staging esophageal cancer.

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 can be estimated by bias indicators and construction of funnel plots. This publication and selection bias may affect the summary estimates. Also, bias among studies can

affect the shape of the funnel plot. In this meta-analysis and systematic review, bias calculations using the Egger[35] and Begg-Mazumdar[36] bias indicators showed no statistically significant bias. Furthermore, funnel plot analyses showed no significant bias for EUS studies.

In conclusion, EUS has excellent sensitivity and specificity in accurately diagnosing T stage esophageal cancer. EUS performs better with advanced (T4) than early (T1) disease. FNA substantially improves the sensitivity and specificity of EUS in evaluating N stage esophageal cancers. EUS should be the test of choice for TN staging of esophageal cancer.

COMMENTS

Background

Prognosis and modality of treatment in patients with esophageal cancer depends on the staging of the tumor. The published data on the accuracy of endoscopic ultrasound (EUS) for staging esophageal cancer is varied. The aim of this meta-analysis and systematic review was to evaluate the accuracy of EUS in staging esophageal cancer.

Research frontiers

To date, there have been many studies on EUS in staging esophageal cancer, but no meta-analyses.

Innovations and breakthroughs

With EUS emerging as a very useful staging tool, its role in esophageal cancer continues to be addressed. Several studies have identified the potential benefits of EUS for esophageal cancer staging; however, results regarding the extent of its benefits have been inconsistent.

Applications

EUS has excellent sensitivity and specificity in accurately diagnosing TN stage of esophageal cancer. EUS performs better with advanced disease (T4) than early disease (T1). FNA substantially improves the sensitivity and specificity of EUS in evaluating N stage cancer. EUS should be strongly considered for staging esophageal cancer.

Terminology

EUS utilizes an echoendoscope which is passed directly into the esophagus, with the ability to visualize the individual histological layers of the esophagus. This approach is particularly useful in evaluating invasion of local disease, especially in esophageal cancer.

Peer review

This manuscript is well designed and prepared study finding an important conclusions. The most important point is that the real time PCR is significantly cheaper than the other commercial test.

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