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CLINICAL RESEARCH

How good is endoscopic ultrasound for TNM staging of gastric cancers? A meta-analysis and systematic review

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Abstract

AIM: To evaluate the accuracy of endoscopic ultrasound (EUS) for staging of gastric cancers.

METHODS: Only EUS studies confirmed by surgery were selected. Only studies from which a 2 × 2 table could be constructed for true positive, false negative, false positive and true negative values were included. Articles were searched in Medline, Pubmed, Ovid journals, Cumulative index for nursing & allied health literature, International pharmaceutical abstracts, old Medline, Medline nonindexed citations, and Cochrane control trial registry. Two reviewers independently searched and extracted data. The differences were resolved by mutual agreement. 2 × 2 tables were constructed with the data extracted from each study. Meta-analysis for 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: Initial search identified 1620 reference articles and of these, 376 relevant articles were selected and reviewed. Twenty-two studies (n = 1896) which met the inclusion criteria were included in this analysis. Pooled sensitivity of T1 was 88.1% (95% CI: 84.5-91.1) and T2 was 82.3% (95% CI: 78.2-86.0). For T3, pooled sensitivity was 89.7% (95% CI: 87.1-92.0). T4 had a pooled sensitivity of 99.2% (95% CI: 97.1-99.9). For nodal staging, the pooled sensitivity for N1 was 58.2% (95% CI: 53.5-62.8) and N2 was 64.9% (95% CI: 60.8-68.8). Pooled sensitivity to diagnose distant metastasis was 73.2% (95% CI: 63.2-81.7). The *P* for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10.

CONCLUSION: EUS results are more accurate with advanced disease than early disease. If EUS diagnoses advanced disease, such as T4 disease, the patient is 500 times more likely to have true anatomic stage of T4 disease.

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Key words: Gastric cancer; Staging; Meta-analysis; Endoscopic ultrasound

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide. Despite the decreasing incidence and mortality, gastric cancer remains the world's second leading cause of cancer-related deaths in the world[1]. A treatment option for patients with gastric cancer depends on an accurate evaluation of the stage of the cancer. The prognosis of patients with gastric cancer is determined by the tumor extent and includes both nodal involvement and direct tumor extension beyond the gastric wall[2,3].

Accurate staging of gastric cancers is essential for well-informed decisions on patient management. Accurate gastric cancer staging needs to address two critical questions: which patients qualify for curative therapy and which patients qualify for palliative therapy? This is becoming increasingly important with improvements in non-surgical treatment regimens. Surgery is the

main stay of curative therapy for gastric cancers. While patients with early localized disease clearly benefit from complete surgical resection, increasing evidence exists that multimodal treatment including chemoradiotherapy is superior to surgery alone for patients with resectable gastric cancer[4]. Accurate local cancer staging provides the information necessary for such important decisions to be made while not denying patients potentially curative surgical resection, with or without neoadjuvant therapy. The development of other non-surgical techniques at both ends of the disease spectrum has also reinforced the need for accurate cancer staging. Endoscopic ultrasound (EUS) in conjunction with endoscopic mucosal resection has become an appropriate alternative to surgery for superficial non-invasive cancers[5].

The 5-year survival of patients with gastric cancer ranges from 5% to 95% depending on the tumor stage[6]. Early gastric cancer or superficial spreading carcinoma is defined as adenocarcinoma limited to the gastric mucosa or submucosa. Patients with early gastric cancer have a favorable prognosis[7] and the survival is > 90% after surgical resection[8-11]. Therefore, a diagnostic tool that helps diagnose the depth of tumor invasion in the gastric mucosa is essential. In those patients considered unfit for curative surgery, accurate staging is essential to allow an informed decision to be made regarding the most appropriate method of palliation. If comparisons of the outcomes of available and future treatment protocols are to be made, comparable input data-specific to the stage of disease should be available from all patients. This is particularly important if the patient does not undergo primary surgical resection, due to the consequent loss of pathological confirmation, as then the stage of the cancer can only be assessed from the best imaging modality or modalities.

Imaging studies like computerized topographic scan have the advantage of being widely available and noninvasive, but is not very accurate for assessing the depth of invasion or the presence of lymph node involvement[12,13]. EUS has emerged as one of the tests for preoperative staging of upper gastrointestinal cancers. The advantage of EUS is the ability to differentiate the layers of gastric mucosa. The accuracy of EUS in staging gastric cancers has been varied, with reports that EUS understages the depth of invasion and overstages the nodal invasion because of inflammation around the tumor or in the lymph nodes[14]. The goal of this meta-analysis and systematic review is to evaluate the accuracy of EUS in staging gastric cancers. Due to multiple studies published that looked at EUS in staging gastric cancers and no published meta-analysis in this area, this meta-analysis was performed in an attempt to answer this very important clinical question.

The EUS criteria for depth of tumor invasion and nodal metastasis have changed over the past two decades. Also, the technology of EUS has changed over this period of time. It is not clear if this change in EUS criteria and technology has had an impact on gastric cancer staging. In this meta-analysis and systematic review, we pooled the available studies to evaluate if changing EUS criteria or technology affects the accuracy of EUS to stage gastric cancers[15].

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[16]. 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[17].

MATERIALS AND METHODS

Study selection criteria

Only EUS studies confirmed by surgery were selected. EUS criteria used for T staging were: T1- the tumor invades the lamina propria or submucosa but does not invade the muscularis propria, T2- the tumor invades but does not extend beyond the muscularis propria, T3- tumor penetrates serosa (i.e. visceral peritoneum) without invasion of adjacent structures, and T4- the tumor invades adjacent structures. The criteria used for nodal metastasis were: larger than 1 cm or hypoechoic or round instead of elliptical. Distal metastasis was defined as metastasis to peritoneum or liver. 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 nonindexed citations, OVID Healthstar, and Cochrane Control Trial Registry. The search terms used were endoscopic ultrasound, EUS, ultrasound, gastric cancer, 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 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)[18,19]. There is no consensus on assessing studies without a control arm and also, these criteria do no apply to studies without control arm[19]. Therefore, for this meta-analysis and systematic review, studies were selected based on completeness of data and studies that met the inclusion criteria.

Statistical analysis

Meta-analysis for the accuracy of EUS in staging gastric cancers was performed by calculating pooled estimates

Table 1 Characteristics of studies included in this meta-analysis for calculating diagnostic accuracy of EUS for gastric cancer staging

No.	Author	Year of publication	No. of patients	Type of study	Confirmatory procedure
1	Grimm *et al*[28]	1993	147	Prospective	Surgery
2	Francois *et al*[29]	1996	29	Consecutive	Surgery
3	Schimizu *et al*[30]	1994	125	Consecutive	Surgery
4	Dittler *et al*[31]	1993	254	Consecutive	Surgery
5	Ziegler *et al*[32]	1993	118	Prospective	Surgery
6	Botet *et al*[33]	1991	50	Prospective	Surgery
7	Xi *et al*[34]	2003	35	Prospective	Surgery
8	Caletti *et al*[35]	1991	42	Prospective	Surgery
9	Akahoshi *et al*[36]	1989	74	Prospective	Surgery
10	Tio *et al*[37]	1989	72	Prospective	Surgery
11	Massari *et al*[38]	1996	99	Prospective	Surgery
12	Saito *et al*[39]	1991	110	Prospective	Surgery
13	Murata *et al*[40]	1988	146	Prospective	Surgery
14	Hunerbein *et al*[41]	1996	19	Consecutive	Surgery
15	Perng *et al*[42]	1996	69	Consecutive	Surgery
16	Tio *et al*[43]	1989	75	Prospective	Surgery
17	Tio *et al*[44]	1986	36	Prospective	Surgery
18	Shimoyama *et al*[45]	2004	45	Consecutive	Surgery
19	Willis *et al*[46]	2000	116	Consecutive	Surgery
20	Rosch *et al*[47]	1992	41	Consecutive	Surgery
21	Javaid *et al*[48]	2003	112	Consecutive	Surgery
22	Potrc *et al*	2006	82	Prospective	Surgery

of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio. EUS studies were grouped into periods of time to standardize the change in EUS technology and also to standardize the change in EUS criteria for lymph node involvement. These periods of time were 1986 to 1994, 1995 to 1999, and 2000 to 2006. Pooling was conducted by both Mantel-Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model). The confidence intervals were calculated using the F distribution method[20]. For 0 value cells, a 0.5 was added as described by Cox[21]. The point estimates in the Forrest plots are proportional to the weight or size of the individual study. The heterogeneity of the sensitivities and specificities were tested by applying the likelihood ratio test[22]. The heterogeneity of likelihood ratios and diagnostic odds ratios were tested using Cochran's Q test based upon inverse variance weights[23]. Heterogeneity among studies was also tested by using summary receiver operating characteristic (SROC) curves. SROC curves were used to calculate area under the curve (AUC). The effect of publication and selection bias on the summary estimates was tested by Eager bias indicator[24] and Begg-Mazumdar indicator[25]. Also, funnel plots were drawn using the standard error and diagnostic odds ratio to look at bias[26,27].

RESULTS

Initial search using the search terms identified 1620 reference articles. Among these, 376 relevant articles were selected and reviewed by two authors independently. Twenty-two studies (n = 1896) which met the inclusion criteria were included in this analysis and data was extracted from these studies[28-49]. All the selected 22 studies were published as full-text articles in peer review journals. Figure 1 shows the search results and Table 1 shows the details of the included studies. The pooled estimates given here are estimates calculated by the fixed effect model.

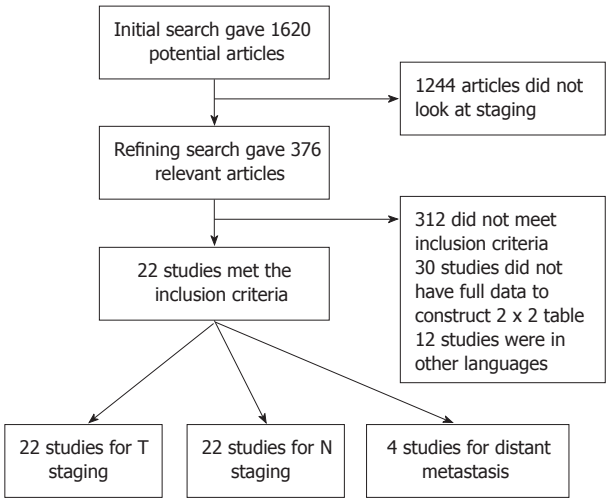


Figure 1 Flow sheet shows search results.

T stage

Pooled sensitivity and specificity of T1 was 88.1% (95% CI: 84.5-91.1) and 100.0% (95% CI: 99.7-100.0) respectively. Figure 2A shows the Forrest plot of sensitivity and specificity of various EUS studies in staging T1 gastric cancers. For T2, the sensitivity was 82.3% (95% CI: 78.2-86.0) and specificity was 95.6% (95% CI: 94.4-96.6). Forest plot in Figure 2B depicts the sensitivity and specificity of EUS in staging T2 cancers. Pooled sensitivity for T3 was 89.7% (95% CI: 87.1-92.0) and specificity was 94.7% (95% CI: 93.3-95.9). Figure 2C depicts sensitivity and specificity of EUS to stage T3 cancers. T4 had a pooled sensitivity of 99.2% (95% CI: 97.1-99.9) and specificity of 96.7% (95% CI: 95.7-97.6). The sensitivity and specificity of EUS to stage T4 in various studies is Figure 2D as a Forrest plot. Pooled likelihood ratios and diagnostic odds ratios for various T stages are shown in Table 2. The pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio computed by random effect model were similar to the fixed effect model. The P for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10.

N stage

The pooled sensitivity and specificity for N1 was 58.2% (95% CI: 53.5-62.8) and 87.2% (95% CI: 84.4-89.7) respectively. N2 had a pooled sensitivity of 64.9% (95% CI: 60.8-68.8) and specificity of 92.4% (95% CI: 89.9-94.4). Pooled likelihood ratios and diagnostic odds ratios for various N stages are shown in Table 2. All the pooled estimates calculated by random effect model were similar to fixed effect model. The chi-squared heterogeneity for all the pooled accuracy estimates showed a $P > 0.10$.

Table 2 Accuracy of EUS with confidence intervals to diagnose T and N stages in gastric cancer patients

	Pooled sensitivity	Pooled specificity	Pooled LR+	Pooled LR-	Pooled DOR
T1	88.1% (84.5-91.1)	100.0% (99.7-100.0)	90.1 (48.9-165.7)	0.17 (0.10-0.28)	605.6 (296.8-1235.6)
T2	82.3% (78.2-86.0)	95.6% (94.4-96.6)	17.3 (10.9-27.5)	0.23 (0.17-0.290	108.6 (56.6-208.1)
T3	89.7% (87.1-92.0)	94.7% (93.3-95.9)	14.3 (10.3-19.8)	0.13 (0.08-0.19)	144.4 (95.4-218.7)
T4	99.2% (97.1-99.9)	96.7% (95.7-97.6)	19.6 (14.1-27.2)	0.07 (0.04-0.12)	507.8 (247.5-1042.1)
N1	58.2% (53.5-62.8)	87.2% (84.4-89.7)	4.1 (2.4-7.1)	0.49 (0.41-0.58)	9.5 (5.3-16.9)
N2	64.9% (60.8-68.8)	92.4% (89.9-94.4)	6.7 (4.1-10.9)	0.39 (0.31-0.49)	26.6 (13.9-50.7)

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

Table 3 Accuracy of EUS with confidence intervals to stage gastric cancers over the past two decades

		No. of studies	Pooled sensitivity	Pooled specificity	Pooled LR+	Pooled LR-	Pooled DOR
T1	1986 to 1994	12	56.3 % (49.7-62.6)	89.1% (85.5-92.1)	4.6 (1.6-13.8)	0.51 (0.38-0.69)	9.3 (2.9-30.1)
	1995 to 1999	4	82.2 % (67.9-92.0)	100.0 % (97.9-100.0)	72.9 (18.2-288.8)	0.13 (0.03-0.68)	562.5 (92.0-3438.4)
	2000 to 1006	5	84.8% (71.1-93.7)	100.0% (98.9-100.0)	88.9 (25.3-312.4)	0.22 (0.13-0.38)	428.9 (96.6-1904.9)
T2	1986 to 1994	12	84.9% (79.8-89.2)	96.7% (95.4-97.8)	20.5 (14.8-28.4)	0.19 (0.13-0.30)	207.0 (109.5-391.6)
	1995 to 1999	4	74.4% (57.9-87.0)	90.9% (85.4-94.8)	6.7 (2.5-18.1)	0.33 (0.19-0.55)	23.7 (5.3-106.2)
	2000 to 1006	5	79.5% (70.8-86.5)	94.6 % (91.3-96.9)	16.8 (5.3-53.8)	0.22 (0.12-0.38)	79.6 (22.9-277.2)
T3	1986 to 1994	12	89.6% (86.3-92.3)	95.3% (93.6-96.7)	15.5 (11.4-21.1)	0.12 (0.07-0.22)	160.2 (95.5-268.7)
	1995 to 1999	4	90.3% (80.1-96.4)	91.3% (85.8-95.2)	11.1 (3.5-35.4)	0.12 (0.06-0.25)	93.3 (30.6-284.6)
	2000 to 1006	5	89.8% (83.3-94.5)	94.8% (91.3-97.2)	13.9 (7.7-25.1)	0.12 (0.04-0.37)	154.7 (55.7-429.5)
T4	1986 to 1994	12	98.9% (95.9-99.9)	97.1% (95.9-98.0)	23.3 (14.6-37.4)	0.07 (0.04-0.14)	626.4 (256.1-1532.5)
	1995 to 1999	4	100% (92.5-100.0)	95.8% (91.5-98.3)	14.3 (7.6-26.9)	0.05 (0.01-0.18)	441.7 (85.6-2279.1)
	2000 to 1006	3	100.0% (87.2-100.0)	95.7% (91.9-98.0)	16.4 (7.9-33.9)	0.07 (0.02-0.33)	260.1 (43.7-1547.4)
N1	1986 to 1994	10	56.3% (49-62.6)	89.1% (85.5-92.1)	4.6 (1.6-13.6)	0.5 (0.4-0.7)	9.3 (2.9-30.1)
	1995 to 1999	4	64.6% (53.3-74.9)	83.5% (74.9-90.1)	3.6 (2.3-5.6)	0.5 (0.4-0.6)	8.8 (4.3-18.1)
	2000 to 2006	5	57.8% (49.0-66.20)	85.5% (79.3-90.4)	4.4 (2.9-6.6)	0.5 (0.3-0.7)	10.2 (4.8-21.8)
N2	1986 to 1994	10	70.6% (65.4-75.5)	94.7% (91.7-96.8)	11.0 (4.6-26.6)	0.3 (0.2-0.4)	63.9 (30.9-132.3)
	1995 to 1999	4	70.2% (59.9-79.2)	83.2% (74.1-90.1)	3.9 (2.5-6.1)	0.4 (0.3-0.5)	11.7 (5.6-24.1)
	2000 to 2006	4	49.0% (40.7-57.30)	93.0% (87.5-96.6)	6.4 (1.7-24.1)	0.6 (0.4-0.7)	12.7 (2.9-56.2)

M stage

Data for EUS accuracy to diagnose distant metastasis was available in four studies[29,35,36,41]. The pooled sensitivity to diagnose distal metastasis was 73.2% (95% CI: 63.2-81.7). EUS specificity was 88.6% (84.8-91.7). The positive likelihood ratio to diagnose distal metastasis was 17.2 (2.8-106.3) and the negative likelihood ration was 0.4 (95% CI: 0.2-0.7). The diagnostic odds ratio of EUS to correctly diagnose distal metastasis was 60.9 (95% CI: 8.2-463.7). All the pooled estimates calculated by random effect model were similar. The *P* for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10. The SROC curve showed an AUC of 0.98 with a standard error (SE) of 0.005. This curve showed a *Q* value of 0.94 with a SE of 0.01, as shown in Figure 3.

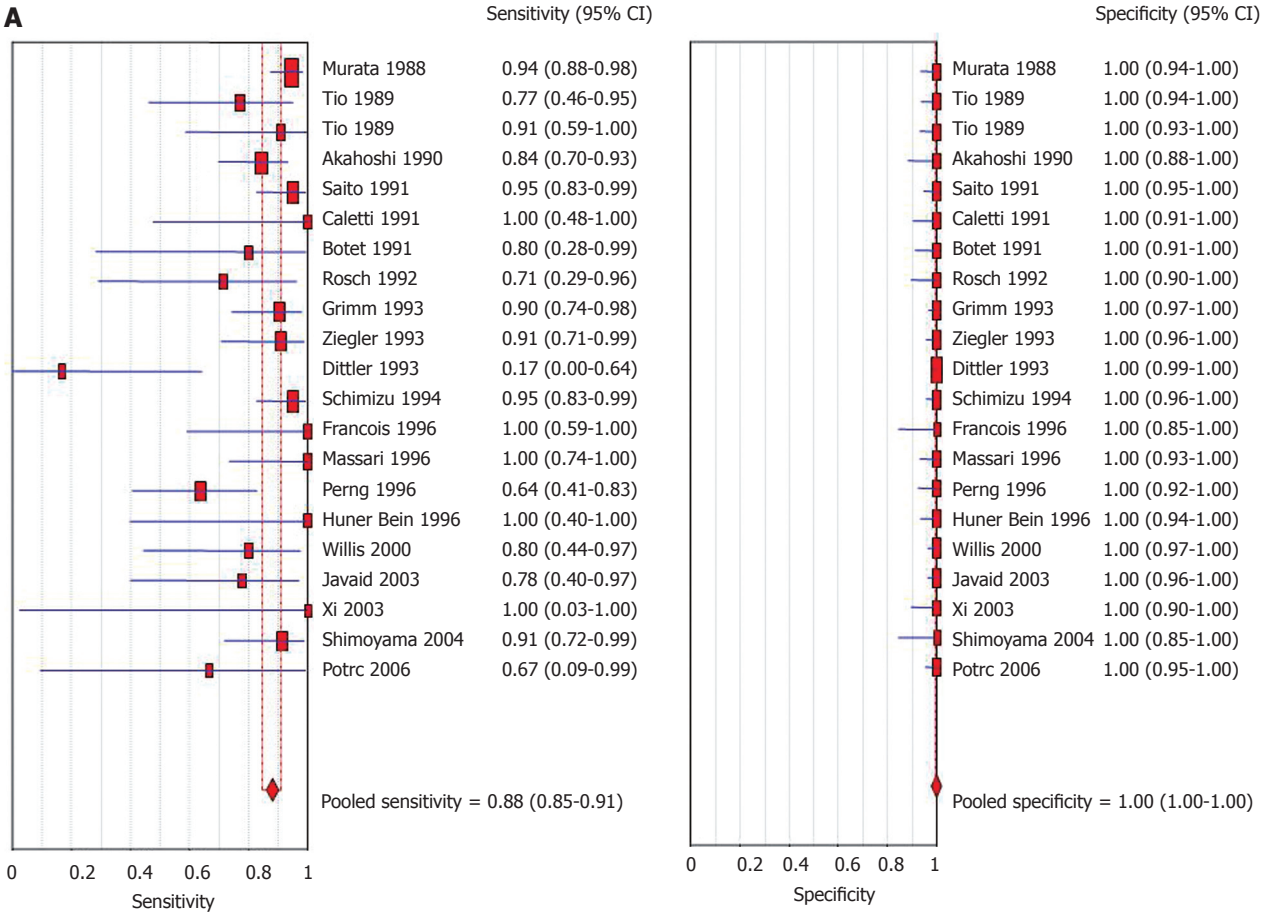
Affect of technology

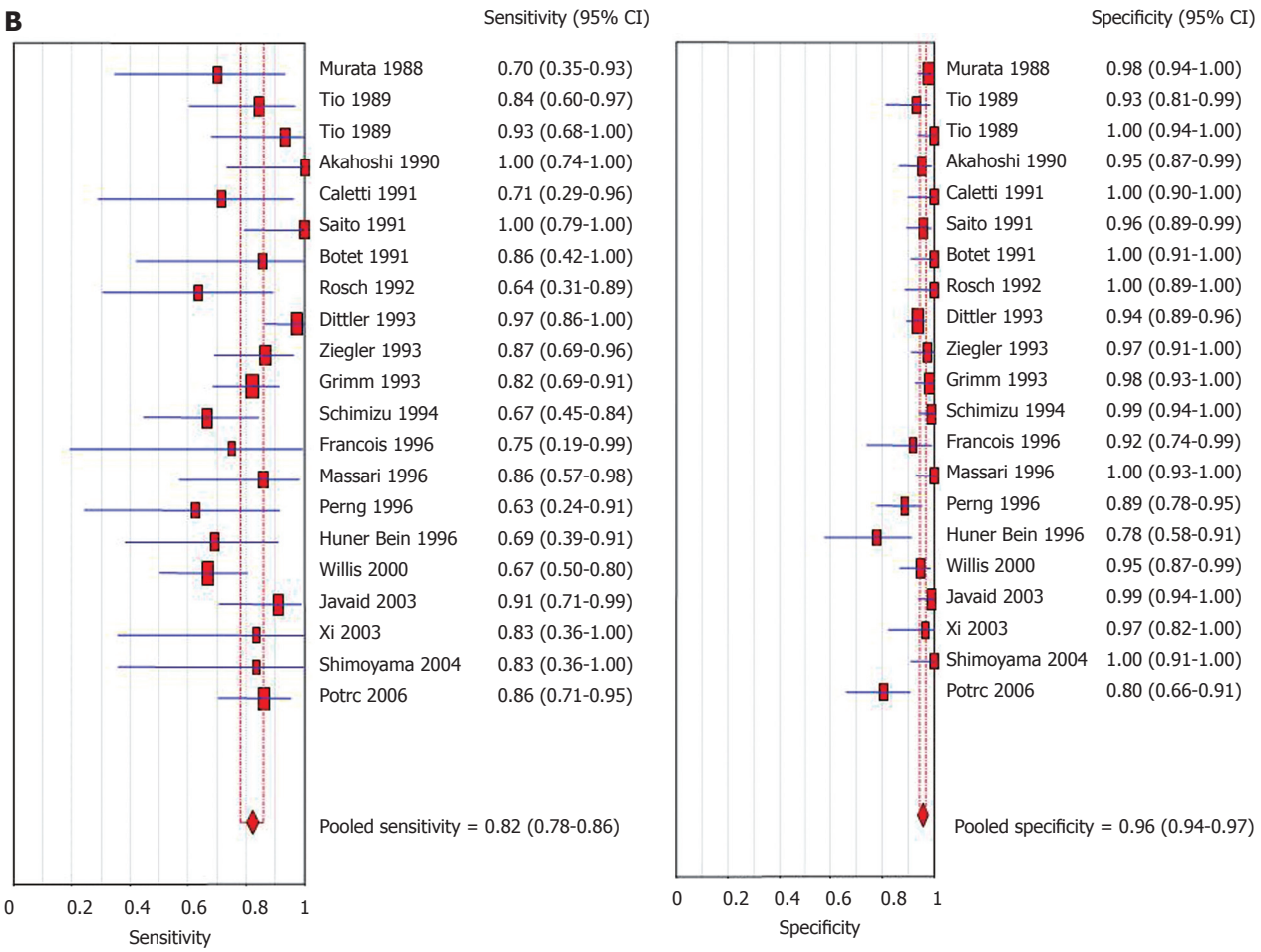
EUS studies were grouped into three periods of time to standardize the change in EUS technology and also to standardize the change in EUS criteria for tumor staging. These periods of time were 1986 to 1994, 1995 to 1999, and 2000 to 2006. The pooled estimates of studies during these periods of time are shown in Table 3. The *P* for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10. The bias calculations using Egger bias indicator gave a value of 0.97 (95% CI = -0.77 to 2.71, *P* = 0.26). The bias calculated by Begg-Mazumdar indicator gave a Kendall's tau value of 0.19, *P* = 0.24. The funnel plot for bias is shown in Figure 4.

DISCUSSION

Correct staging of patients with gastric cancer helps to direct precise therapy and predict prognosis[7-9]. Majority of patients in all the included studies had adenocarcinomas. Patient with other types of gastric cancers couldn't be excluded from the analysis. Gastric cancer staging aids in determining non-operative versus operative management, pre-operative adjuvant chemoradiation, and local excision or endoscopic therapy versus wide resection[50]. Imaging modalities such as trans-abdominal B-mode ultrasonography, computed tomography, or magnetic resonance imaging lack the ability to differentiate layers of the gastric mucosa[51,52].

The studies included in this analysis used established criteria for gastric cancer staging[53]. The definition for T staging given in the methodology was used in the included studies. This meta-analysis and systematic review shows that the pooled sensitivity of EUS for tumor invasion (T stage) is high and it is higher for advanced disease when compared to early disease. The pooled specificity for depth of tumor invasion is very high for all the T stages. Diagnostic odds ratio is defined as the odds of having a positive test in patients with


A
Sensitivity (95% CI)
Specificity (95% CI)
Murata 1988 0.94 (0.88-0.98) 1.00 (0.94-1.00)
Tio 1989 0.77 (0.46-0.95) 1.00 (0.94-1.00)
Tio 1989 0.91 (0.59-1.00) 1.00 (0.93-1.00)
Akahoshi 1990 0.84 (0.70-0.93) 1.00 (0.88-1.00)
Saito 1991 0.95 (0.83-0.99) 1.00 (0.95-1.00)
Caletti 1991 1.00 (0.48-1.00) 1.00 (0.91-1.00)
Botet 1991 0.80 (0.28-0.99) 1.00 (0.91-1.00)
Rosch 1992 0.71 (0.29-0.96) 1.00 (0.90-1.00)
Grimm 1993 0.90 (0.74-0.98) 1.00 (0.97-1.00)
Ziegler 1993 0.91 (0.71-0.99) 1.00 (0.96-1.00)
Dittler 1993 0.17 (0.00-0.64) 1.00 (0.99-1.00)
Schimizu 1994 0.95 (0.83-0.99) 1.00 (0.96-1.00)
Francois 1996 1.00 (0.59-1.00) 1.00 (0.85-1.00)
Massari 1996 1.00 (0.74-1.00) 1.00 (0.93-1.00)
Perng 1996 0.64 (0.41-0.83) 1.00 (0.92-1.00)
Huner Bein 1996 1.00 (0.40-1.00) 1.00 (0.94-1.00)
Willis 2000 0.80 (0.44-0.97) 1.00 (0.97-1.00)
Javaid 2003 0.78 (0.40-0.97) 1.00 (0.96-1.00)
Xi 2003 1.00 (0.03-1.00) 1.00 (0.90-1.00)
Shimoyama 2004 0.91 (0.72-0.99) 1.00 (0.85-1.00)
Potrc 2006 0.67 (0.09-0.99) 1.00 (0.95-1.00)
Pooled sensitivity = 0.88 (0.85-0.91)
Pooled specificity = 1.00 (1.00-1.00)
0 0.2 0.4 0.6 0.8 1
Sensitivity
Specificity


B
Sensitivity (95% CI)
Specificity (95% CI)
Murata 1988 0.70 (0.35-0.93) 0.98 (0.94-1.00)
Tio 1989 0.84 (0.60-0.97) 0.93 (0.81-0.99)
Tio 1989 0.93 (0.68-1.00) 1.00 (0.94-1.00)
Akahoshi 1990 1.00 (0.74-1.00) 0.95 (0.87-0.99)
Caletti 1991 0.71 (0.29-0.96) 1.00 (0.90-1.00)
Saito 1991 1.00 (0.79-1.00) 0.96 (0.89-0.99)
Botet 1991 0.86 (0.42-1.00) 1.00 (0.91-1.00)
Rosch 1992 0.64 (0.31-0.89) 1.00 (0.89-1.00)
Dittler 1993 0.97 (0.86-1.00) 0.94 (0.89-0.96)
Ziegler 1993 0.87 (0.69-0.96) 0.97 (0.91-1.00)
Grimm 1993 0.82 (0.69-0.91) 0.98 (0.93-1.00)
Schimizu 1994 0.67 (0.45-0.84) 0.99 (0.94-1.00)
Francois 1996 0.75 (0.19-0.99) 0.92 (0.74-0.99)
Massari 1996 0.86 (0.57-0.98) 1.00 (0.93-1.00)
Perng 1996 0.63 (0.24-0.91) 0.89 (0.78-0.95)
Huner Bein 1996 0.69 (0.39-0.91) 0.78 (0.58-0.91)
Willis 2000 0.67 (0.50-0.80) 0.95 (0.87-0.99)
Javaid 2003 0.91 (0.71-0.99) 0.99 (0.94-1.00)
Xi 2003 0.83 (0.36-1.00) 0.97 (0.82-1.00)
Shimoyama 2004 0.83 (0.36-1.00) 1.00 (0.91-1.00)
Potrc 2006 0.86 (0.71-0.95) 0.80 (0.66-0.91)
Pooled sensitivity = 0.82 (0.78-0.86)
Pooled specificity = 0.96 (0.94-0.97)
0 0.2 0.4 0.6 0.8 1
Sensitivity
Specificity

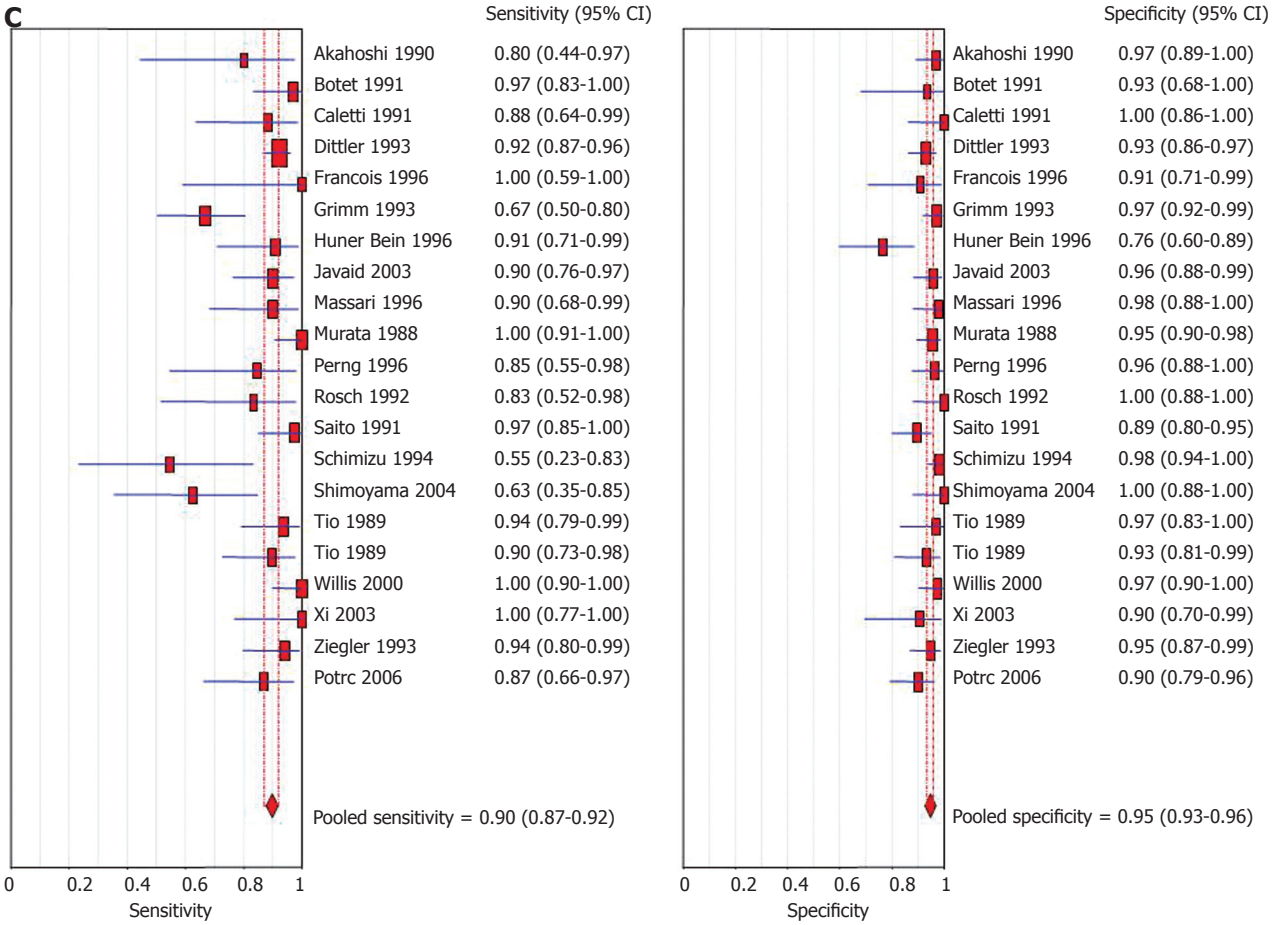


Figure 2 Forrest plot showing sensitivity and specificity of EUS in diagnosing T stage of gastric cancers. **A**: T1 Stage; **B**: T2 Stage; **C**: T3 Stage; **D**: T4 Stage.

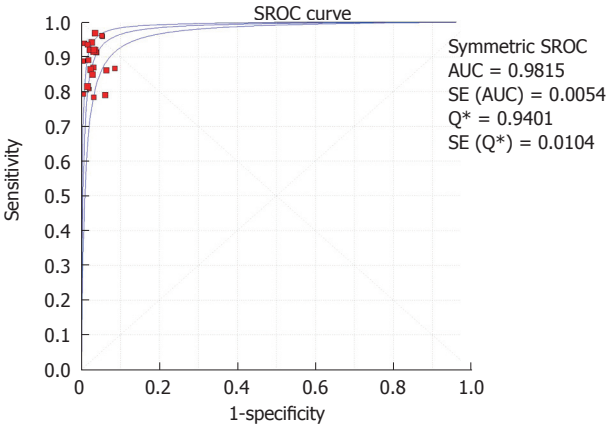


Figure 3 Summary receiver operator curve showing AUC.

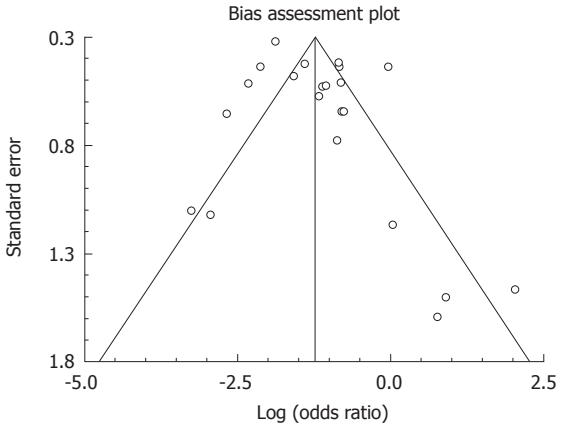


Figure 4 Funnel plot showing bias assessment.

true anatomic stage of the disease when compared to patients who don't have the disease. EUS has a very high diagnostic odds ratio for T staging. For example, if EUS demonstrates a patient has T1 disease, the patient has odds of 605 times to have the correct anatomic stage of T1 disease. This helps physicians offer curative therapy either surgical or endoscopic with confidence to patients with early disease[10]. Another perspective is: if a small lesion is found with the tissue diagnosis of gastric cancer, EUS would be an excellent test to examine the depth of tumor invasion due to a very high sensitivity and specificity.

The negative likelihood ratio of a test is a measure of how well the test performs in excluding a disease state. Lower the negative likelihood ratio, the better the test performs in excluding a disease. The positive likelihood ratio is a measure of how well the same test identifies a disease state. For T staging, EUS has a low negative likelihood ratio for T4 disease when compared to T1 disease and a high positive likelihood ratio for all T stages. This indicates that EUS performs better in excluding T4 disease than T1 disease. Another perspective of looking at it 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 anatomic T1 disease and can have curative therapy. This helps physicians offer endoscopic treatments such as EMR or ESD with confidence for T1 gastric cancer as alternatives to curative surgery[54-58].

According to our meta-analysis, EUS is more accurate to diagnose advanced than early gastric cancer. If EUS diagnoses advanced disease, such as T4 disease, the patient is 500 times more likely to have true anatomic T4 stage of disease and will benefit from palliative therapy. This helps physicians to offer with confidence surgical and non-surgical palliative therapies such as placement of self-expanding metal stents for obstruction[59]. For nodal staging of gastric cancers, all the pooled accuracy estimates of EUS are higher for N2 (advanced disease) when compared to N1. The accuracy of EUS in diagnosing N stage is not high. Also, it is not clear if using all the three criteria together or in combination for nodal involvement improves the diagnostic accuracy. The role of FNA in nodal staging of gastric cancers could not be evaluated because of lack of substantial number of studies with the data. Obtaining tissue, however, is expected to improve accuracy of EUS/FNA but more studies are needed before this is concluded.

Over the last two decades, the sensitivity of EUS for T staging improved, especially for early disease (T1). Thus EUS is vital in answering the question which patients qualify for curative therapy. EUS, however, as an imaging modality did not improve for N staging. The specificity for both T and N staging remained high during the past two decades. For distant metastasis, though the number of studies with data was smaller, the pooled specificity is high but the sensitivity is not as high. EUS as a diagnostic tool is not designed to look at distant metastasis.

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 the value for AUC was very close to 1, indicating that EUS is an excellent diagnostic test for staging gastric cancers.

Publication bias and selection bias can affect the summary estimates. Studies with statistically significant results tend to be published and cited. Smaller studies can show larger treatment effects due to fewer case-mix differences (e.g. patient with only early or late disease) than larger trials. This bias can be estimated by bias indicators and by drawing funnel plots. Bias among studies can affect the shape of the funnel plot. In this meta-analysis and systematic review, bias calculations using Eager bias indicator[24] and Begg-Mazumdar indicator[25] showed no statistically significant bias. Funnel plot also showed no significant bias.

In conclusion, EUS is an accurate and minimally invasive diagnostic tool to evaluate T stage of a patient with gastric cancer. EUS results are more accurate with advanced disease than early disease. If EUS diagnoses advanced disease, such as T4 disease, the patient is 500 times more likely to have true anatomic T4 stage of disease. Considering that new curative and palliative endoscopic therapies are emerging as an alternative

to surgery in gastric cancer, EUS should be strongly considered for staging. Our meta-analysis supports the use of EUS in determining if curative or palliative therapies are the most appropriate approach for a particular stage of the disease. Further studies are needed to improve accuracy of EUS in detecting early nodal invasion.

COMMENTS

Background

Gastric cancer is one of the most common cancers worldwide. The prognosis of patients with gastric cancer is determined by the tumor extent and includes both nodal involvement and direct tumor extension beyond the gastric wall. Endoscopic ultrasound (EUS) has emerged as one of the tests for preoperative staging of upper gastrointestinal cancers. The goal of this meta-analysis and systematic review by Puli *et al* was to evaluate the accuracy of EUS in staging gastric cancers.

Research frontiers

The accuracy of EUS in staging gastric cancers has been varied, with reports that EUS understages the depth of invasion and overstages the nodal invasion because of inflammation around the tumor or in the lymph nodes.

Innovations and breakthroughs

Due to multiple studies published that looked at EUS in staging gastric cancers but no published meta-analysis in this area, this meta-analysis was performed in an attempt to answer this very important clinical question of how good EUS is in TNM staging of gastric cancers.

Applications

EUS is an accurate and minimally invasive diagnostic tool to evaluate the T stage of a patient with gastric cancer. EUS results are more accurate with advanced disease than early disease. If EUS diagnoses advanced disease, such as T4 disease, the patient is 500 times more likely to have true anatomic T4 stage of disease. Considering that new curative and palliative endoscopic therapies are emerging as an alternative to surgery in gastric cancer, EUS should be strongly considered for staging. Our meta-analysis supports the use of EUS in determining if curative or palliative therapies are the most appropriate approach for a particular stage of the disease. Further studies are needed to improve accuracy of EUS in detecting early nodal invasion.

Terminology

Meta-analysis for the accuracy of EUS in staging gastric cancers was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio. Pooled was conducted by both Mantel-Haenszel method (fixed effects model) and DerSimonian Laird method (random effects model).

Peer review

This is an interesting study; also it is a comprehensive review article, comparing the results of some authors' studies. The effectiveness of endoscopic ultrasound use for TNM staging of gastric cancers was discussed.

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