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Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer (Review)

Mocellin S, Pasquali S

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[Diagnostic Test Accuracy Review]

Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer

Simone Mocellin[1], Sandro Pasquali[1]

[1]Meta-Analysis Unit, Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy

Contact address: Simone Mocellin, Meta-Analysis Unit, Department of Surgery, Oncology and Gastroenterology, University of Padova, Via Giustiniani 2, Padova, Veneto, 35128, Italy. simone.mocellin@unipd.it, mocellins@hotmail.com.

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ABSTRACT

Background

Endoscopic ultrasound (EUS) is proposed as an accurate diagnostic device for the locoregional staging of gastric cancer, which is crucial to developing a correct therapeutic strategy and ultimately to providing patients with the best chance of cure. However, despite a number of studies addressing this issue, there is no consensus on the role of EUS in routine clinical practice.

Objectives

To provide both a comprehensive overview and a quantitative analysis of the published data regarding the ability of EUS to preoperatively define the locoregional disease spread (i.e., primary tumor depth (T-stage) and regional lymph node status (N-stage)) in people with primary gastric carcinoma.

Search methods

We performed a systematic search to identify articles that examined the diagnostic accuracy of EUS (the index test) in the evaluation of primary gastric cancer depth of invasion (T-stage, according to the AJCC/UICC TNM staging system categories T1, T2, T3 and T4) and regional lymph node status (N-stage, disease-free (N0) versus metastatic (N+)) using histopathology as the reference standard. To this end, we searched the following databases: the*Cochrane Library* (the Cochrane Central Register of Controlled Trials (CENTRAL)), MEDLINE, EMBASE, NIHR Prospero Register, MEDION, Aggressive Research Intelligence Facility (ARIF), ClinicalTrials.gov, Current Controlled Trials MetaRegister, and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), from 1988 to January 2015.

Selection criteria

We included studies that met the following main inclusion criteria: 1) a minimum sample size of 10 patients with histologically-proven primary carcinoma of the stomach (target condition); 2) comparison of EUS (index test) with pathology evaluation (reference standard) in terms of primary tumor (T-stage) and regional lymph nodes (N-stage). We excluded reports with possible overlap with the selected studies.

Data collection and analysis

For each study, two review authors extracted a standard set of data, using a dedicated data extraction form. We assessed data quality using a standard procedure according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria. We performed diagnostic accuracy meta-analysis using the hierarchical bivariate method.

Main results

We identified 66 articles (published between 1988 and 2012) that were eligible according to the inclusion criteria. We collected the data on 7747 patients with gastric cancer who were staged with EUS. Overall the quality of the included studies was good: in particular, only five studies presented a high risk of index test interpretation bias and two studies presented a high risk of selection bias.

For primary tumor (T) stage, results were stratified according to the depth of invasion of the gastric wall. The meta-analysis of 50 studies (n = 4397) showed that the summary sensitivity and specificity of EUS in discriminating T1 to T2 (superficial) versus T3 to T4 (advanced) gastric carcinomas were 0.86 (95% confidence interval (CI) 0.81 to 0.90) and 0.90 (95% CI 0.87 to 0.93) respectively. For the diagnostic capacity of EUS to distinguish T1 (early gastric cancer, EGC) versus T2 (muscle-infiltrating) tumors, the meta-analysis of 46 studies (n = 2742) showed that the summary sensitivity and specificity were 0.85 (95% CI 0.78 to 0.91) and 0.90 (95% CI 0.85 to 0.93) respectively. When we addressed the capacity of EUS to distinguish between T1a (mucosal) versus T1b (submucosal) cancers the meta-analysis of 20 studies (n = 3321) showed that the summary sensitivity and specificity were 0.87 (95% CI 0.81 to 0.92) and 0.75 (95% CI 0.62 to 0.84) respectively. Finally, for the metastatic involvement of lymph nodes (N-stage), the meta-analysis of 44 studies (n = 3573) showed that the summary sensitivity and specificity were 0.83 (95% CI 0.79 to 0.87) and 0.67 (95% CI 0.61 to 0.72), respectively.

Overall, as demonstrated also by the Bayesian nomograms, which enable readers to calculate post-test probabilities for any target condition prevalence, the EUS accuracy can be considered clinically useful to guide physicians in the locoregional staging of people with gastric cancer. However, it should be noted that between-study heterogeneity was not negligible: unfortunately, we could not identify any consistent source of the observed heterogeneity. Therefore, all accuracy measures reported in the present work and summarizing the available evidence should be interpreted cautiously. Moreover, we must emphasize that the analysis of positive and negative likelihood values revealed that EUS diagnostic performance cannot be considered optimal either for disease confirmation or for exclusion, especially for the ability of EUS to distinguish T1a (mucosal) versus T1b (submucosal) cancers and positive versus negative lymph node status.

Authors' conclusions

By analyzing the data from the largest series ever considered, we found that the diagnostic accuracy of EUS might be considered clinically useful to guide physicians in the locoregional staging of people with gastric carcinoma. However, the heterogeneity of the results warrants special caution, as well as further investigation for the identification of factors influencing the outcome of this diagnostic tool. Moreover, physicians should be warned that EUS performance is lower in diagnosing superficial tumors (T1a versus T1b) and lymph node status (positive versus negative). Overall, we observed large heterogeneity and its source needs to be understood before any definitive conclusion can be drawn about the use of EUS can be proposed in routine clinical settings.

PLAIN LANGUAGE SUMMARY

Ultrasound for determining the spread of stomach cancer

Review question

There is much debate on the diagnostic performance of endoscopic ultrasound (EUS) in the preoperative staging of gastric cancer. The aim of this review was to collect the available evidence and then to calculate how well EUS stages stomach cancer.

Background

EUS is a diagnostic test that can be used to determine how far (stage) cancer of the stomach reaches prior to surgery. It consists of an endoscope coupled with an ultrasound device capable of scanning the stomach wall, which shows the different layers of the stomach. Changes from the normal ultrasonographic patterns due to the tumor growth can be used to determine the extent of cancer in the stomach wall (T-stage) and the lymph nodes related to the stomach (N-stage). Since the correct staging of the tumor enables physicians to personalize cancer treatment, it is important to understand the reliability of staging devices.

Study characteristics

We conducted a meta-analysis according to the most recent methods for diagnostic tests. The last literature search was performed in January 2015. We included 66 studies (of 7747 patients) in the review.

Key results

We found that EUS can distinguish between superficial (T1 - T2) and advanced (T3 - T4) primary tumors with a sensitivity and a specificity greater than 85%. This performance is maintained for the discrimination between T1 and T2 superficial tumors. However, EUS diagnostic accuracy is lower when it comes to distinguishing between the different types of early tumors (T1a versus T1b) and between tumors with versus those without lymph node disease.

Quality of the evidence

Overall, EUS provides physicians with some helpful information on the stage of gastric cancer. Nevertheless, in the light of the variability of the results reported in the international medical literature, its limitations in terms of performance must be kept in mind in order to make

the most out of the diagnostic potential of this tool. Finally, more work is needed to assess whether some technical improvements and the combination with other staging instruments may increase our ability to correctly stage the disease and thus optimize patient treatment.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings Table

General information		
General issue	What is the diagnostic performance of endoscopic ultrasound (EUS) in assessing disease stage in people with gastric carcinoma ?	
Specific questions	What is the diagnostic performance of EUS in assessing primary tumor depth ?	Superficial (T1 - T2) versus advanced (T3 - T4) tumors
		Early (T1) versus muscular (T2) tumors
		Mucosal (T1a) versus submucosal (T1b) tumors
	What is the diagnostic performance of EUS in assessing regional lymph node status ?	Non-metastatic (N0) versus metastatic (N+) lymph nodes
Patients	Patients diagnosed with gastric carcinoma	
Settings	Pre-treatment evaluation of disease stage	
Index tests	Endoscopic ultrasound (EUS)	
Reference standard	Histology of surgical or endoscopic specimen	
Importance	Choosing best treatment or treatment sequence of gastric carcinoma	
Studies	66 studies enrolling 7747 patients	
Quality concerns	Overall judgement	Good quality
	Applicability concerns	None
	Patient selection bias	None
	Index test interpretation bias	High risk: 5 studies
	Reference test interpretation bias	None
	Flow and timing selection bias	High risk: 2 studies Unclear risk: 2 studies
T1 - T2 versus T3 - T4 tumors		
Studies	50 (patients enrolled: 4397)	
Summary results	Sensitivity: 0.86 (95% CI: 0.81 to 0.90). Specificity: 0.90 (95% CI: 0.87 to 0.93)	
Consequences	In a hypothetical cohort of 1000 patients (T1 - T2 prevalence: 50%)	Correctly classified: 880
		Overstaged: 70
		Understaged: 50

T1 versus T2 tumors		
Studies	46 (patients enrolled: 2742)	
Summary results	Sensitivity: 0.85 (95% CI: 0.78 to 0.91). Specificity: 0.90 (95% CI: 0.85 to 0.93)	
Consequences	In a hypothetical cohort of 1000 patients (T1 prevalence: 70%)	Correctly classified: 865
		Overstaged: 105
		Understaged: 30
T1a versus T1b tumors		
Studies	20 (patients enrolled: 3321)	
Summary results	Sensitivity: 0.87 (95% CI: 0.81 to 0.92). Specificity: 0.75 (95% CI: 0.62 to 0.84)	
Consequences	In a hypothetical cohort of 1000 patients (T1a prevalence: 70%)	Correctly classified: 834
		Overstaged: 91
		Understaged: 75
N0 versus N+ tumors		
Studies	44 (patients enrolled: 3573)	
Summary results	Sensitivity: 0.83 (95% CI: 0.79 to 0.87). Specificity: 0.67 (95% CI: 0.61 to 0.72)	
Consequences	In a hypothetical cohort of 1000 patients (N+ prevalence: 50%)	Correctly classified: 750
		Overstaged: 85
		Understaged: 165

BACKGROUND

Despite its declining incidence in Western countries, gastric cancer is still one of the most common cancers in the world (Ferlay 2010; Shah 2010), the fourth most commonly occurring cancer (9% of all cancers) after cancer of the lung, breast, and colorectum, and the second most common cancer-related cause of death (10% of all cancer deaths) after lung cancer. In 2002, the incidence of gastric cancer was estimated at 934,000 cases, 56% of the new cases being derived from Eastern Asia, 41% from China, and 11% from Japan. On the whole, 65% to 70% of incident cases and deaths from gastric cancer are occurring in less developed countries. In the US, 21,000 new cases of this malignancy were estimated to occur in 2010, leading to 10,500 expected deaths (Jemal 2010).

Radical surgery still represents the mainstay of treatment with curative intent (Dicken 2005; Jackson 2009). However, new approaches are gaining importance in the therapeutic management of these patients. For instance, endoscopic mucosal resection (EMR) is proposed as an alternative to surgery for people with early gastric cancer (EGC) in the presence of favorable prognosis features (e.g. histologically well-differentiated carcinoma limited to the mucosa, diameter less than 2 cm, absence of ulceration) (Bennett 2009; Hirasawa 2011; Kang 2011; Othman 2011). Moreover, different adjuvant and neoadjuvant chemotherapy regimens (combined or not with radiotherapy) have been shown to provide significant survival advantage to people with advanced gastric cancer (AGC) (House 2008; Jiang 2010; Paoletti 2010; Wagner 2010).

These strategies require reliable disease staging procedures in order to guarantee the most appropriate treatment (i.e. with the highest therapeutic index, the ratio between efficacy and toxicity) for each patient, according to the principles of personalized medicine. As for all solid tumors, the disease stage for gastric cancer is defined by the three categories of the TNM classification: T-stage (indicating the primary tumor invasion through the layers of the gastric wall; T1: tumor invading mucosa-submucosa layer; T2: muscolaris propria layer; T3: subserosa layer; T4: serosa layer or adjacent organs), N-stage (indicating the regional lymph node involvement; N0: no metastasis; N1 - 3: presence of increasing number of metastatic lymph nodes) and M-stage (indicating the presence/absence of distant metastasis, such as hepatic or peritoneal metastasis; M0 - 1) (Edge 2010).

Therefore, after the diagnosis of primary carcinoma of the stomach is made (usually by means of pathology evaluation of tumor biopsies obtained during a standard gastroscopy), staging is assessed both preoperatively (clinical staging) by means of imaging techniques, and postoperatively by pathology examination of the surgical specimen (pathological staging). Knowing the disease stage before surgery (clinical staging) can be extremely useful in providing patients with the best therapeutic option: for instance, AGC (i.e., T3 - T4 tumors or tumors with lymph node metastasis (N +)) can be treated with neoadjuvant (preoperative) chemotherapy (or radiotherapy, or both) (House 2008; Jiang 2010; Paoletti 2010; Wagner 2010). On the other hand, early gastric cancer (T1 tumors) with no lymph node involvement (N0) can be treated with endoscopic rather than surgical resection (Bennett 2009; Hirasawa 2011; Kang 2011; Othman 2011).

Computed tomography (CT) is currently the most frequently used radiological tool for the preoperative staging of gastric cancer (Jensen 2007; Ly 2008); however, CT accuracy is high mainly for distant metastasis (M category, e.g., hepatic metastasis), whereas its accuracy for locoregional staging (i.e., definition of the T and N categories) is much lower, ranging in most series from 65% to 85% (Hur 2006; Kawaguchi 2011; Kim 2005; Kumano 2005; Stell 1996). For instance, a recent meta-analysis shows that CT scan sensitivity and specificity for the identification of lymph node status are 77% and 78%, respectively (Seevaratnam 2012). No better results appear to be achievable with other techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET) (Ha 2011; Kim 2011; Seevaratnam 2012). Overall, only a limited proportion of people with locally-advanced gastric cancer and an even smaller percentage of those with early gastric cancer can be identified preoperatively and can thus benefit from personalized treatments.

Endoscopic ultrasound (EUS) has been proposed as an accurate device for the locoregional staging of gastric cancer (Byrne 2002; Hargunani 2009; Polkowski 2009). Our aim is to systematically review and meta-analyze the available evidence regarding the diagnostic accuracy of EUS in discriminating between different primary tumor depths of invasion (T-stage), as well as in identifying metastasis within regional lymph nodes (N-stage).

A glossary of terms is provided in Appendix 1.

Target condition being diagnosed

This review addresses the preoperative locoregional staging of primary gastric carcinoma to distinguish between EGC, which is suitable for endoscopic resection, and AGC, which is likely to benefit from neoadjuvant therapies. We have not considered other gastric malignancies (e.g., lymphomas, gastrointestinal stromal tumors (GIST)).

Index test(s)

In this review endoscopic ultrasonography (EUS) represents the index test. It consists of an endoscope equipped with an ultrasound probe that can scan the stomach wall in order to detect alterations in its normal layers caused by primary tumor growth, as well as the presence of metastatic lymph nodes. Usually EUS does not require patient sedation and is performed like a standard gastroscopy with the instrument being introduced into the stomach through the mouth, the only difference being the additional time required to scan the stomach wall. For this reason and because complications are virtually absent, it is usually performed on an outpatient basis. The ultrasound transducer, which is integrated in the distal end of the endoscope to allow its positioning close to the gastric wall, comes in two main types: the linear scanner gives a scanning range of 180°, whereas the radial scanner offers the advantage of a full panoramic view (360°).

Clinical pathway

People with suspected gastric cancer, based on history and clinical findings, generally undergo gastroscopy to make the disease diagnosis, usually defined by the pathology evaluation of the biopsy performed during the endoscopy. Then the malignant disease is staged to assess its spread through the gastric wall to adjacent organs/lymph nodes or to distant body sites; this step is crucial to setting up the best therapeutic strategy and thus to maximizing the likelihood of cure. False positive findings from a staging procedure (e.g., classifying an early disease as advanced)

might lead to over-treatment (e.g., unnecessary neoadjuvant chemotherapy); false negative findings might lead to patient under-treatment.

Prior test(s)

No test is usually performed before EUS.

Role of index test(s)

The index test (EUS) is currently utilized in clinical practice by many physicians to preoperatively stage gastric cancer. However there is no consensus on whether or not EUS should be routinely used for this as part of a standardized approach.

Alternative test(s)

Other diagnostic tools that can be used for gastric cancer staging are computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). None of them is deemed sufficiently accurate to be considered as the optimal imaging technique for the preoperative evaluation of disease spread, although all are widely used in clinical practice. In particular, neither CT scan, nor MRI, nor PET are useful for the definition of early stages of gastric cancer, whereas they are commonly utilized to diagnose locally-advanced gastric cancer (T3 - T4 or N+ cases, or both). While the usefulness of these diagnostic tools in the locoregional staging of gastric carcinoma is debated, there is a general consensus about their use in defining the presence of distant metastatic disease, e.g., presence or absence of metastasis in the liver or lungs.

Rationale

With regard to preoperative assessment of disease spread, one of the most promising tools for the locoregional staging of gastric carcinoma is EUS (Byrne 2002; Hargunani 2009; Polkowski 2009). This endoscopy-based diagnostic device can both distinguish the different layers that compose the gastric wall and visualize the perigastric lymph nodes by means of a miniaturized ultrasound probe. Based on numerous reports published over more than two decades, EUS is often reported as a highly accurate method for the locoregional staging of gastric cancer. However, findings are heterogeneous, e.g., sensitivity and specificity values can range from 50% to 100% (Hizawa 2002; Kelly 2001; Kwee 2007; Kwee 2008; Kwee 2009; Puli 2008; Reddy 2008; Shimoyama 2004; Weber 2004), and although thousands of people with gastric cancer have been enrolled in EUS-based studies, no formal quantitative review of the available evidence has been published that comprehensively examines the staging performance of EUS using the most appropriate statistical tools for the meta-analysis of diagnostic accuracy data (a hierarchical approach) (Harbord 2008; Leeflang 2008; Macaskill 2010; Reitsma 2005).

Our review aims to fill this gap in the medical literature by quantitatively summarizing the diagnostic role of EUS in the staging of primary gastric carcinoma.

OBJECTIVES

To provide both a comprehensive overview and a quantitative analysis of the published data regarding the ability of endoscopic ultrasonography (EUS) to preoperatively define the locoregional disease spread (i.e., primary tumor depth (T-stage) and regional lymph node status (N-stage)) in people with primary gastric carcinoma.

Secondary objectives

To provide the tools to calculate EUS diagnostic accuracy measures based on pre-test information, such as gastric cancer T-stage and N-stage prevalence (Bayes nomograms).

To assess whether EUS performs differently in different subgroups of patients identified by the following parameters: year of publication, country (Western versus Eastern), EUS technical features (radial versus linear array; ultrasound frequency (MHz)), definition of target condition (for N-stage: lymph node morphology versus size), gastric tumor site (any site versus cardia region only) and prevalence of target condition.

METHODS

Criteria for considering studies for this review

Types of studies

We include studies that meet the following inclusion criteria:

1. A minimum sample size of 10 patients with histologically-proven primary carcinoma of the stomach;
2. Evaluation of endoscopic ultrasonography (EUS) compared with histopathology of primary tumor (T-stage) and regional lymph nodes (N-stage);
3. Sufficient data to construct a two-by-two contingency table such that the cells in the table could be labeled as true positive, false positive, true negative, and false negative (see the Target conditions for more details).

This type of study typically include both retrospective and prospective series of patients. As long as the above information is available,we did not exclude any specific type of study design.

We excluded studies that had possible overlap with the selected studies (i.e. studies from the same study group, institution, and period of inclusion). We excluded studies reporting on EUS performed before preoperative chemotherapy and or radiotherapy (neoadjuvant therapy) in order to avoid the confounding effect of disease downstaging by neoadjuvant treatments.

Participants

For this review, patients were people with gastric carcinoma undergoing preoperative locoregional disease staging (T-stage and N-stage) by means of EUS and postoperative pathology evaluation of the surgical specimen, including those having early gastric cancer (EGC) or advanced gastric cancer (AGC). We imposed no restrictions by age, gender or any other category.

Index tests

The index test is EUS. We compared the results of EUS to those of pathology evaluation (reference test) in terms of both T-stage and N-stage (see Target conditions for more details).

We did not consider any comparator test.

Target conditions

The target condition was gastric cancer locoregional staging, for both primary tumor depth and regional lymph node status.

For lymph node status (N-stage), we considered a patient either negative if no lymph node was metastatic (N0) or positive if one or more lymph nodes were metastatic (N+), as assessed by pathology evaluation.

For the primary tumor invasion of the gastric wall (T-stage), we considered two main conditions according to the clinical questions that EUS aims to answer:

1. In order to identify patients who would best benefit from surgery without preoperative radio-chemotherapy, EUS was to be investigated for its ability to distinguish superficial tumors (T1 - T2) versus advanced tumors (AGC, T3 - T4, which are likely to benefit from neoadjuvant preoperative chemotherapy); in this case, a patient was considered either positive if his/her gastric cancer was classified as T1 - T2 by pathology examination, or negative if his/her gastric cancer is classified as T3 - T4.
2. Within the frame of superficial cancers (T1 - T2), in order to identify patients with superficial tumors amenable to endoscopic resection (T1 tumors), EUS was investigated for its ability to distinguish T1 tumors (EGC) versus T2 tumors; in this case, a patient was considered either positive if his/her gastric cancer is classified as T1 by pathology evaluation, or negative if his/her gastric cancer is classified as T2.

Finally, where the data permitted and within the frame of EGC (T1 tumors), EUS was also tested for its ability to further discriminate between T1a and T1b tumors, since it is believed that the former type of cancers benefit the most from endoscopic mucosal resection (EMR). To this end, a patient was considered either positive if his/her gastric cancer was classified as T1a by pathology evaluation, or negative if his/her gastric cancer was classified as T1b.

Reference standards

The reference standard was routine histopathology evaluation (i.e., microscopic examination of hematoxylin-eosin stained samples) of primary tumor and regional lymph nodes. Since pathological examination of the surgical specimen is the only way to know precisely the depth of invasion through the gastric wall as well as the status of regional lymph nodes, all eligible patients must have undergone surgery and all tumors must have undergone routine pathology evaluation. According to the pathology report, four T categories (T1 to T4) indicate the extent of gastric wall invasion by the primary tumor; the status of the regional lymph nodes (positive versus negative) was also taken into consideration.

Search methods for identification of studies

We performed a comprehensive search of the literature to identify articles that examined the diagnostic accuracy of EUS (the index test) in the evaluation of primary gastric cancer depth of invasion (T-stage, according to the AJCC/UICC TNM staging system categories T1, T2, T3 and T4) and regional lymph node status (N-stage, metastatic versus disease-free) using histopathology as the reference standard.

Electronic searches

We grouped key words to combine four 'concepts' that must be included in a paper reporting on the subject under investigation in this review:

1. malignant neoplasm (cancer, carcinoma)
2. body site (gastric, stomach)
3. diagnostic method (endoscopic ultrasound, EUS)
4. disease staging

We systematically searched the following databases.

1. *The Cochrane Library* (the Cochrane Central Register of Controlled Trials (CENTRAL)) (2015, Issue 1) (Appendix 2)
2. MEDLINE (from 1988 to January 2015) (Appendix 3)
3. EMBASE (from 1988 to January 2015) (Appendix 4)
4. NIHR Prospero Register
5. MEDION (http://www.mediondatabase.nl/)
6. ARIF (www.arif.bham.ac.uk/databases.shtml)
7. ClinicalTrials.gov (clinicaltrials.gov/)
8. Current Controlled Trials MetaRegister (www.controlled-trials.com/mrct/)
9. WHO ICTRP (www.who.int/ictrp/en/)

Searching other resources

We searched for additional references by cross-checking bibliographies of retrieved full-text papers.

Data collection and analysis

Both review authors (SM and SP) conducted the literature search as well as data collection and management. Review author SM conducted the statistical analyses.

Selection of studies

Both review authors (SM and SP) independently selected the studies, resolving discrepancies by iteration, discussion and consensus. Where we retrieved articles in languages other than English, we were able to assess those in Italian, French and Spanish for eligibility.

Data extraction and management

We extracted relevant data from the articles selected for inclusion in the meta-analysis. In addition to the accuracy data, we also recorded the following information for each study:

1. Overall study characteristics, including the first author, country, language, and date of publication;
2. Study patient characteristics;
3. Features of the index test, e.g. type of echoendoscope, ultrasound frequency, and EUS criteria for tumor depth and lymph node status.

In case of missing data, we contacted the authors of the study to obtain the missing information. None of the three authors we contacted (Caletti 1993; Dittler 1993; Murata 1988) was able to provide data.

When raw data were presented in three-by-three or four-by-four tables (e.g., when the tumor depth or lymph node stage are

defined by more than two categories), we constructed two-by-two contingency tables by considering a given T, or any N-positive category, as the 'positive' state to be distinguished from the other T categories, or from the N-negative cases. For instance, if an article presented data in a table reporting the number of N0, N1, N2 and N3 cases, we collapsed the data into a table with N0 and N+ (sum of N1, N2 and N3) cases.

We extracted data separately on primary tumor depth (T-stage) and regional lymph node status (N-stage).

We assembled all data in a dedicated database built within an Excel spreadsheet, where each row corresponded to a single study and variables of interest were recorded in the columns.

Assessment of methodological quality

We assessed data quality using a standard procedure according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria (Whiting 2011). When there was at least one 'no' or 'unclear' response to a signaling question for a given domain, we scored the risk of bias as high or unclear, respectively. See Appendix 5 for details of the findings.

Statistical analysis and data synthesis

We performed statistical analysis according to Cochrane guidelines for diagnostic test accuracy (DTA) reviews (Macaskill 2010).

We used coupled forest plots to display the number of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN), as well as sensitivity and specificity, with their 95% confidence intervals (CI), for all included studies. Visual inspection of forest plots can provide a clue to heterogeneity within single studies. We also used summary receiver operating characteristic (SROC) plots to display the results of individual studies in a ROC space, each study being plotted as a single sensitivity-specificity point.

As currently recommended for meta-analysis of diagnostic accuracy studies (Harbord 2008; Leeflang 2008; Macaskill 2010; Reitsma 2005; Rutter 2001), we used hierarchical models to obtain summary estimates of EUS performance in terms of ability to discriminate primary gastric cancer depth of invasion (T-stage) and regional lymph node status (N-stage).

According to the bivariate method (Reitsma 2005), we calculated overall sensitivity and specificity and their 95% confidence intervals (CIs) and predictive intervals, based on the binomial distributions of the true positives and true negatives. Besides accounting for study size and between-study heterogeneity, the bivariate model adjusts for the frequently observed negative correlation between the sensitivity and the specificity of the index test (threshold effect). An additional advantage of using the bivariate model is that the bivariate nature of the original data can be maintained throughout the analysis, allowing the generation of reliable summary estimates of sensitivity and specificity. For the bivariate model, the summary estimates of sensitivity and specificity represent an 'average' operating point across studies. We analyzed primary tumor depth (T-stage) and regional lymph node status (N-stage) separately.

We evaluated the clinical (or patient-relevant) utility of EUS using likelihood ratios, which we computed directly from the summary estimates of sensitivity and specificity, to enable the calculation of post-test probability (based on the Bayes' theorem) by means of the Fagan's nomogram (Deeks 2004). The Fagan's nomogram is a graphical tool which in routine clinical practice allows one to use the results of a diagnostic test to estimate a patient's probability of having a disease (post-test probability) based on two pieces of information: the pre-test probability (usually the incidence of the disease/condition) and the test result. In this nomogram, a straight line drawn from a patient's pre-test probability of disease (left axis) through the likelihood ratio of the test (middle axis) intersects with the post-test probability of disease (right axis).

We conducted statistical analyses using both Review Manager 5 software (RevMan 2014) as well as the Metandi and Midas programs for the STATA software (Stata 2009).

Since currently available imaging tools are associated with accuracy sensitivity and specificity values around 80% (see Background section), we considered this as a 'desirable' value with which the EUS diagnostic performance can be compared.

Investigations of heterogeneity

As it is common in diagnostic accuracy studies, we anticipated that there would be substantial between-study variation in reported pairs of sensitivity and specificity values.

Coupled forest plots, which display both sensitivity and specificity of all included studies, provide a visual clue to heterogeneity of the results on a single-study basis.

In order to formally investigate potential sources of heterogeneity other than the threshold effect, we used subgroup analysis and meta-regression by including covariates (study sample size, publication year, type of EUS array, study quality, country, stomach site) in the bivariate model, which enabled us to assess the effect of various factors on the diagnostic accuracy of EUS.

Sensitivity analyses

We conducted sensitivity analyses to assess the impact on the summary effects of low-quality studies, as defined by the identification of a high risk of bias for one or more QUADAS-2 items, as well as the presence of specific types of primary gastric cancer morphology (e.g., ulcerated tumors) or location (e.g., cardia region of the stomach).

We also used the 'leave-one-out' procedure to assess the impact of each study on the meta-analysis results (leading study effect).

Assessment of reporting bias

We conducted formal testing for small-study effects (which include publication bias) by a regression of diagnostic odds ratio (DOR), which describes the odds of positive test results in patients with disease compared with the odds of positive test results in those without disease, on a natural logarithm scale against 1/sqrt ESS (effective sample size), weighting by ESS. $P < 0.10$ for the slope coefficient indicates significant asymmetry of the funnel plot (Deeks 2005).

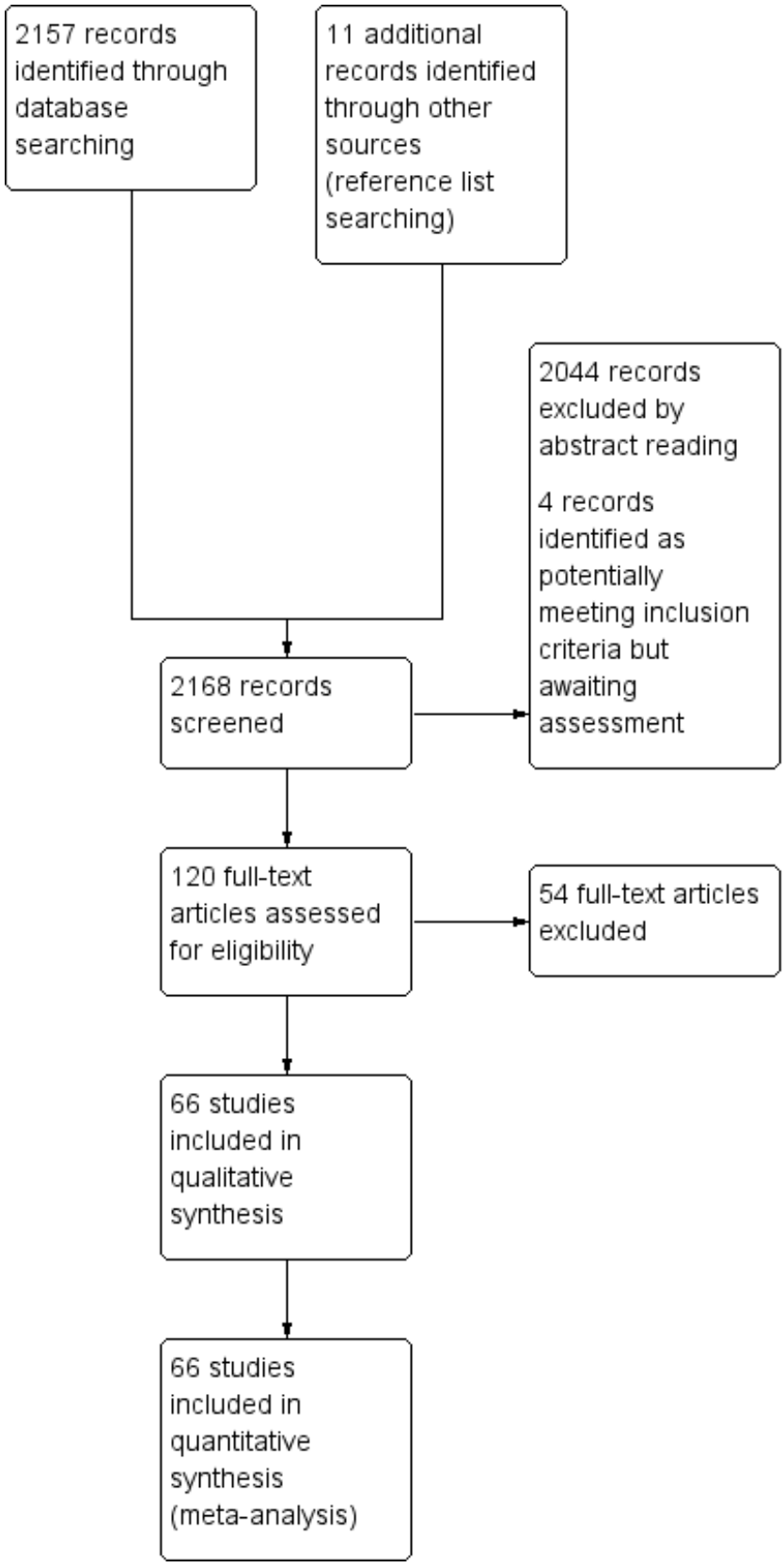
RESULTS

Results of the search

The literature search identified 2168 potentially relevant studies (Figure 1). By reading abstracts we excluded 2044 articles, and by reading full-text versions we eliminated another 54 articles.

We identified four citations as potentially meeting the inclusion criteria but could not assess them by the time of publication, and will address them in a future update. Ultimately, 66 articles were eligible according to the inclusion criteria. The main characteristics of the eligible studies, which were published from 1988 through 2012, are reported in the Characteristics of included studies section. The main characteristics of the excluded studies are reported in the Characteristics of excluded studies section. Considering the included studies, overall 7747 patients were enrolled in 16 different countries, with a mean of 117 patients enrolled per study (range: 14 to 930). Most of these studies (41/66, 62%) were published after 1999. The available evidence came primarily from retrospective studies (50/66, 76%), which enrolled Asian patients in 39 series (59%). The target condition was gastric carcinoma arising from any site of the stomach in 60 out of 66 studies (91%), whereas in the remaining series the authors focused on the tumors arising in the cardia region, Finally, the radial type of endoscopic ultrasound (EUS) array was the more often utilized compared to the linear array (55/58 articles (95%) reporting the type of array adopted).

Figure 1. Study flow diagram.



Methodological quality of included studies

Overall, the quality of the included studies was good, as illustrated in the QUADAS-2 results summary (Figure 2) and graph (Figure 3), and also summarized in Summary of findings 1. No concerns about applicability or patient selection bias or interpretation of reference test results were raised by the analysis of the available data. However, five studies (Bhandari 2004; Garlipp 2011; Heye 2009; Potrc 2006; Xi 2003) presented a high risk of index test interpretation bias due to the lack of threshold definition for the classification of T-stage or N-stage or both. Two other studies (Akashi 2006; Mouri 2009) presented a high risk of selection bias due to the lack of inclusion of all patients: in particular, 37 and 31 patients respectively were not included, due to uninterpretable EUS findings. In another two studies (Hizawa 2002; Yanai 1997) the same issue occurred for only seven and four patients respectively: accordingly we deemed the risk of bias in these cases as unclear. Overall, uninterpretable results were rarely reported, although this is not a guarantee that EUS findings are always easily interpretable; it might just reflect the attitude of the endoscopist to provide a classification 'at any cost'. In most studies the interval between the index test and the reference test was unreported, but we believe that this occurrence is unlikely to undermine the reliability of the results, since the diagnosis of a malignant disease such as gastric carcinoma is usually considered an indication for surgery and thus for pathological evaluation within a very short time (some days/a few weeks). This in turn is unlikely to be sufficient for the disease stage to change.

Figure 2. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

Figure 2. (Continued)

Figure 2. (Continued)

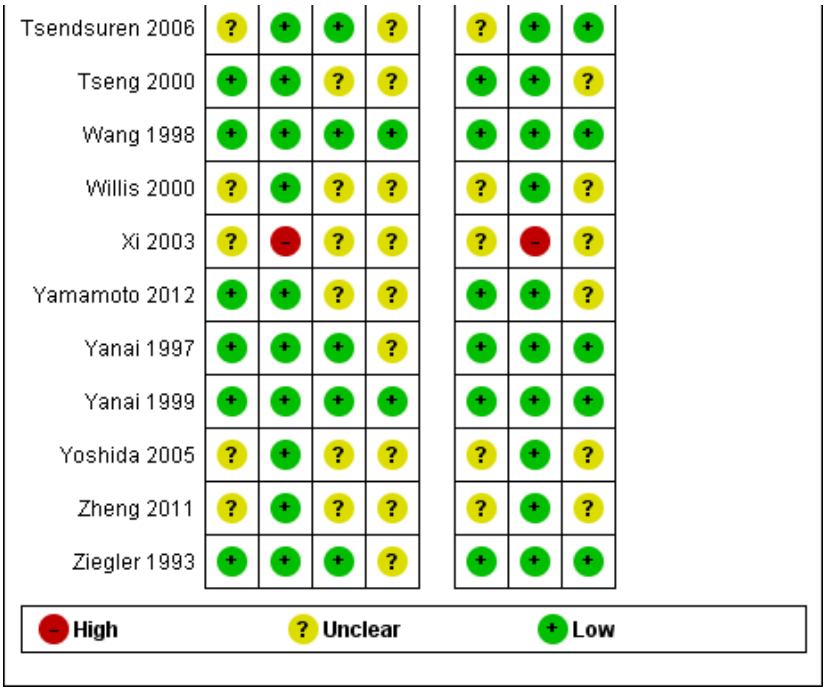
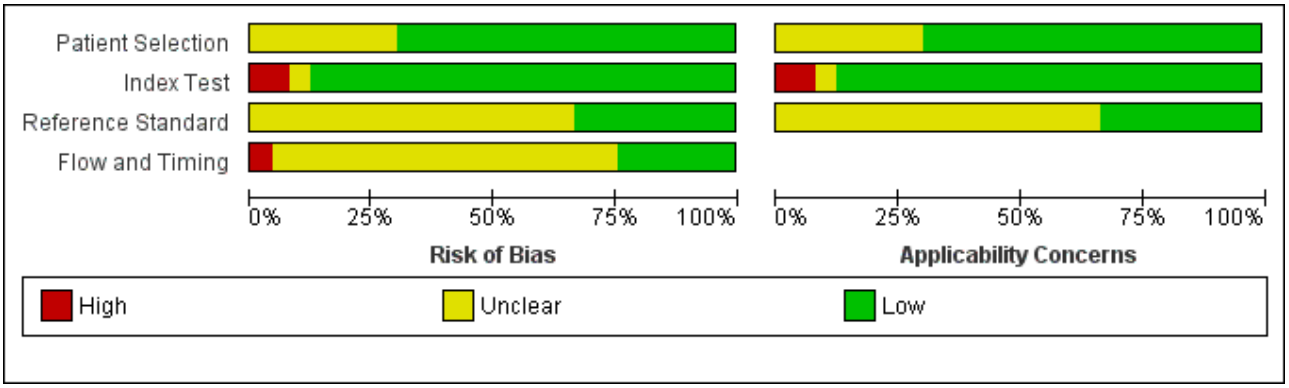


Figure 3. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies



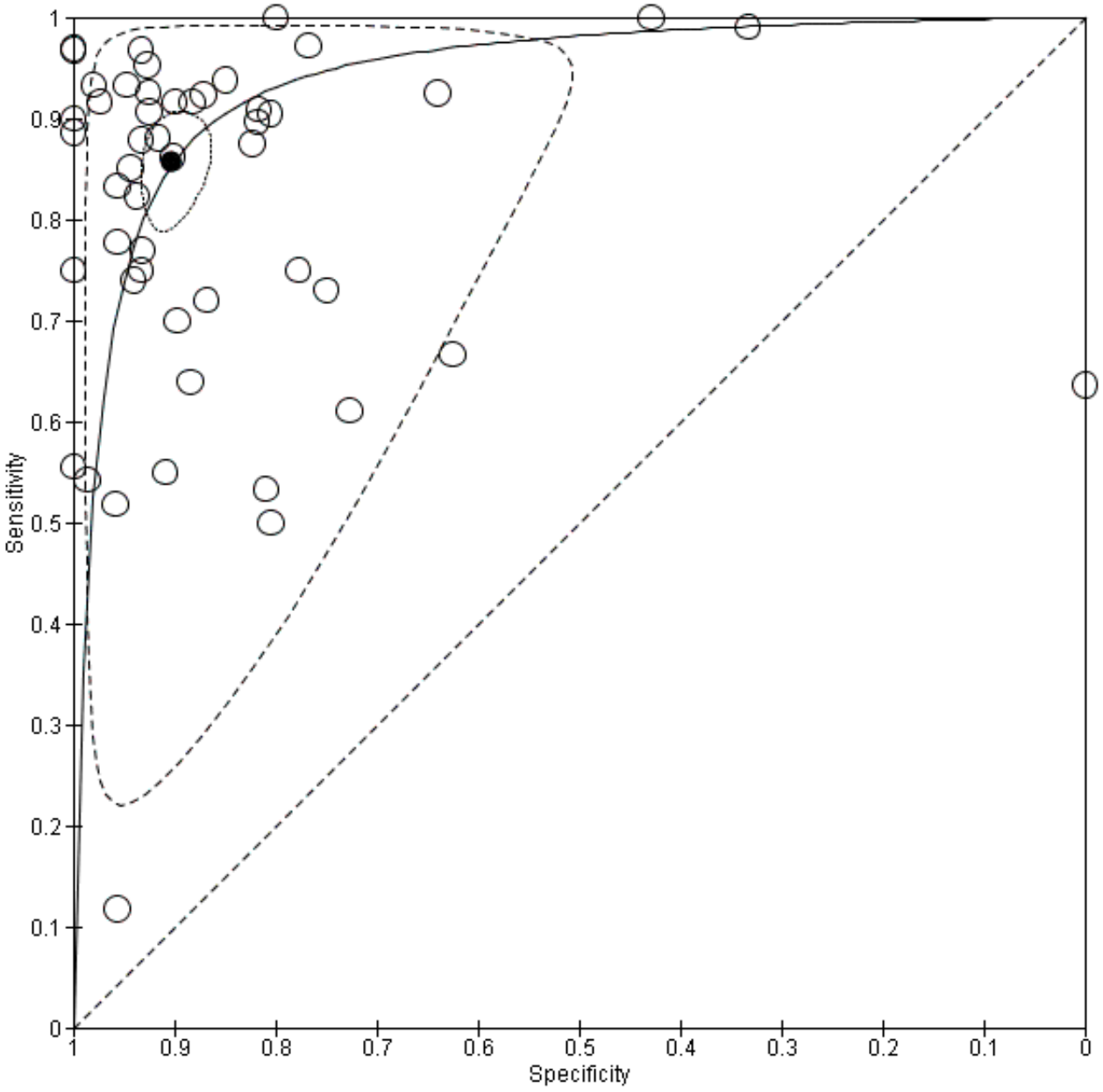
Findings

Primary tumor depth (T-stage)

We first addressed the issue of EUS accuracy in discriminating **T1 - T2 (superficial) versus T3 - T4 (advanced) gastric carcinomas**. We therefore carried out a meta-analysis of the eligible studies reporting relevant data. For this analysis (Data table 1), 50 studies were available, with a total of 4397 patients.

The sensitivity and specificity of the single studies are shown in Data table 1. The summary receiver operating curve (SROC) curve along with the summary point and the 95% confidence and prediction regions are illustrated in Figure 4. The summary sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were 0.86 (95% confidence interval (CI): 0.81 to 0.90), 0.90 (95% CI: 0.87 to 0.93), 8.9 (95% CI: 6.8 to 11.6), 0.16 (95% CI: 0.12 to 0.22), and 56 (95% CI: 37 to 85), respectively.

Figure 4. Summary ROC Plot of studies assessing the accuracy of EUS in discriminating T1 - T2 versus T3 - T4 gastric carcinomas. Each study sensitivity/specificity value is represented by an empty circle. The summary point for sensitivity/specificity is represented by a black filled circle. Dotted closed line: 95% confidence region of the summary point. Dashed closed line: 95% prediction region.



As shown in Figure 4 by both confidence and prediction regions, the results indicate a lower variability for specificity as compared to sensitivity, suggesting that EUS might be more reliable in correctly identifying T3 - T4 cases compared to T1 - T2 cases.

Although both summary sensitivity and specificity values were relatively satisfactory, between-study heterogeneity was substantial, as visually assessable through both the forest plot (Data table 1) and predictive ellipse (Figure 4).

The Fagan plot (Figure 5) illustrates that EUS may be clinically useful because it increases the previous probability of being classified as T1 - T2 from 50% (average prevalence of T1 - T2 cases) to 90% when positive, and it lowers the same probability to 14% when negative. However, the likelihood ratio (LR) scattergram (Figure 6) shows that the summary point of positive and negative LR is located in the lower right quadrant, suggesting that EUS accuracy - although close to values desirable for a diagnostic tool - is not optimal either for tumor depth confirmation or exclusion.

Figure 5. Fagan plot estimating how much the result of EUS changes the probability that a patient has a T1 - T2 (rather than T3 - T4) gastric cancer, considering a given pre-test probability (here the mean pre-test probability found in eligible studies is shown as an example).

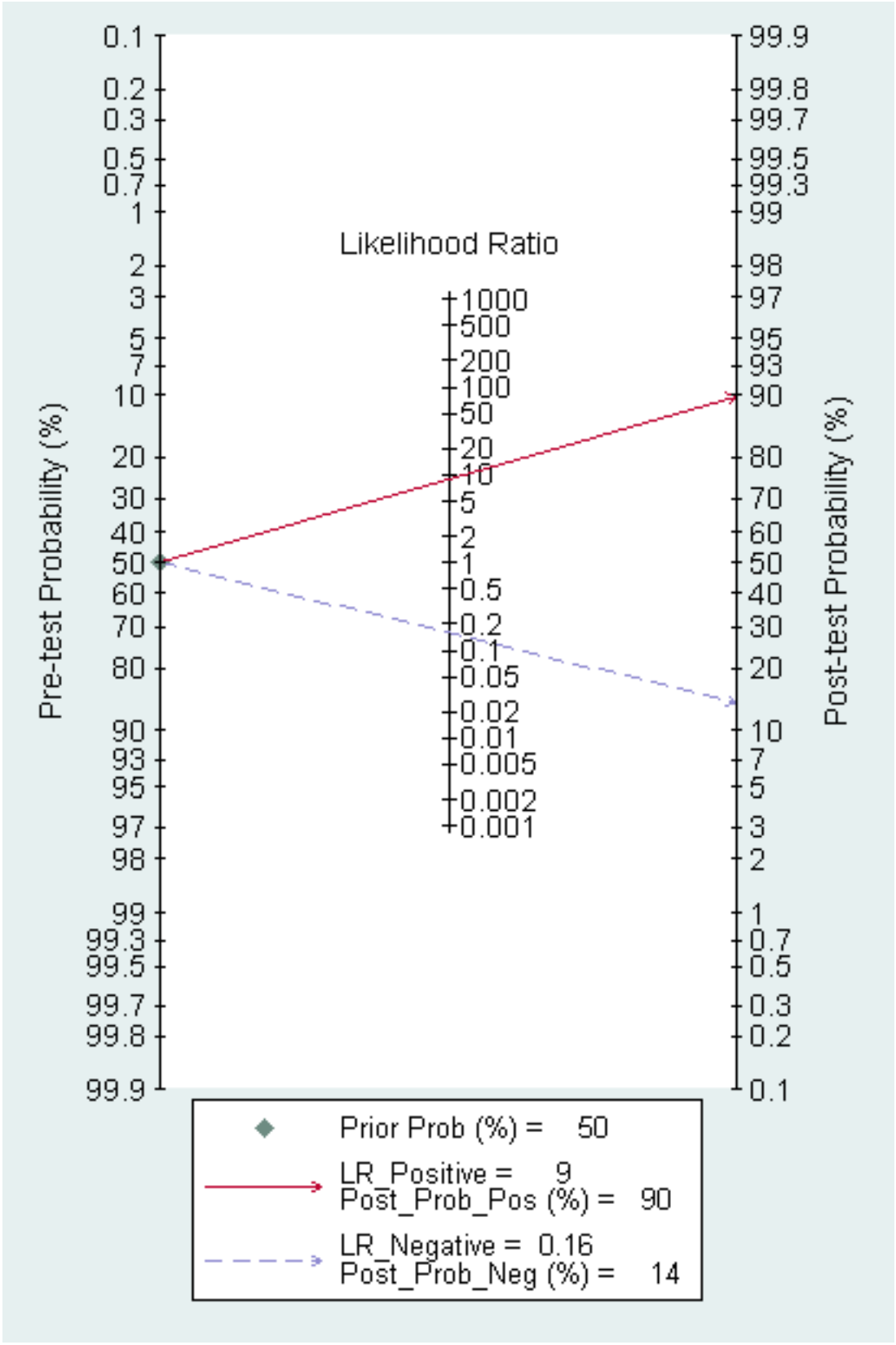
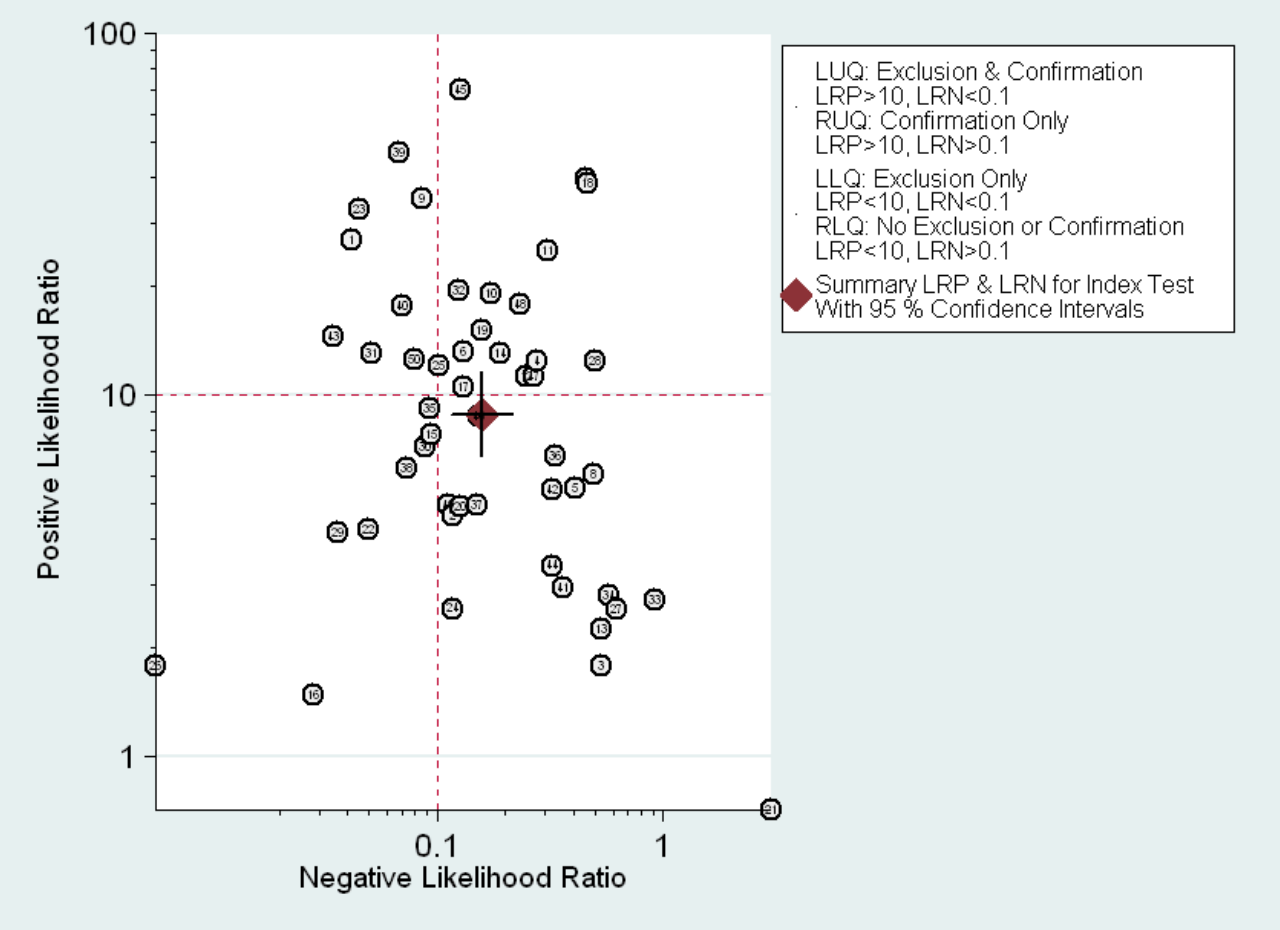


Figure 6. EUS ability to discriminate between T1-T2 and T3-T4 gastric carcinomas. Likelihood ratio (LR) scattergram defining quadrants of informativeness based on desirable thresholds (positive LR>10, negative LR<0.1): left upper quadrant (test suitable both for diagnosis exclusion and confirmation), right upper (confirmation only), left lower (exclusion only), right lower (neither confirmation nor exclusion).



These findings imply that in a hypothetical cohort of 1000 people with gastric carcinoma, EUS would correctly classify 880 of them, but would also over-stage 70 patients by classifying them as T3 - T4 instead of T1 - T2, and under-stage 50 patients by classifying them as T1 - T2 instead of T3 - T4 (see Summary of findings 1).

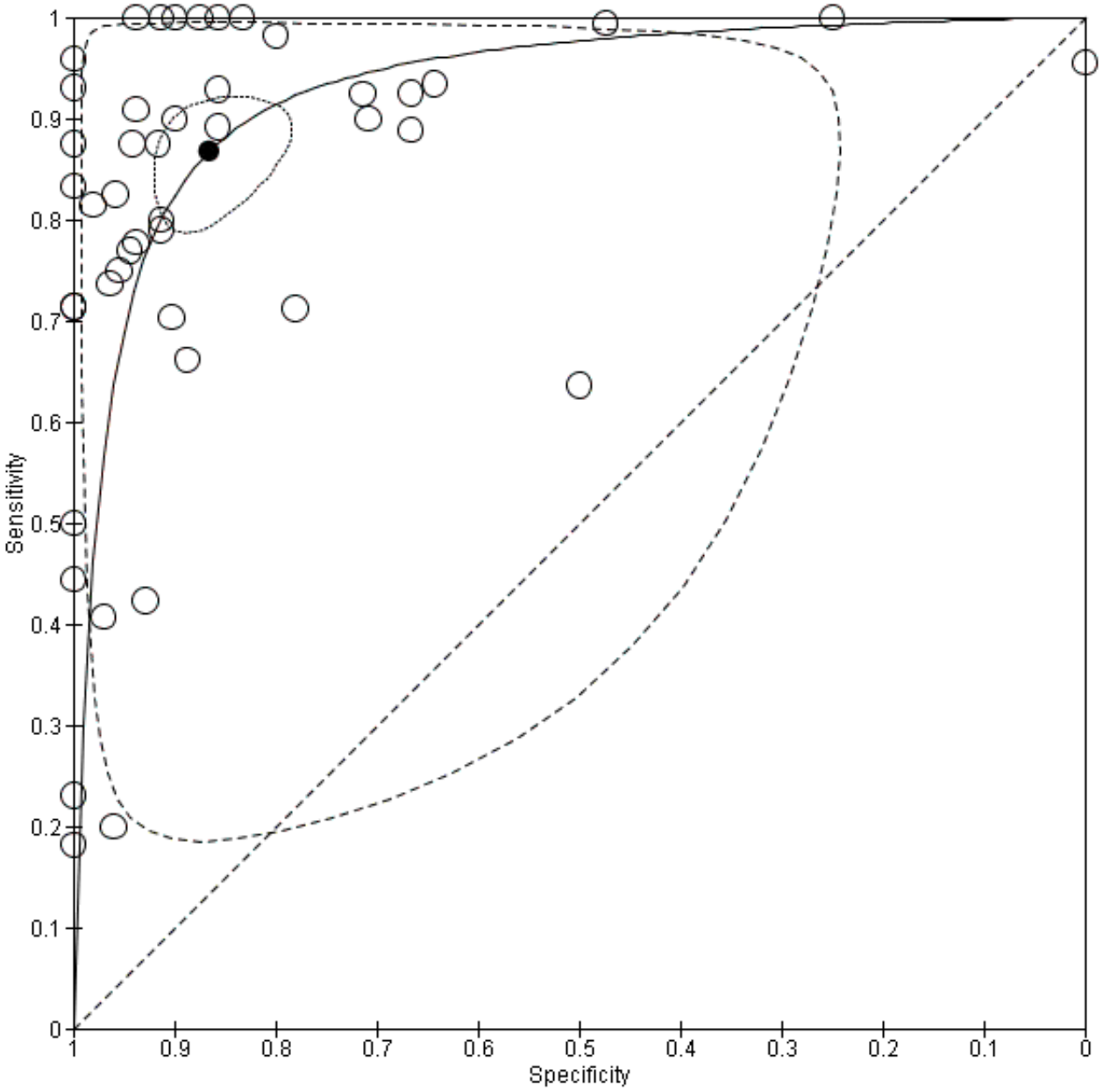
Since the proportion of heterogeneity likely caused by the threshold effect was low (12%), we looked for other sources of heterogeneity. In this regard subgroup analysis (Table 1) demonstrated that publication year has a significant impact on EUS diagnostic performance, since studies conducted before the year 2000 reported on average significantly higher sensitivity (0.91 (95% CI 0.87 to 0.96) versus 0.81 (95% CI 0.75 to 0.88)) and specificity (0.94 (95% CI 0.91 to 0.96) versus 0.88 (95% CI 0.84 to 0.9)). Also the type of EUS array appeared to be correlated with diagnostic performance, with radial array being more accurate than linear array (Table 1); however, only four studies used the latter type of array, which makes it unwise to draw any definitive conclusion on this topic. The other subgroup and sensitivity analyses were not informative.

Regression testing for funnel plot asymmetry (Deeks 2005) showed no evidence of statistically significant small-study effect bias (P = 0.48).

Exclusion of studies with a high risk of bias did not significantly change the above findings (Table 1).

For EUS diagnostic ability to distinguish **T1 (early gastric cancer, EGC) versus T2 (muscle-infiltrating) tumors**, the meta-analysis of 46 studies (n = 2742; Data table 2) (see forest plot and SROC curve in Data table 2 and Figure 7, respectively) showed that the summary sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were 0.85 (95% CI 0.78 to 0.91), 0.90 (95% CI 0.85 to 0.93), 8.5 (95% CI 5.9 to 12.3), 0.17 (95% CI 0.12 to 0.24), and 50 (95% CI 32 to 79), respectively.

Figure 7. Summary ROC Plot of 46 studies investigating the EUS ability to discriminate between T1 versus T2 gastric carcinomas.



Although both summary sensitivity and specificity values were relatively satisfactory, between-study heterogeneity was substantial, as visually assessable through both the forest plot (Data table 2) and predictive ellipse (Figure 7).

The Fagan plot (Figure 8) illustrates that EUS may be clinically useful because it increases the previous probability of being classified as T1 from 70% (average prevalence of T1 cases) to 94% when positive, and it lowers the same probability to 26% when negative. However, the likelihood ratio (LR) scattergram (Figure 9) shows that the summary point of positive and negative LR is located in the lower right quadrant, suggesting that EUS accuracy, although close to ideal values, is not optimal either for disease depth confirmation or exclusion.

Figure 8. Fagan plot estimating how much the result of EUS changes the probability that a patient has a T1 (rather than T2) gastric cancer, considering a given pre-test probability (here the mean pre-test probability found in eligible studies is shown as an example).

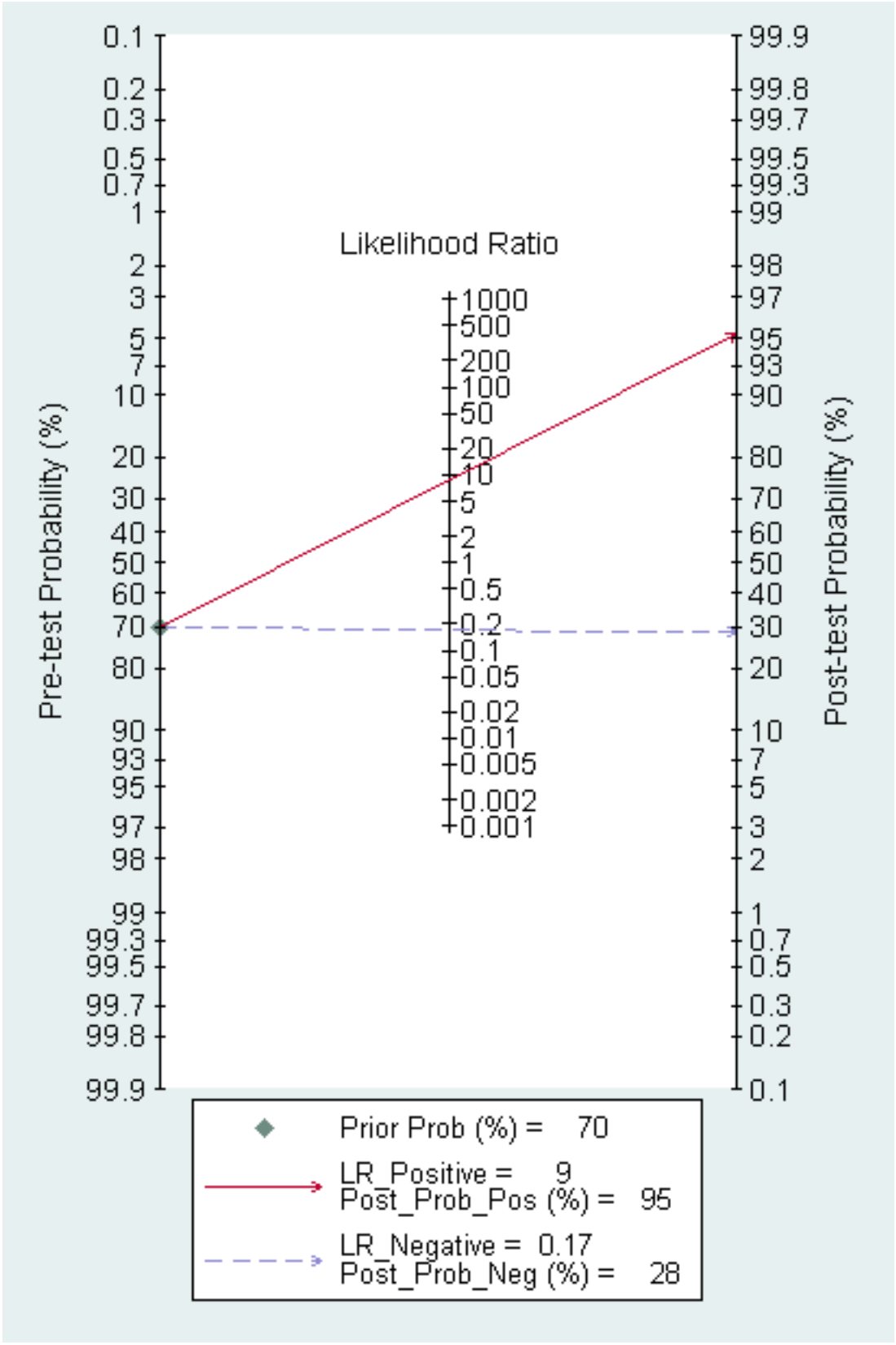
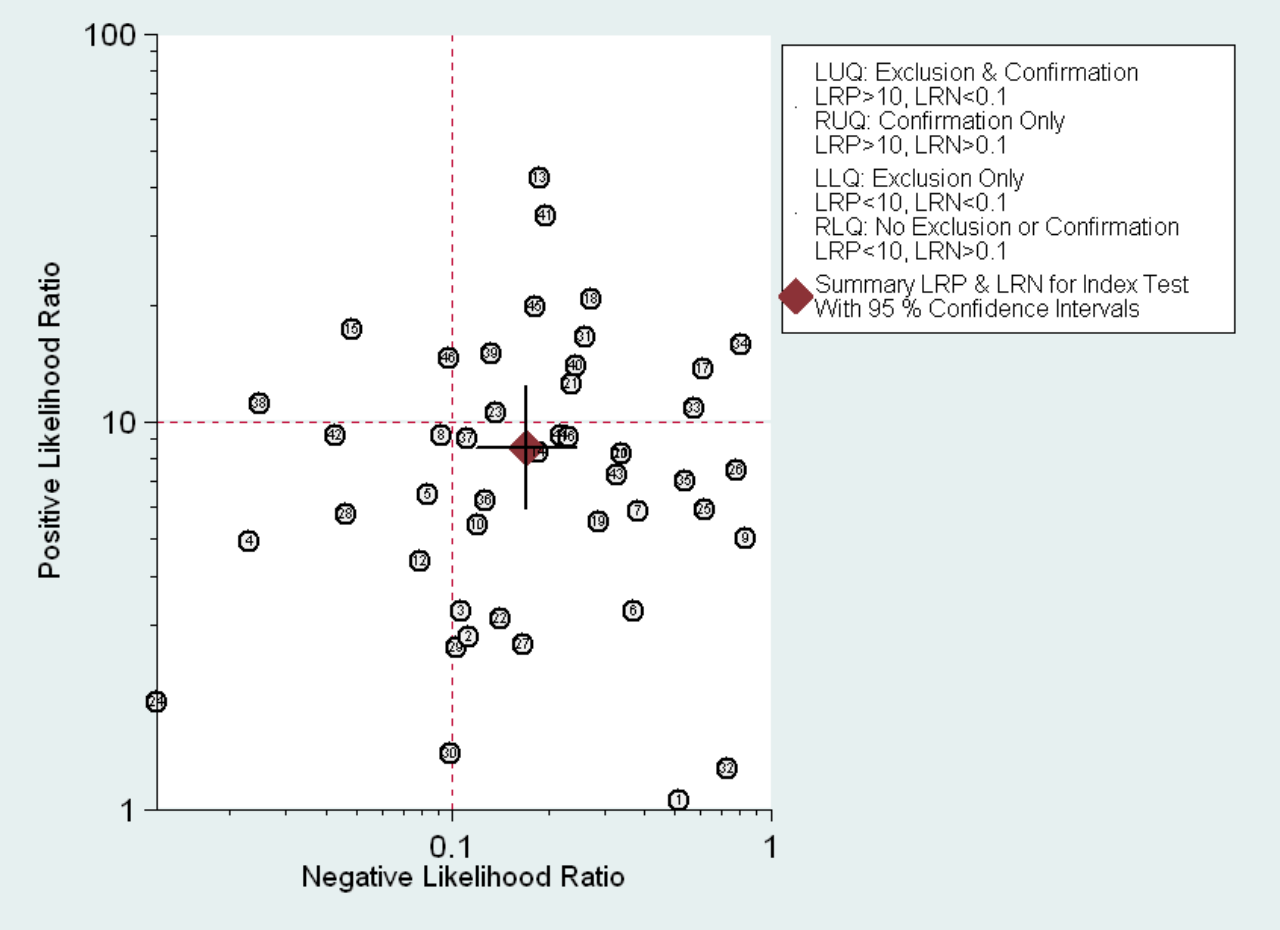


Figure 9. EUS ability to discriminate between T1 and T2 gastric carcinomas. Likelihood ratio (LR) scattergram defining quadrants of informativeness based on desirable thresholds (positive LR>10, negative LR<0.1): left upper quadrant (test suitable both for diagnosis exclusion and confirmation), right upper (confirmation only), left lower (exclusion only), right lower (neither confirmation nor exclusion).



These findings imply that in a hypothetical cohort of 1000 people with gastric carcinoma, EUS would correctly classify 865 of them, but would also over-stage 105 patients by classifying them as T2 instead of T1, and under-stage 30 patients by classifying them as T1 instead of T2 (see Summary of findings 1).

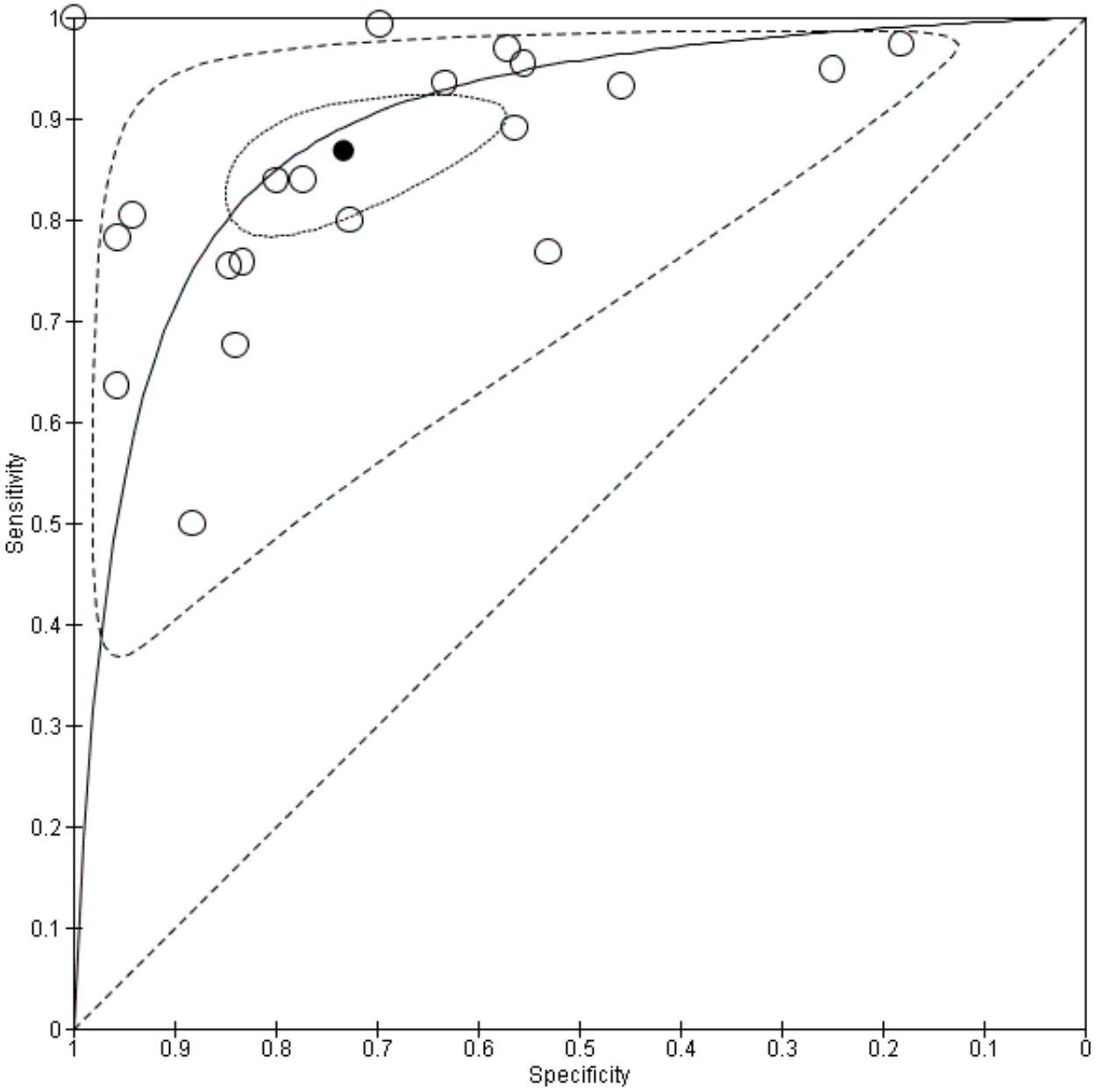
Since the proportion of heterogeneity likely caused by the threshold effect was moderate (30%), we looked for further sources of heterogeneity. Subgroup analysis suggested that sample size, country of origin and type of EUS array might have a (limited) impact on EUS diagnostic performance (Table 2). However, these results are to be interpreted cautiously because of the low number of studies in some comparison groups. The other subgroup and sensitivity analyses were not informative.

Regression testing for funnel plot asymmetry showed no evidence of statistically significant small-study effect bias (P = 0.58).

Exclusion of studies with a high risk of bias did not significantly change the above findings (Table 2).

We then focused on the EUS ability to distinguish between **T1a (mucosal) versus T1b (submucosal) cancers**: the meta-analysis of 20 studies (n = 3321; Data table 3) (see forest plot and SROC curve in Data table 3 and Figure 10, respectively) showed that the summary sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio DOR were 0.87 (95% CI 0.81 to 0.92), 0.75 (95% CI 0.62 to 0.84), 3.4 (95% CI 2.3 to 5.0), 0.17 (95% CI 0.12 to 0.24), and 20 (95% CI 12 to 33), respectively.

Figure 10. Summary ROC Plot of 20 studies investigating the diagnostic ability of EUS to discriminate between T1a versus T1b tumors.



Summary sensitivity (but not specificity) value was relatively high, but between-study heterogeneity was substantial as visually assessable through both the forest plot (Data table 3) and predictive ellipse (Figure 10).

The Fagan plot (Figure 11) illustrates that EUS may be clinically useful because it increases the previous probability of being classified as T1 from 70% (average prevalence of T1a cases) to 88% when positive, and it lowers the same probability to 30% when negative. However, the likelihood ratio (LR) scattergram (Figure 12) shows that the summary point of positive and negative LR is located in the lower right quadrant, suggesting that EUS accuracy is not optimal either for disease depth confirmation or exclusion.

Figure 11. Fagan plot estimating how much the result of EUS changes the probability that a patient has a T1a (rather than T1b) gastric cancer, considering a given pre-test probability (here the mean pre-test probability found in eligible studies is shown as an example).

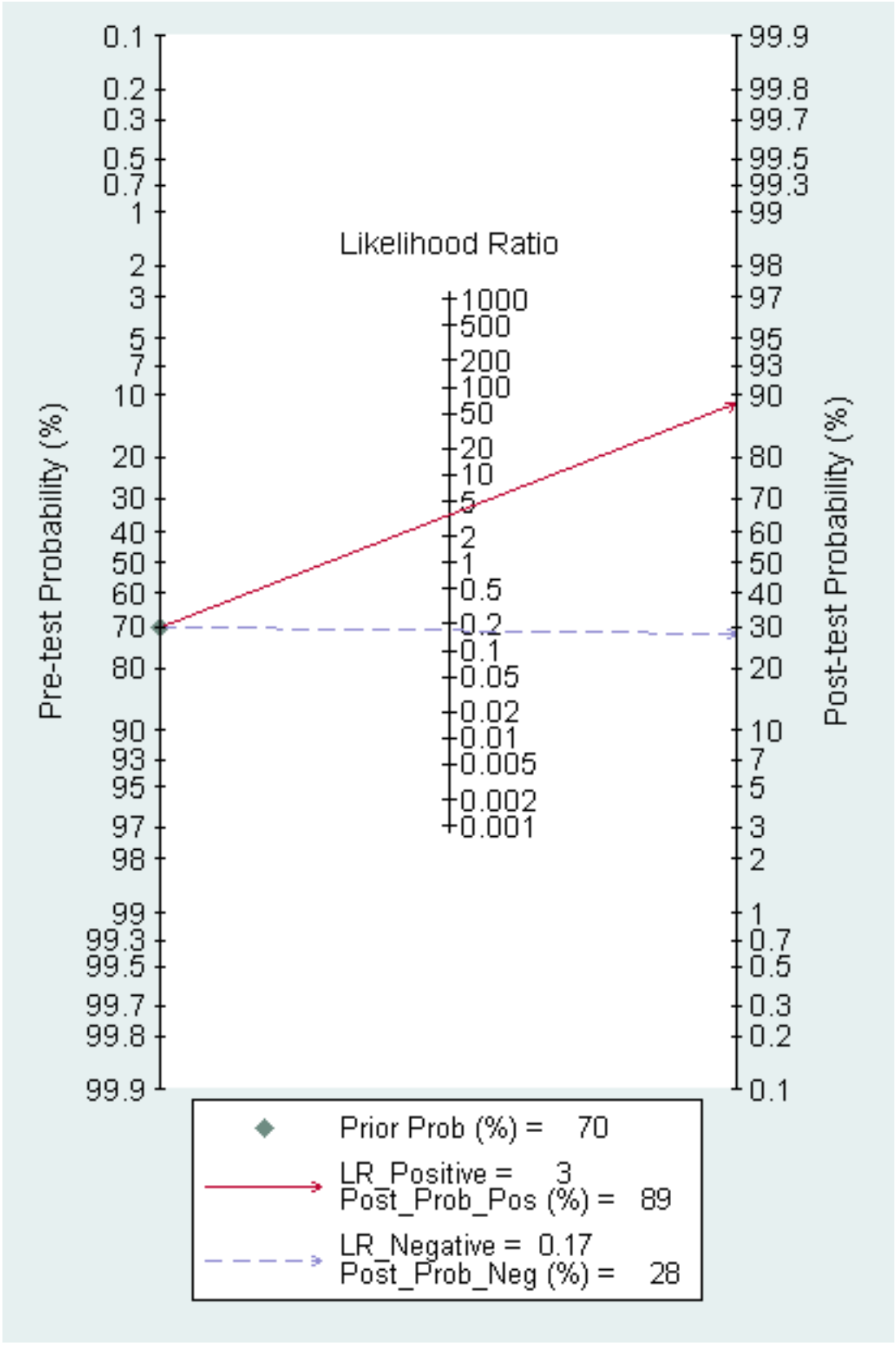
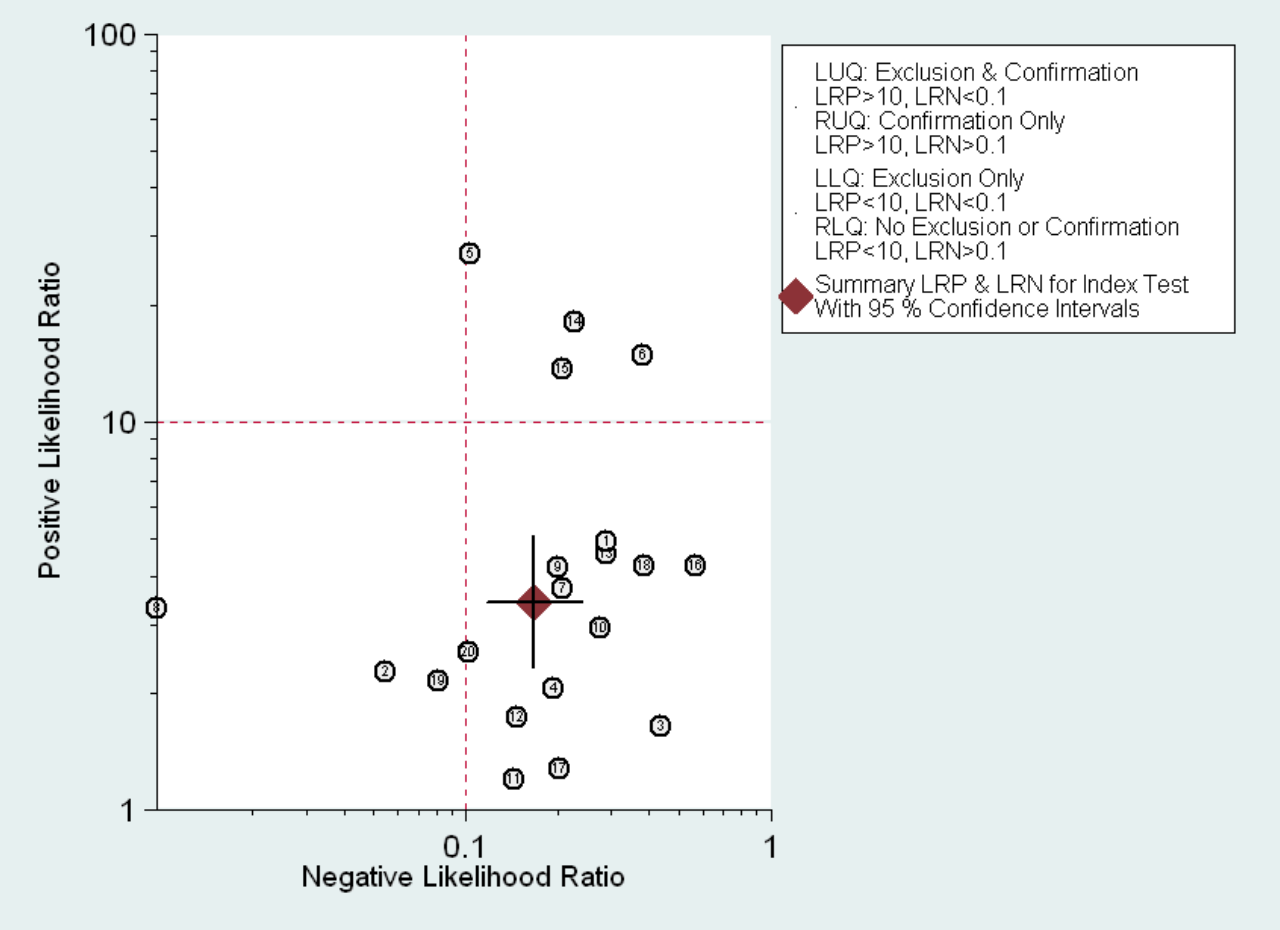


Figure 12. EUS ability to discriminate between T1a and T1b gastric carcinomas. Likelihood ratio (LR) scattergram defining quadrants of informativeness based on desirable thresholds (positive LR>10, negative LR<0.1): left upper quadrant (test suitable both for diagnosis exclusion and confirmation), right upper (confirmation only), left lower (exclusion only), right lower (neither confirmation nor exclusion).



These findings imply that in a hypothetical cohort of 1000 people with gastric carcinoma, EUS would correctly classify 834 of them, but would also over-stage 91 patients by classifying them as T1b instead of T1a, and under-stage 75 patients by classifying them as T1a instead of T1b (see Summary of findings 1).

The proportion of heterogeneity likely caused by the threshold effect was 49%. Subgroup and sensitivity analyses suggested that none of the covariates we considered was associated with between-study heterogeneity (Table 3).

Regression testing for funnel plot asymmetry showed evidence of statistically significant small-study effect bias (P = 0.04).

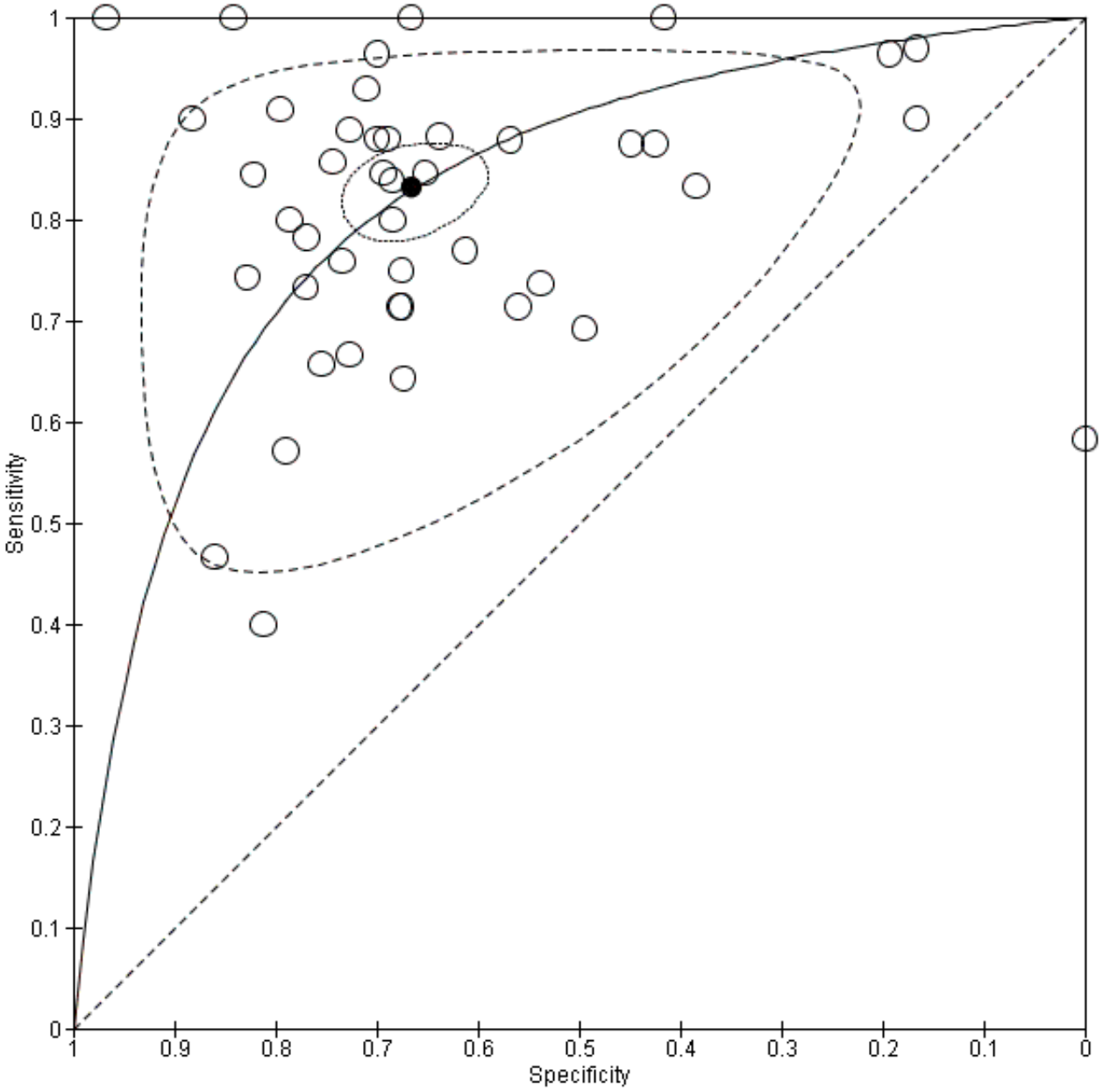
Exclusion of studies with a high risk of bias did not significantly change the above findings (Table 3).

Lymph node status (N-stage)

We then carried out a meta-analysis of the eligible studies reporting data on N-stage (positive versus negative) to evaluate the diagnostic ability of EUS to assess the status of regional lymph nodes in people with gastric carcinoma. Forty-four studies were available, with a total of 3573 patients (Data table 4).

The sensitivity and specificity of each single study are shown in Data table 4. The SROC curve along with the summary point and the 95% confidence and prediction regions are illustrated in Figure 13.

Figure 13. Summary ROC Plot of 44 studies addressing the issue of EUS ability to discriminate between lymph node negative (N0) and positive (N+) cases.



Summary sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were 0.83 (95% CI 0.79 to 0.87), 0.67 (95% CI 0.61 to 0.72), 2.5 (95% CI 2.1 to 2.9), 0.25 (95% CI 0.20 to 0.31), and 10 (95% CI 7 to 13), respectively.

Summary sensitivity (but not specificity) value was relatively high, but between-study heterogeneity was substantial as visually assessable through both the forest plot (Data table 4) and predictive ellipse (Figure 13).

The Fagan plot (Figure 14) shows that EUS may be clinically informative because it increases the previous probability of being classified as N+ from 50% (average prevalence of N+ cases) to 62% when positive, and it lowers the same probability to 14% when negative. However, the likelihood ratio (LR) scattergram (Figure 15) shows that the summary point of positive and negative LR is located in the lower right quadrant, suggesting that EUS accuracy is not optimal either for lymph node metastatic involvement confirmation or exclusion.

Figure 14. Fagan plot estimating how much the result of EUS changes the probability that a patient has a N+ (metastatic lymph nodes) (rather than a N0, disease free lymph nodes) gastric cancer, considering a given pre-test probability (here the mean pre-test probability found in eligible studies is shown as an example).

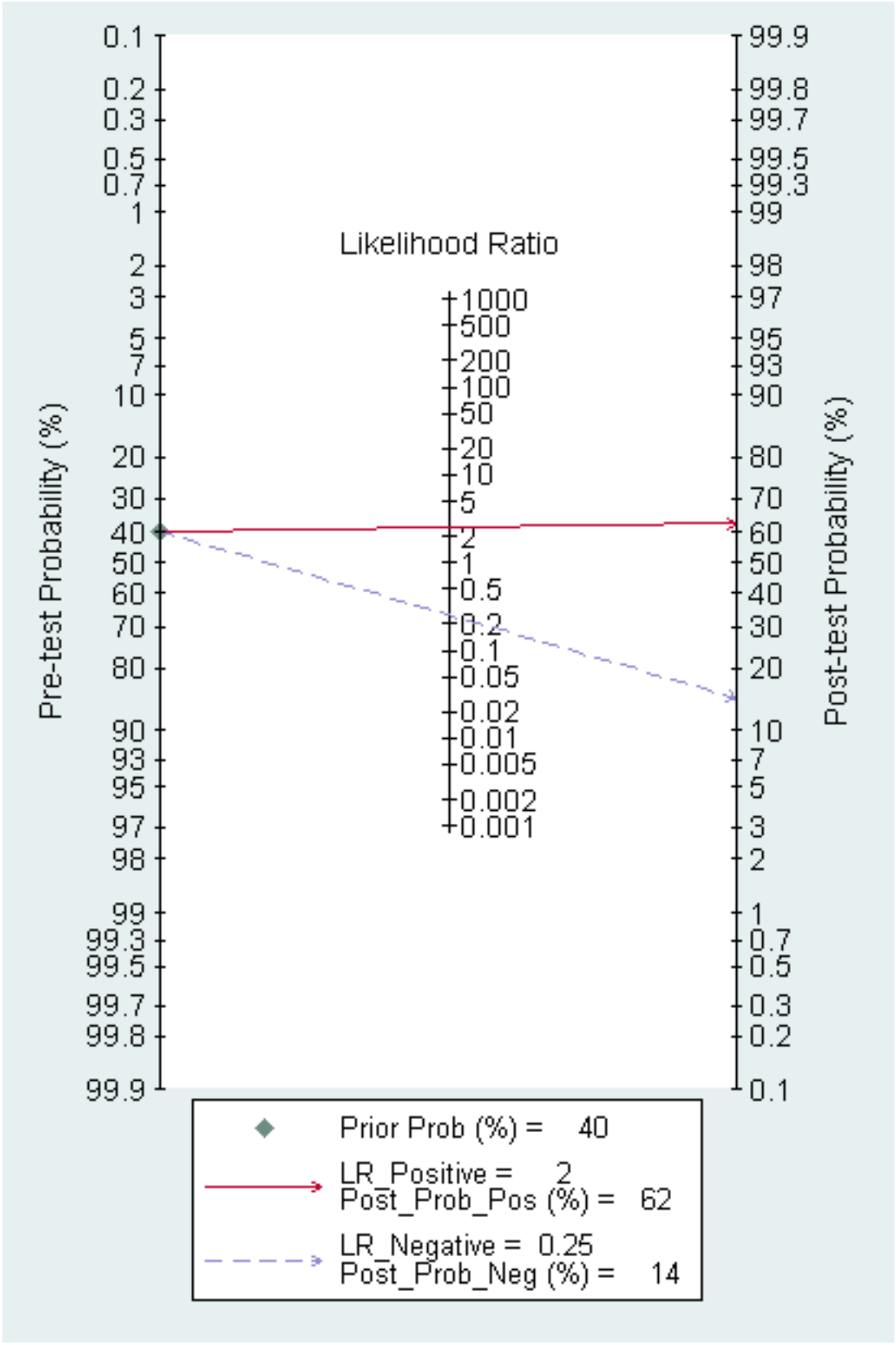
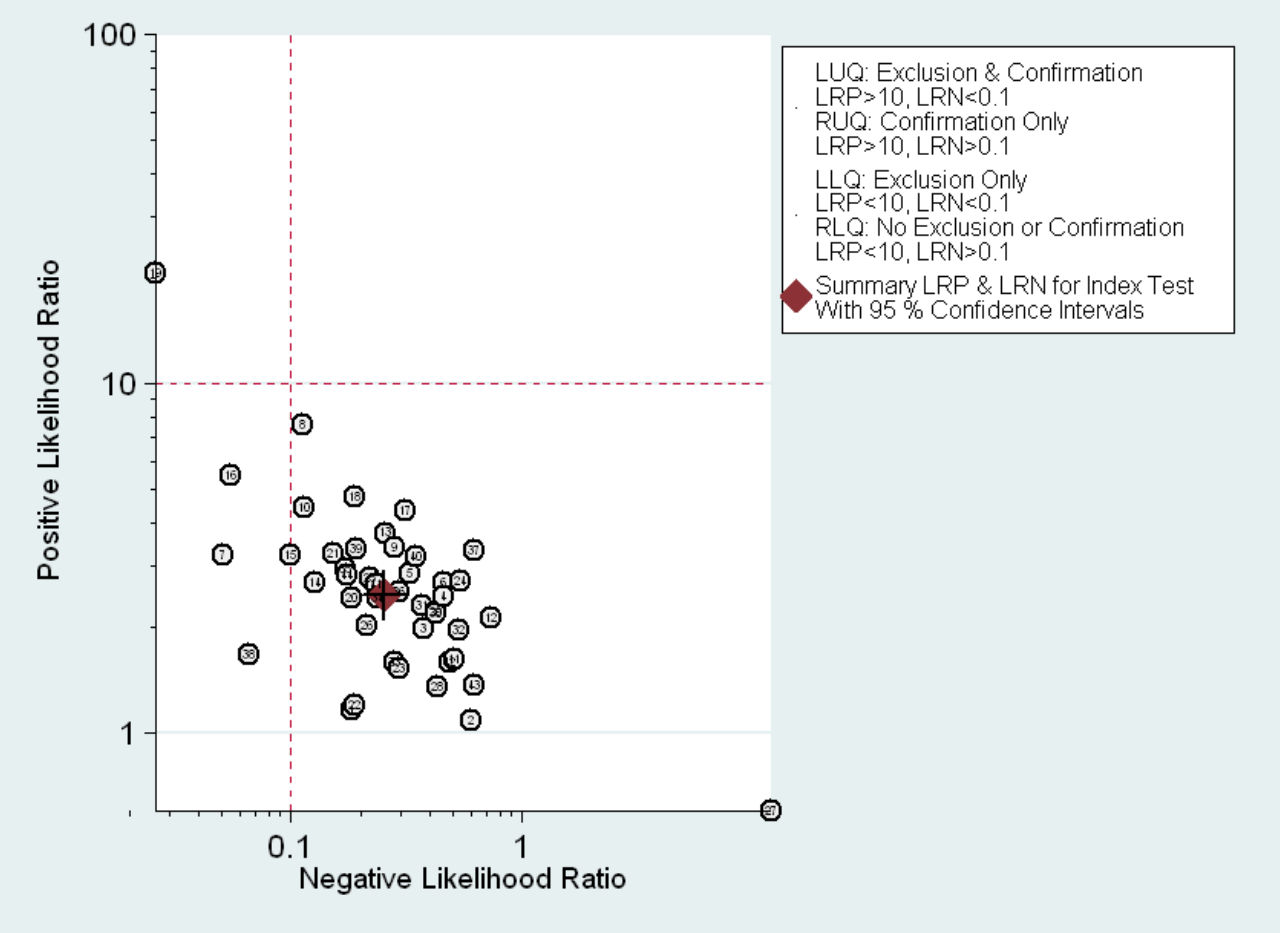


Figure 15. EUS ability to discriminate between N+ (metastatic lymph nodes) and N0 (disease free lymph nodes) gastric carcinomas. Likelihood ratio (LR) scattergram defining quadrants of informativeness based on desirable thresholds (positive LR>10, negative LR<0.1): left upper quadrant (test suitable both for diagnosis exclusion and confirmation), right upper (confirmation only), left lower (exclusion only), right lower (neither confirmation nor exclusion).



These findings imply that in a hypothetical cohort of 1000 people with gastric carcinoma, EUS would correctly classify 750 of them, but would also over-stage 85 patients by classifying them as T1b instead of T1a, and under-stage 165 patients by classifying them as T1a instead of T1b (see Summary of findings 1).

The proportion of heterogeneity likely caused by the threshold effect was moderate (17%). Subgroup and sensitivity analyses (Table 4) suggested that none of the covariates we considered were associated with between-study heterogeneity, although analysis by country of origin was of borderline significance.

Regression testing for funnel plot asymmetry showed no evidence of statistically significant small-study effect bias (P = 0.96).

Exclusion of studies with a high risk of bias did not significantly change the above findings (Table 4).

DISCUSSION

In this systematic review of the diagnostic performance of endoscopic ultrasound (EUS) for the locoregional staging of gastric cancer we collected the data from the largest series of patients ever considered in the international medical literature (n = 7747). Using modern statistical methods specifically dedicated to diagnostic meta-analysis, i.e., the hierarchical bivariate model, we quantitatively summarized the available evidence and found that overall EUS provides clinically useful information regarding gastric cancer locoregional spread. EUS summary sensitivities and specificities ranged from 0.83 to 0.87 and from 0.90 to 0.67 respectively, all significantly higher than the 0.50 'null' value. This means that EUS performs better than the prediction made with a flip of a coin: the 95% confidence intervals of those summary estimates do not in fact cross the 0.50 value, which is the probability value of being 'diseased' (e.g. the probability of having metastatic lymph nodes) assigned to each patient by the flip of a coin (i.e., 50%). This finding is strengthened by the results of the Bayesian analysis (see Fagan plots), which demonstrate that EUS also

performs better than a 'smart observer', that is, one who knows the prevalence of the condition (e.g. percentage of T1 gastric cancers as a proportion of all gastric cancers) and thus would assign this probability value to patients, which would ultimately increase the predictive accuracy compared to the more simplistic flip-of-a-coin approach. Consider the T1 versus T2 setting as an example: if the proportion of T1 tumors is 0.70 (based on previous epidemiological studies), one could use this value to classify patients by assigning to each patient the probability of being T1 equal to the prevalence of the condition (0.70): this would lead to an accuracy of 70% based on the fact that 70% of patients would be correctly identified by randomly classifying 70% of them as T1. This approach would yield a better diagnostic performance compared to the flip-of-a-coin approach, which would assign a 0.50 probability to all patients, and thus would achieve 50% accuracy. Compared to these two approaches, EUS can better discriminate between T1 and T2 cases, since it changes the likelihood of being T1 from 70% to 94% when the test is positive and it lowers the same probability to 26% when tests are negative (overall accuracy: 93%). This could be very helpful for clinicians during the decision-making process of patient therapeutic management.

Critical issues

Despite these favorable findings, some critical aspects must be emphasized to correctly appreciate the limitations of this diagnostic tool.

First, the remarkable heterogeneity of results we found across eligible studies, most of which (50/66, 76%) are retrospective in design, casts some doubts on the reliability and reproducibility of EUS in the locoregional staging of gastric carcinoma. Unfortunately, we did not identify any technical (e.g. EUS probe frequency) or tumor-related (e.g. stomach site) feature that might explain such variability in results reported in the relevant literature, which does not allow us to suggest any strategy that might improve the performance of EUS. Notably, we could not explore the experience of the endoscopist as a source of heterogeneity, as no such information is available in the literature. However, we failed to detect an association between heterogeneity and the sample size (a potential surrogate for the experience of the endoscopy center). The only suspected source of heterogeneity we could identify was the year of publication (better and more homogeneous results in earlier studies), which was especially evident for distinguishing T1 - T2 from T3 - T4 tumors; this finding might be due to a 'first study' effect, i.e. more enthusiasm surrounding the procedure during the first years after its implementation in the clinical setting. However, we cannot rule out the possibility that the diffusion of EUS in clinical practice following the initial encouraging results might have led to the use of this tool by less experienced endoscopists, with an increased probability of less accurate interpretations of the test. Due to the lack of data, we could not explore the effect of other potential sources of heterogeneity, such as primary tumor characteristics, e.g., diameter, morphology (flat versus ulcerated versus vegetant), and experience of the endoscopist; these and other factors therefore remain to be investigated to better define the limits of EUS in the locoregional staging of gastric carcinoma.

Second, not all parameters of diagnostic performance reached ideal values, i.e., values believed to be desirable for the implementation of a diagnostic tool in clinical practice. In particular, the EUS summary specificity for the diagnosis of mucosal (T1a) versus submucosal (T1b) tumors and for the diagnosis of lymph node metastasis (N0 versus N+) was 0.75 and 0.67 respectively, which are below the desirable value of 0.8. Moreover, since the diagnostic ability of a test depends not only on its discriminatory value but also on the prevalence of the disease, we considered the likelihood ratios (LRs) associated with EUS performance, as illustrated in the LR matrices (see Figure 6; Figure 9; Figure 12; Figure 15). EUS showed an acceptable performance for the differentiation of T1 - T2 from T3 - T4 tumors and T1 from T2 tumors, but not for distinguishing T1a from T1b tumors or for diagnosis of lymph node status (N0 versus N+).

Comparison with existing literature

Two systematic reviews (without meta-analysis) and three meta-analyses have been published on this topic between 2007 and 2011. The two reviews, one dedicated to primary tumor depth and the other to lymph node status, concluded that EUS is a reliable imaging modality in staging tumor depth but not for the definition of lymph node status (Kwee 2007; Kwee 2009). These conclusions are similar to those we present here, although our work provides formal evidence to sustain these hypotheses as well as a quantification of the average performance of this endoscopic tool. This information, along with the Bayesian nomograms, enables clinicians to get a precise sense of the risk of making errors, both in terms of false-positive and false-negative predictions, while using EUS, which ultimately can help them optimize the therapeutic management of patients based on statistically-estimated diagnostic accuracy parameters and not on dichotomous personal opinions (i.e. 'works' versus 'does not work') on EUS performance, such as those deriving from qualitative reviews. Between 2001 and 2011, three meta-analyses were also published on both primary tumor depth staging and regional lymph node staging of gastric cancer with EUS (Kelly 2001; Mocellin 2011; Puli 2008). The reliability of the first two articles (Kelly 2001; Puli 2008) is undermined by the use of a statistical method, based on the Moses-Littenberg model, that is no longer considered scientifically sound for the meta-analysis of diagnostic accuracy studies (Harbord 2008; Leeflang 2008; Macaskill 2010; Reitsma 2005; Rutter 2001). Furthermore, the number of included studies (13 and 22 respectively) was much lower than our retrieval rate and analysis (n = 66). The third meta-analysis (Mocellin 2011), which was conducted with modern statistics on 54 studies, reported results slightly better than those described here: this difference might be due to the lower number of studies included in that meta-analysis and is in line with the above-mentioned trend towards better results in earlier series.

In conclusion, by analyzing the data from the largest series ever considered, we found that the diagnostic accuracy of EUS can be considered clinically useful, although not optimal, to guide physicians in the locoregional staging of patients with gastric carcinoma. However, the heterogeneity of the results warrants some caution, as well as further investigation for the identification of factors influencing the outcome of this diagnostic tool. Physicians should also be warned that EUS performance is slightly lower in diagnosing superficial tumors (T1a versus T1b) and lymph node status (positive versus negative).

Summary of main results

The main results of our review, summarized in Summary of findings 1, are the following:

- By analyzing the data from 66 articles published from 1988 through 2012, we collected data on 7747 people with gastric cancer who were staged with endoscopic ultrasonography (EUS): this represents the largest series ever reported on this topic.
- The meta-analysis of 50 studies (n = 4397) showed that the summary sensitivity and specificity of EUS in discriminating T1 - T2 (superficial) versus T3 - T4 (advanced) gastric carcinomas were 0.86 (95% CI 0.81 to 0.90) and 0.90 (95% CI 0.87 to 0.93), respectively.
- For the diagnostic capacity of EUS to distinguish T1 (early gastric cancer, EGC) versus T2 (muscle-infiltrating) tumors, the meta-analysis of 46 studies (n = 2742) showed that the summary sensitivity and specificity were 0.85 (95% CI 0.78 to 0.91) and 0.90 (95% CI 0.85 to 0.93) respectively. When we addressed the capacity to distinguish between T1a (mucosal) versus T1b (submucosal) cancers the meta-analysis of 20 studies (n = 3321) showed that the summary sensitivity and specificity were 0.87 (95% CI 0.81 to 0.92) and 0.75 (95% CI 0.62 to 0.84) respectively.
- For the metastatic involvement of lymph nodes (N-stage), the meta-analysis of 44 studies (n = 3573) showed that the summary sensitivity and specificity were 0.83 (95% CI 0.79 to 0.87) and 0.67 (95% CI 0.61 to 0.72) respectively.
- Overall, EUS accuracy can be considered clinically useful to guide physicians in the locoregional staging of patients with gastric cancer.
- However, between-study heterogeneity was not negligible: unfortunately, we could not identify any consistent source of the observed heterogeneity, and thus all the results presented here must be interpreted cautiously.
- Moreover, the analysis of positive and negative likelihood values revealed that EUS diagnostic performance cannot be considered optimal either for disease confirmation or for exclusion, especially for distinguishing T1a (mucosal) from T1b (submucosal) cancers and positive from negative lymph node status.

Strengths and weaknesses of the review

The main strength of this review is the number of patients enrolled (n = 7747), which is the highest ever reported and guarantees a good representation of the results obtained with this diagnostic tool worldwide. Moreover, we provide not only conventional meta-analysis results, such as summary estimates of diagnostic performance measures, but also findings from additional analyses such as Bayesian analysis, which add further information of clinical use, including Fagan plots and likelihood ratio matrices. The main limitation of this review is that, despite the high number of patients enrolled, heterogeneity is remarkably high, which may partially undermine the reliability and reproducibility of most reported results. Furthermore, the data available in the literature did not allow identification of possible sources of heterogeneity.

Applicability of findings to the review question

The number of studies identified (66) and the number of patients enrolled (7747) were sufficient to address the review question, i.e., quantification of EUS diagnostic performance in the locoregional staging of gastric carcinoma. Patients enrolled, technical features of both index test and reference standard, and clinical settings were homogeneously suitable for our analysis across all studies. As expected in diagnostic test accuracy meta-analysis, heterogeneity was a problem: unfortunately, we could not identify consistent sources of heterogeneity, which did not allow us to suggest factors potentially influencing the performance of this diagnostic tool.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings partly support the use of endoscopic ultrasonography (EUS) for the locoregional staging of people with gastric carcinoma. EUS diagnostic performance, although not optimal, may be considered clinically useful to guide physicians in disease staging and thus in the development of the most appropriate therapeutic strategy on an individual-patient basis, according to personalized medicine principles. However, physicians should be warned that EUS performance is lower in diagnosing superficial tumors (T1a versus T1b) and lymph node status (positive versus negative). The remarkable heterogeneity of the evidence currently available warrants some caution in interpreting the present results. Overall, we observed considerable heterogeneity and its sources need to be understood before any definitive conclusion can be drawn about the use of EUS can be proposed in a routine clinical setting.

Implications for research

The valid but suboptimal diagnostic accuracy of EUS for the locoregional staging of gastric cancer, with special regard to the diagnosis of superficial T1 tumors and lymph node status, prompts further investigation to improve the performance of this tool, especially for the diagnosis of superficial tumors (T1a versus T1b) and lymph node status (positive versus negative). Technological improvements, such as the combination of EUS with fine needle aspiration of suspicious lymph nodes (Dumonceau 2011), may lead to the optimization of gastric cancer staging, which should ultimately ameliorate the therapeutic management of these patients. It will also be important to compare the diagnostic performance of different tools (e.g., EUS, CT, MRI) and to investigate the diagnostic potential of combining these tools in order to optimize disease staging and ultimately to personalize patient treatment.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahn 2009

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 71. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T3 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 5 mm)		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 (67/71) vs T2, 2) N0 (65/71) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No uninterpretable findings reported		
Comparative			
Notes	Country: Korea Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Ahn 2009 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Akahoshi 1991

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 74. Age: 17 - 85 yrs. Gender: 49 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (61/74) vs T3 - T4, 2) T1 (40/59) vs T2 Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice
Methodological quality	

Akahoshi 1991 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Akahoshi 1998

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 73. Age: 36 - 84 yrs. Gender: 55 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 - T2, N0/N+ and T1a - T1b cases enrolled

Akahoshi 1998 *(Continued)*

Index tests	Index test: EUS; array: radial; frequency (MHz): 15; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 (66/73) vs T2, 2) N0 (40/46) vs N+, 3) T1a (53/61) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection for T1 cases) Reference and index test completely independent
Flow and timing	Information on all target conditions was not available for all cases No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**

Akahoshi 1998 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
		Unclear

Akashi 2006

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 267. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 - T4 and T1a - T1b cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 12 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 (237/267) vs T2, 2) T1a (164/237) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection for T1 cases) Reference and index test completely independent		
Flow and timing	No withdrawal reported 37 undefined cases reported (as defined by EUS) All cases verified by reference standard test		
Comparative			
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Akashi 2006 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Ang 2006

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 57. Age: 23 - 85 yrs. Gender: 54 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Representative spectrum? YesT1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: unreported; criterion for N-stage definition: lymph node size (> 1 cm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (21/57) vs T3 - T4, 2) T1 (14/19) vs T2, 3) N0 (26/57) vs N+ Reference standard: pathology evaluation of surgical specimen

Ang 2006 *(Continued)*

	Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Singapore Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Ang 2006 *(Continued)*

		Unclear	

Arocena 2006

Study characteristics			
Patient sampling	Prospective study		
Patient characteristics and setting	Sample size: 17. Age: 56 - 81 yrs. Gender: 14 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: unreported; frequency (MHz): 12.5; criterion for T-stage definition: unreported; criterion for N-stage definition: lymph node morphology and size (> 5 mm)		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (9/17) vs T3 - T4, 2) N0 (6/17) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Spain Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			

Arocena 2006 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Barbour 2007

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 206. Age: 25 - 85 yrs. Gender: 173 men Patients diagnosed with gastric cancer (cardia region) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled (cardia region of the stomach)
Index tests	Index test: EUS; array: unreported; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 1 cm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (100/184) vs T3 - T4, 2) T1 (55/74) vs T2, 3) N0 (112/206) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test

Barbour 2007 *(Continued)*

Comparative	
Notes	Country: USA Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Bentrem 2007

Study characteristics			
Patient sampling	Prospective study		
Patient characteristics and setting	Sample size: 218. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: unreported; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (133/211) vs T3 - T4, 2) T1 (54/85) vs T2, 3) N0 (108/218) vs N+ Reference standard: pathology evaluation of surgical specimen Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: USA Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			

Bentrem 2007 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Bhandari 2004

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 48. Age: 27 - 81 yrs. Gender: 40 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: unreported; criterion for N-stage definition: unreported
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (33/48) vs T3 - T4, 2) T1 (28/29) vs T2, 3) N0 (28/48) vs N+ Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection for T1 cases) Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Korea Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice
Methodological quality	

Bhandari 2004 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Blackshaw 2008

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 44. Age: 48 - 79 yrs. Gender: 38 men Patients diagnosed with gastric cancer (cardia region) and undergoing surgery

Blackshaw 2008 *(Continued)*

	Spectrum: T1 - T4 and N0/N+ cases enrolled (cardia region of the stomach)
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 6 mm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (9/44) vs T3 - T4, 2) N0 (10/44) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: UK Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**

Blackshaw 2008 *(Continued)*

DOMAIN 4: Flow and Timing	
Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Unclear

Bohle 2011

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 62. Age: 63 yrs. Gender: 48 men Patients diagnosed with gastric cancer and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 10 mm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (40/62) vs T3 - T4, 2) T1 (15/40) vs T2, 3) N0 (23/62) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Bohle 2011 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Botet 1991

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 50. Age: 33 - 81 yrs. Gender: 26 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Representative spectrum? YesT1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (12/50) vs T3 - T4, 2) T1 (4/11) vs T2; 3) N0 (11/50) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent

Botet 1991 *(Continued)*

Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: USA Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Caletti 1993

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 35. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (12/35) vs T3 - T4, 2) T1 (5/10) vs T2; 3) N0 (7/32) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Italy Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Caletti 1993 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Cerizzi 1991

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 21. Age (mean): 63. Gender: 12 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: linear; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (4/21) vs T3 - T4, 2) N0 (5/21) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Italy Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Cerizzi 1991 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Chen 2002

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 57. Age: 32 - 82 yrs. Gender: 36 men Patients diagnosed with gastric cancer (any site) and undergoing surgery

Chen 2002 *(Continued)*

	Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: unreported; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (13/57) vs T3 - T4, 2) T1 (7/10) vs T2, 3) N0 (15/57) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Taiwan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**

Chen 2002 *(Continued)*

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Choi 2010

Study characteristics			
Patient sampling	Prospective study		
Patient characteristics and setting	Sample size: 930. Age (mean): 60 yrs. Gender: 658 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (487/930) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Korea Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Choi 2010 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

De Manzoni 1999

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 29. Age (mean): 65 yrs. Gender: unreported Patients diagnosed with gastric cancer (cardia region) and undergoing surgery Spectrum: T1 - 4 and N0/N+ cases only enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (18/29) vs T3 - T4, 2) N0 (5/29) vs N+ Reference standard: pathology evaluation of surgical specimen or endoscopic mucosal resection

De Manzoni 1999 *(Continued)*

	Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Italy Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

De Manzoni 1999 *(Continued)*

	Unclear

Dittler 1993

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 254. Age: 28 - 79. Gender: 165 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): unreported; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (79/254) vs T3 - T4, 2) T1 (27/65) vs T2, 3) N0 (71/254) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Dittler 1993 *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

François 1996

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 29. Age: 38 - 84 yrs. Gender: 24 men Patients diagnosed with gastric cancer (cardia region) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled (cardia region of the stomach)
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (12/29) vs T3 - T4; 2) T1 (8/11) vs T2; 3) N0 (10/29) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: France

François 1996 *(Continued)*

	Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Furukawa 2011

Study characteristics	
Patient sampling	Retrospective study

Furukawa 2011 *(Continued)*

Patient characteristics and setting	Sample size: 175. Age (mean): 66 yrs. Gender: 133 men Patients diagnosed with gastric cancer and undergoing surgery or endoscopic mucosal resection Patients with T1 - T4 tumors enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (143/175) vs T3 - T4; 2) T1 (126/143) vs T2 Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Furukawa 2011 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Ganpathi 2006

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 102. Age (mean): 63 yrs. Gender: 72 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 1 cm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (42/102) vs T3 - T4, 2) T1 (18/37) vs T2, 3) N0 (35/99) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawals reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Singapore Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Ganpathi 2006 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Garlipp 2011

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 165. Age (mean): 65 yrs. Gender: 123 men Patients diagnosed with gastric cancer (any site) and undergoing surgery T1 - T4 cases enrolled
Index tests	Index test: EUS; array: unreported; frequency (MHz): unreported; criterion for T-stage definition: unreported

Garlipp 2011 *(Continued)*

Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (51/165) vs T3 - T4, 2) T1 (23/51) vs T2 Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Quality: many missing data Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			

Garlipp 2011 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Grimm 1993

Study characteristics			
Patient sampling	Prospective study		
Patient characteristics and setting	Sample size: 148. Age (mean): 61 yrs. Gender: 122 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (94/147) vs T3 - T4, 2) T1 (37/80) vs T2, 3) N0 (58/148) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Grimm 1993 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Habermann 2004

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 51. Age: 47 - 76 yrs. Gender: 34 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T2 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 8 mm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (29/51) vs T3 - T4, 2) N0 (19/50) vs N+ Reference standard: pathology evaluation of surgical specimen

Habermann 2004 *(Continued)*

	Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Habermann 2004 *(Continued)*

	Low

Hamada 1997

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 149. Age: 17 - 84 yrs. Gender: 102 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Sprectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) N0 (102/149) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Hamada 1997 *(Continued)*

		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Heye 2009

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 14. Age: 47 - 87 yrs. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery T1 - T4 cases enrolled (no data on lymph node status reported)
Index tests	Index test: EUS; array: unreported; frequency (MHz): unreported; criterion for T-stage definition: unreported
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (11/14) vs T3 - T4, 2) T1 (1/7) vs T2 Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Quality: many data unreported

Heye 2009 *(Continued)*

	Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Hizawa 2002

Study characteristics			
Patient sampling	Retrospective study		

Hizawa 2002 *(Continued)*

Patient characteristics and setting	Sample size: 227. Age: 17 - 84 yrs. Gender: 102 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection T1a - T1b cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 12 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (165/220) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent
Flow and timing	No withdrawal reported 7 uninterpretable cases reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Hizawa 2002 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Hwang 2010

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 277. Age (mean): 53 yrs. Gender: 171 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 5 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node size (> 8 mm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (252/277) vs T3 - T4, 2) T1 (180/233) vs T2, 3) N0 (164/247) vs N+ Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection for T1 cases) Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Korea Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Hwang 2010 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Hünerbein 1998

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 22. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled

Hünerbein 1998 *(Continued)*

Index tests	Index test: EUS; array: radial; frequency (MHz): 12.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (12/22) vs T3 - T4, 2) T1 (7/12) vs T2, 3) N0 (9/20) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Hünerbein 1998 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Hünerbein 2004

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 49. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 - T4 cases enrolled (no data on lymph node status)		
Index tests	Index test: EUS; array: radial; frequency (MHz): 12.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (33/49) vs T3 - T4, 2) T1 (18/33) vs T2, 3) T1a (4/14) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Hünerbein 2004 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Javaid 2004

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 112. Age: 35 - 75 yrs. Gender: 60 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (32/112) vs T3 - T4, 2) T1 (8/29) vs T2, 3) N0 (32/112) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent

Javaid 2004 *(Continued)*

Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: India Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Kim 2007

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 206. Age (mean): 57 yrs. Gender: 79 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 - T4 cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (199/206) vs T3 - T4, 2) T1 (180/199) vs T2, 3) T1a (110/180) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Korea Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Kim 2007 *(Continued)*

		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Kim 2010

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 169. Age: 32 - 82 yrs. Gender: 122 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1a - T1b cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (125/169) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Korea Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Kim 2010 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Kutup 2012

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 123. Age (mean): 61 yrs. Gender: 78 men Patients diagnosed with gastric cancer (any site) and undergoing surgery

Kutup 2012 *(Continued)*

	Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 5 mm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (82/123) vs T3 - T4, 2) T1 (26/82) vs T2, 3) N0 (42/123) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**

Kutup 2012 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
		Unclear

Lok 2008

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 75. Age (mean): 67 yrs. Gender (M:F): 3:1 Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 12 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (27/75) vs T3 - T4, 2) T1 (8/14) vs T2, 3) N0 (26/75) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Hong Kong Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Lok 2008 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Mancino 2000

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 79. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (36/79) vs T3 - T4, 2) T1 (27/35) vs T2, 3) N0 (33/77) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent

Mancino 2000 *(Continued)*

Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Italy Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Massari 1996

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 65. Age: 24 - 79 yrs. Gender: 53 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (26/65) vs T3 - T4, 2) T1 (12/26) vs T2, 3) N0 (12/65) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Italy Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Massari 1996 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Mouri 2009

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 222. Age (mean): 66 yrs. Gender: 174 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1a - T1b cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 12 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (148/191) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent
Flow and timing	No withdrawal reported 31 uninterpretable cases reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice
Methodological quality	

Mouri 2009 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Murata 1988

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 146. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery

Murata 1988 *(Continued)*

	Spectrum: T1 - T4 cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 10; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (105/146) vs T3 - T4; 2) T1 (88/100) vs T2; 3) T1a (55/85) vs T1b Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**

Murata 1988 *(Continued)*

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Nakamura 1999a

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 31. Age (mean): 61 yrs. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T2 cases enrolled		
Index tests	Index test: EUS; array: unreported; frequency (MHz): unreported; criterion for N-stage definition: lymph node morphology		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) N0 (18/31) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Nakamura 1999a *(Continued)*

		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Nomura 1999

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 30. Age (mean): 58 yrs. Gender: 24 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 - T4 cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (20/30) vs T3 - T4; 2) T1 (16/20) vs T2; 3) T1a (5/16) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent

Nomura 1999 *(Continued)*

Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Ohashi 1999

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 30. Age (mean): 58 yrs. Gender: 24 men Patients diagnosed with gastric cancer (any site) and undergoing endoscopic mucosal resection Spectrum: T1 cases only enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a vs T1b Reference standard: pathology evaluation of endoscopic mucosal resection Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Ohashi 1999 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Okada 2011

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 526. Age (mean): 67 yrs. Gender: 385 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (369/526) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice
Methodological quality	

Okada 2011 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Okamura 1999

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 41. Age: unreported. Gender: 34 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1 cases enrolled

Okamura 1999 *(Continued)*

Index tests	Index test: EUS; array: radial; frequency (MHz): 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (29/41) vs T1b Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Okamura 1999 *(Continued)*

Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Low

Park 2008

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 40. Age: 36 - 70 yrs. Gender: 30 men Patients diagnosed with gastric cancer (any site) and undergoing preoperative neoadjuvant chemotherapy followed by surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (17/40) vs T3 - T4, 2) N0 (7/38) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No no withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Korea All patients underwent preoperative neoadjuvant chemotherapy Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Park 2008 *(Continued)*

		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Pedrazzani 2005

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 51. Age: 27 - 84 yrs. Gender (M:F): 6:1 Patients diagnosed with gastric cancer (cardia only) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled (cardia region of the stomach)
Index tests	Index test: EUS; array: linear; frequency (MHz): 7.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (30/51) vs T3 - T4, 2) T1 (8/16) vs T2, 3) N0 (14/51) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent

Pedrazzani 2005 *(Continued)*

Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Italy Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Perng 1996

Study characteristics			
Patient sampling	Prospective study		
Patient characteristics and setting	Sample size: 76. Age: 28 - 72 yrs. Gender: 40 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node size (> 1 cm)		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (36/76) vs T3 - T4, 2) T1 (21/33) vs T2, 3) N0 (32/69) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Taiwan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Perng 1996 *(Continued)*

		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Polkowski 2004

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 88. Age (mean): 63 yrs. Gender: 56 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node size (> 8 mm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (20/88) vs T3 - T4, 2) T1 (9/14) vs T2, 3) N0 (14/60) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Poland

Polkowski 2004 *(Continued)*

	Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Potrc 2006

Study characteristics	
Patient sampling	Prospective study

Potrc 2006 *(Continued)*

Patient characteristics and setting	Sample size: 82. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: unreported; criterion for N-stage definition: unreported
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (48/82) vs T3 - T4, 2) T1 (11/42) vs T2, 3) N0 (24/82) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Slovenia Quality: Many data unreported Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Potrc 2006 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Repiso 2010

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 36. Age: 36 - 81. Gender: 32 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology and size (> 1 cm)		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (16/36) vs T3 - T4, 2) T1 (10/15) vs T2, 3) N0 (13/36) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Spain Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			

Repiso 2010 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Saito 1991

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 110. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall

Saito 1991 *(Continued)*

Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (60/110) vs T3 - T4, 2) T1 (45/56) vs T2, 3) T1a (22/41) vs T1b Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Saito 1991 *(Continued)*

Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Shimizu 1994

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 128. Age: unreported. Gender: unreported Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 cases enrolled		
Index tests	Index test: EUS; array: unreported; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (90/128) vs T3 - T4, 2) T1 (77/84) vs T2, 3) T1a (45/71) vs T1b Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**

Shimizu 1994 *(Continued)*

DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Shimoyama 2004

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 45. Age: 37 - 89. Gender: 37 men Patients diagnosed with gastric cancer (cardia only) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled (cardia region of the stomach)
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage positivity: EUS-based 5-layer structure of gastric wall; criterion for N-stage positivity: lymph node morphology and size (> 1 cm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (37/45) vs T3 - T4, 2) T1 (21/27) vs T2, 3) N0 (25/45) vs N+, 4) T1a (4/17) vs T1b Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported

Shimoyama 2004 *(Continued)*

	All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Tan 2007

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 63. Age: 29 - 75 yrs. Gender: 37 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (25/63) vs T3 - T4, 2) T1 (7/18) vs T2, 3) N0 (25/63) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: China Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			

Tan 2007 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		Unclear	

Tio 1989

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 80. Age: 13 - 87 yrs. Gender: 51 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (31/76) vs T3 - T4, 2) T1 (13/30) vs T2, 3) N0 (30/80) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Netherlands Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice
Methodological quality	

Tio 1989 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Tsendsuren 2006

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 41. Age: 28 - 80 yrs. Gender: 29 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled

Tsendsuren 2006 *(Continued)*

Index tests	Index test: EUS; array: linear; frequency (MHz): 5 - 7.5; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node shape
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (32/41) vs T3 - T4, 2) T1 (12/24) vs T2, 3) N0 (17/41) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: China Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Tsendsuren 2006 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Tseng 2000

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 74. Age: 26 - 83 yrs. Gender: 40 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node size (> 1 cm)		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (35/74) vs T3 - T4, 2) T1 (12/31) vs T2, 3) N0 (35/74) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Taiwan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Tseng 2000 *(Continued)*

		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Wang 1998

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 119. Age: 26 - 82 yrs. Gender: 75 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node size (> 1 cm)
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (58/119) vs T3 - T4, 2) T1 (27/50) vs T2, 3) N0 (45/119) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent

Wang 1998 *(Continued)*

Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Taiwan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Willis 2000

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 116. Age: 33 - 86 yrs. Gender: 72 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (56/116) vs T3 - T4, 2) T1 (10/42) vs T2, 3) N0 (62/116) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Willis 2000 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Xi 2003

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 32. Age: 28 - 78 yrs. Gender: 25 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: unreported; criterion for N-stage definition: unreported
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (9/32) vs T3 - T4, 2) N0 (19/32) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: China Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice
Methodological quality	

Xi 2003 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Yamamoto 2012

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 75. Age: 41 - 86 yrs. Gender: 62 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection

Yamamoto 2012 *(Continued)*

	Spectrum: T1 cases only enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 12 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (59/75) vs T1b Reference standard: pathology evaluation of surgical specimen or endoscopic mucosal resection Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**

Yamamoto 2012 *(Continued)*

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Yanai 1997

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 100. Age: 31 - 87 yrs. Gender: 76 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1a - T1b cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (71/96) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent		
Flow and timing	No withdrawal reported 4 uninterpretable cases reported (as defined by EUS) All cases verified by reference standard test		
Comparative			
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Yanai 1997 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
		Unclear	

Yanai 1999

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 49. Age: 32 - 81 yrs. Gender: 40 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1a - T1b cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (22/49) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent

Yanai 1999 *(Continued)*

Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Yoshida 2005

Study characteristics			
Patient sampling	Retrospective study		
Patient characteristics and setting	Sample size: 293. Age: 38 - 91 yrs. Gender: 222 men Patients diagnosed with gastric cancer (any site) and undergoing surgery or endoscopic mucosal resection Spectrum: T1a - T1b cases enrolled		
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 20; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall		
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1a (263/293) vs T1b Reference standard: pathology evaluation of surgical specimen (or endoscopic mucosal resection) Reference and index test completely independent		
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test		
Comparative			
Notes	Country: Japan Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**

Yoshida 2005 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Zheng 2011

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 165. Age (mean): 58 yrs. Gender: 127 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled
Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage definition: EUS-based 5-layer structure of gastric wall; criterion for N-stage definition: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (91/162) vs T3 - T4, 2) T1 (42/91) vs T2, 3) N0 (65/162) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: China Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice
Methodological quality	

Zheng 2011 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Unclear	

Ziegler 1993

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 108. Age: 29 - 82 yrs. Gender: 58 men Patients diagnosed with gastric cancer (any site) and undergoing surgery Spectrum: T1 - T4 and N0/N+ cases enrolled

Ziegler 1993 *(Continued)*

Index tests	Index test: EUS; array: radial; frequency (MHz): 7.5 - 12; criterion for T-stage positivity: EUS-based 5-layer structure of gastric wall; criterion for N-stage positivity: lymph node morphology
Target condition and reference standard(s)	Target conditions: gastric carcinoma 1) T1 - T2 (54/108) vs T3 - T4, 2) T1 (22/50) vs T2, 3) N0 (50/108) vs N+ Reference standard: pathology evaluation of surgical specimen Reference and index test completely independent
Flow and timing	No withdrawal reported No uninterpretable findings reported All cases verified by reference standard test
Comparative	
Notes	Country: Germany Relevant clinical information: same clinical data available for test results interpretation as those available when test used in practice

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
		Low	**Low**
DOMAIN 2: Index Test All tests			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
		Low	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			

Ziegler 1993 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Unclear
Did all patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
	Unclear

EUS: endoscopic ultrasound

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abe 1993	Review article (no original data)
Aibe 1986	Article in Japanese
Aibe 1992	No raw data reported (no data necessary for building 2x2 classification tables)
Ajani 2004	EUS performed before neoadjuvant chemotherapy (EUS used to assess response to therapy, not to stage gastric cancer)
Akahoshi 1992	Overlapping with Akahoshi 1991
Akahoshi 1997	Overlapping with Akahoshi 1998
Asaki 1989	The article reports on EUS combined with submucosography (no data on EUS alone)
Bösing 2003	Article in German
Chen 2004	No stomach specific data (miscellany of esophageal and gastric cancer)
Chen 2010	Article in Chinese on contrast enhanced EUS (no data on EUS alone)
Davies 2006	No raw data reported (no data necessary for building 2 x 2 classification tables)
Dewitt 2005	No separate data (mixed esophageal and gastric cancer data)
Fiore 2006	No stomach specific data (miscellany of gastric and esophageal data)
Futawatari 2008	Article on tumor volume (not on tumor infiltration of the gastric wall)
Ghiţă 2011	No raw data reported (no data necessary for building 2 x 2 classification tables)
Giovannini 1993	No separate data for gastric carcinoma (miscellany of carcinoma, lymphoma and carcinoid cases)
Gorshkov 2001	Article in Russian
Greenberg 1994	Fewer than 10 patients with gastric cancer are analyzed
Grimm 1992	Data overlapping with Grimm 1993

Study	Reason for exclusion
Grotenhuis 2013	No gastric cancer data (only distal esophageal cancer)
Heeren 2004	No raw data reported (no data necessary for building 2x2 classification tables)
Heintz 1991a	Article in German
Heintz 1991b	Article in German
Heyer 1998	Article in German
Hirata 1989	Article in Japanese
Holden 1996	No raw data reported (no data necessary for building 2 x 2 classification tables)
Hünerbein 1995	No data on EUS (only data on laparoscopic ultrasonography)
Hünerbein 1996	Data overlapping with Hunerbein 1998
Kang 2010	No raw data reported (no data necessary for building 2 x 2 classification tables)
Kida 1998	No raw data reported (no data necessary for building 2 x 2 classification tables)
Kienle 2002	No separate data (mixed esophageal and gastric cancer data)
Kroep 2003	Data on tumor response to treatment (no data on tumor staging)
Lavonius 2002	Data on laparoscopic ultrasound only (no EUS data)
Li 2012	No data on EUS reported: only data on DCEUS (double contrast enhanced ultrasound) were reported
Matthes 2006	No separate data for gastric carcinoma (miscellany of carcinoma, lymphoma and carcinoid cases)
Meining 2002	No raw data reported (no data necessary for building 2 x 2 classification tables)
Mortensen 2007	No separate data for gastric carcinoma (miscellany of carcinoma, lymphoma and carcinoid cases)
Nagler 2011	Review article (no original data)
Nakamura 1999b	Overlapping with Nakamura 1999
Nakamura 2000	Overlapping with Nakamura 1999
Ohashi 1989	No raw data reported (no data necessary for building 2 x 2 classification tables)
Okai 1991	Data on type of tumor growth (not on tumor staging)
Park 2011	No raw data reported (no data necessary for building 2 x 2 classification tables)
Patel 2007	EUS performed before neoadjuvant chemotherapy (EUS used to assess response to therapy, not to stage gastric cancer)
Pedrazzani 2007	No raw data reported (no data necessary for building 2 x 2 classification tables)
Power 2009	No raw data reported (no data necessary for building 2 x 2 classification tables)

Study	Reason for exclusion
Rau 1995	Article in German
Richards 2000	No separate data (miscellany of esophageal and gastric cancer data)
Rösch 1992	No raw data reported (no data necessary for building 2 x 2 classification tables)
Songür 1996	No raw data reported (no data necessary for building 2 x 2 classification tables)
Tsuzuki 2011	No raw data reported (no data necessary for building 2 x 2 classification tables)
Venkataraman 2010	Hydrogastric sonography data only (no EUS data)
Wakelin 2002	No separate data (miscellany of esophageal and gastric cancer data)
Yoshinaga 2012	No raw data reported (no data necessary for building 2 x 2 classification tables)

EUS: endoscopic ultrasonography

Characteristics of studies awaiting classification *[ordered by study ID]*

Feng 2013

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 610
Index tests	EUS, MSCT
Target condition and reference standard(s)	Target condition: gastric cancer Reference standard: pathology evaluation of surgical specimen
Flow and timing	EUS staging followed by surgery and then pathology evaluation
Comparative	Results demonstrated that the overall accuracies of EUS and MSCT for preoperative staging were not significantly different
Notes	Country: China

Lei 2013

Study characteristics	
Patient sampling	Prospective study
Patient characteristics and setting	Sample size: 38
Index tests	EUS, MRI, MRI + EUS

Lei 2013 *(Continued)*

Target condition and reference standard(s)	Target condition: gastric cancer Reference standard: pathology evaluation of surgical specimen
Flow and timing	EUS staging followed by surgery and then pathology evaluation
Comparative	The accuracy was similar and improved significantly when the 2 procedures were combined
Notes	Country: China

Mehmedović 2014

Study characteristics	
Patient sampling	Prospective study (unclear)
Patient characteristics and setting	Sample size: 277. Gender: 171 men, 106 women
Index tests	EUS MDCT
Target condition and reference standard(s)	Target condition: gastric cancer Reference standard: pathology evaluation of surgical specimen
Flow and timing	EUS staging followed by surgery and then pathology evaluation
Comparative	Unclear
Notes	Country: Bosnia and Herzegovina

Spolverato 2015

Study characteristics	
Patient sampling	Retrospective study
Patient characteristics and setting	Sample size: 223
Index tests	EUS
Target condition and reference standard(s)	Target condition: gastric cancer Reference standard: pathology evaluation of surgical specimen
Flow and timing	EUS staging followed by surgery and then pathology evaluation
Comparative	N/A
Notes	Country: USA

EUS: endoscopic ultrasonography
MDCT: multi-detector computed tomography
MRI: magnetic resonance imaging

MSCT: multi slice computed tomography

D A T A

Presented below are all the data for all of the tests entered into the review.

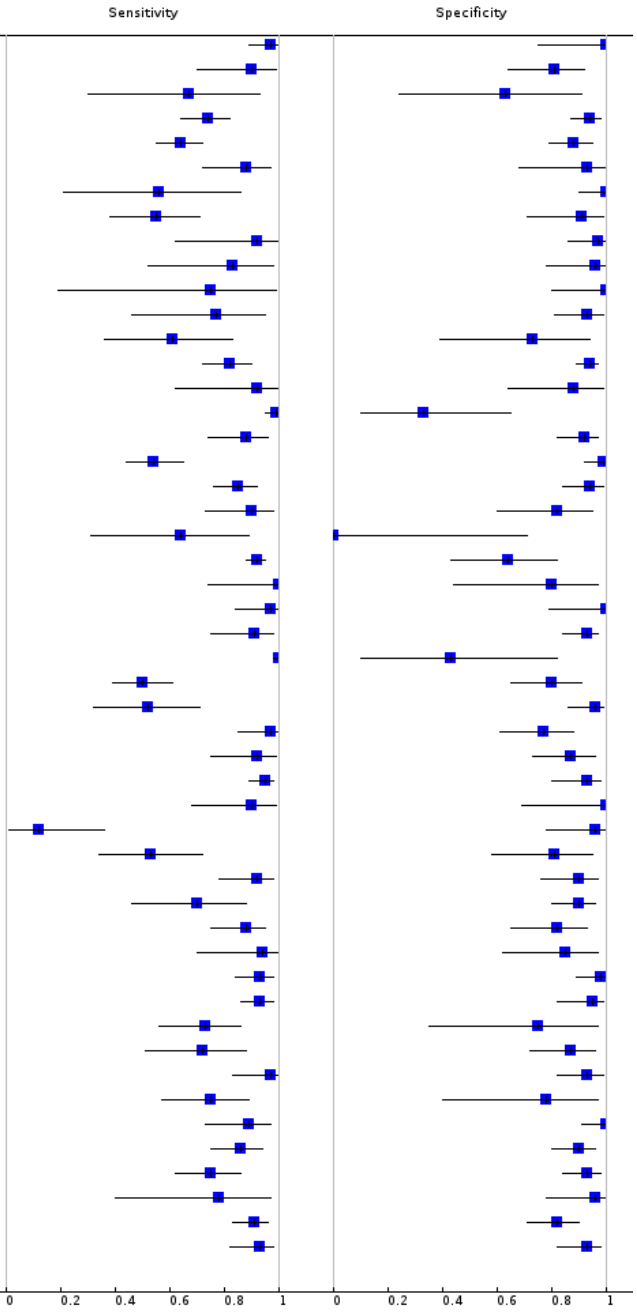
Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 T12 vs T34	50	4397
2 T1 vs T2	46	2742
3 T1a vs T1b	20	3321
4 N0 vs N+	44	3573

Test 1. T12 vs T34.

Review: Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer
Test: 1 T12 vs T34

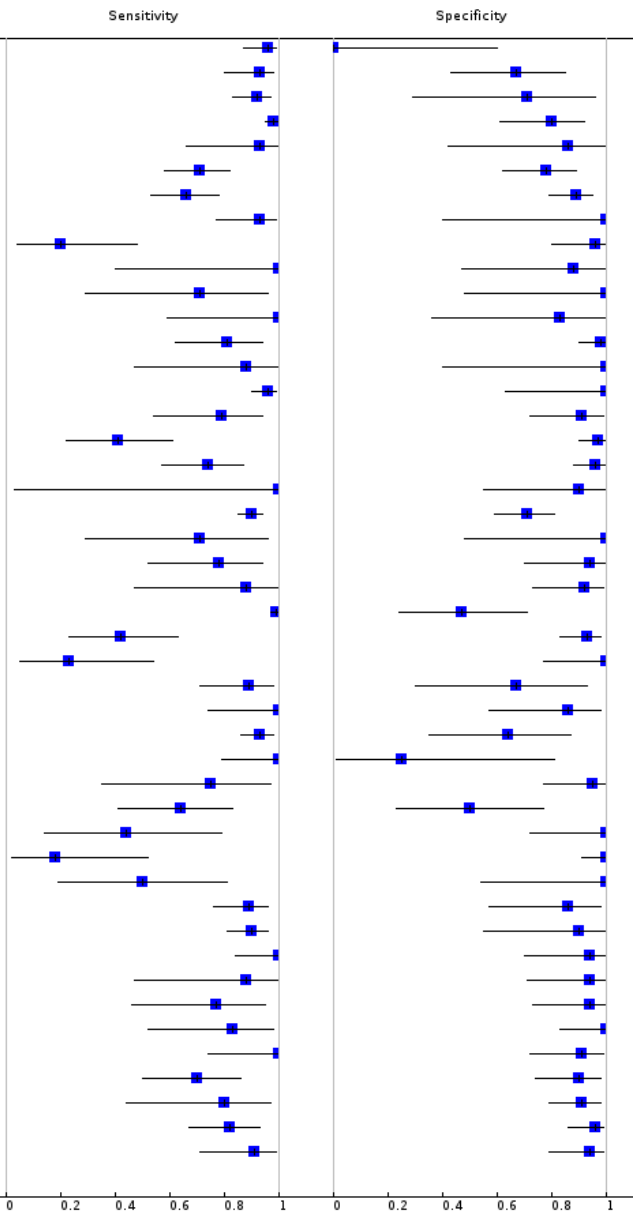
Study	TP	FP	FN	TN	Sensitivity	Specificity
Akahoshi 1991	59	0	2	13	0.97 [0.89, 1.00]	1.00 [0.75, 1.00]
Ang 2006	19	7	2	29	0.90 [0.70, 0.99]	0.81 [0.64, 0.92]
Arocena 2006	6	3	3	5	0.67 [0.30, 0.93]	0.63 [0.24, 0.91]
Barbour 2007	74	5	26	79	0.74 [0.64, 0.82]	0.94 [0.87, 0.98]
Bentrem 2007	85	9	48	69	0.64 [0.55, 0.72]	0.88 [0.79, 0.95]
Bhandari 2004	29	1	4	14	0.88 [0.72, 0.97]	0.93 [0.68, 1.00]
Blackshaw 2008	5	0	4	35	0.56 [0.21, 0.86]	1.00 [0.90, 1.00]
Bohle 2011	22	2	18	20	0.55 [0.38, 0.71]	0.91 [0.71, 0.99]
Botet 1991	11	1	1	37	0.92 [0.62, 1.00]	0.97 [0.86, 1.00]
Caletti 1993	10	1	2	22	0.83 [0.52, 0.98]	0.96 [0.78, 1.00]
Cerizzi 1991	3	0	1	17	0.75 [0.19, 0.99]	1.00 [0.80, 1.00]
Chen 2002	10	3	3	41	0.77 [0.46, 0.95]	0.93 [0.81, 0.99]
De Manzoni 1999	11	3	7	8	0.61 [0.36, 0.83]	0.73 [0.39, 0.94]
Dittler 1993	65	11	14	164	0.82 [0.72, 0.90]	0.94 [0.89, 0.97]
François 1996	11	2	1	15	0.92 [0.62, 1.00]	0.88 [0.64, 0.99]
Furukawa 2011	105	8	1	4	0.99 [0.95, 1.00]	0.33 [0.10, 0.65]
Ganpathi 2006	37	5	5	55	0.88 [0.74, 0.96]	0.92 [0.82, 0.97]
Garlipp 2011	51	1	43	70	0.54 [0.44, 0.65]	0.99 [0.92, 1.00]
Grimm 1993	80	3	14	50	0.85 [0.76, 0.92]	0.94 [0.84, 0.99]
Habermann 2004	26	4	3	18	0.90 [0.73, 0.98]	0.82 [0.60, 0.95]
Heye 2009	7	3	4	0	0.64 [0.31, 0.89]	0.0 [0.0, 0.71]
Hwang 2010	233	9	19	16	0.92 [0.88, 0.95]	0.64 [0.43, 0.82]
Hünerbein 1998	12	2	0	8	1.00 [0.74, 1.00]	0.80 [0.44, 0.97]
Hünerbein 2004	32	0	1	16	0.97 [0.84, 1.00]	1.00 [0.79, 1.00]
Javaid 2004	29	6	3	74	0.91 [0.75, 0.98]	0.93 [0.84, 0.97]
Kim 2007	199	4	0	3	1.00 [0.98, 1.00]	0.43 [0.10, 0.82]
Kutup 2012	41	8	41	33	0.50 [0.39, 0.61]	0.80 [0.65, 0.91]
Lok 2008	14	2	13	46	0.52 [0.32, 0.71]	0.96 [0.86, 0.99]
Mancino 2000	35	10	1	33	0.97 [0.85, 1.00]	0.77 [0.61, 0.88]
Massari 1996	24	5	2	34	0.92 [0.75, 0.99]	0.87 [0.73, 0.96]
Murata 1988	100	3	5	38	0.95 [0.89, 0.98]	0.93 [0.80, 0.98]
Nomura 1999	18	0	2	10	0.90 [0.68, 0.99]	1.00 [0.69, 1.00]
Park 2008	2	1	15	22	0.12 [0.01, 0.36]	0.96 [0.78, 1.00]
Pedrazzani 2005	16	4	14	17	0.53 [0.34, 0.72]	0.81 [0.58, 0.95]
Perng 1996	33	4	3	36	0.92 [0.78, 0.98]	0.90 [0.76, 0.97]
Polkowski 2004	14	7	6	61	0.70 [0.46, 0.88]	0.90 [0.80, 0.96]
Potrc 2006	42	6	6	28	0.88 [0.75, 0.95]	0.82 [0.65, 0.93]
Repiso 2010	15	3	1	17	0.94 [0.70, 1.00]	0.85 [0.62, 0.97]
Saito 1991	56	1	4	49	0.93 [0.84, 0.98]	0.98 [0.89, 1.00]
Shimizu 1994	84	2	6	36	0.93 [0.86, 0.98]	0.95 [0.82, 0.99]
Shimoyama 2004	27	2	10	6	0.73 [0.56, 0.86]	0.75 [0.35, 0.97]
Tan 2007	18	5	7	33	0.72 [0.51, 0.88]	0.87 [0.72, 0.96]
Tio 1989	30	3	1	42	0.97 [0.83, 1.00]	0.93 [0.82, 0.99]
Tsendsuren 2006	24	2	8	7	0.75 [0.57, 0.89]	0.78 [0.40, 0.97]
Tseng 2000	31	0	4	39	0.89 [0.73, 0.97]	1.00 [0.91, 1.00]
Wang 1998	50	6	8	55	0.86 [0.75, 0.94]	0.90 [0.80, 0.96]
Willis 2000	42	4	14	56	0.75 [0.62, 0.86]	0.93 [0.84, 0.98]
Xi 2003	7	1	2	22	0.78 [0.40, 0.97]	0.96 [0.78, 1.00]
Zheng 2011	80	13	8	58	0.91 [0.83, 0.96]	0.82 [0.71, 0.90]
Ziegler 1993	50	4	4	50	0.93 [0.82, 0.98]	0.93 [0.82, 0.98]



Test 2. T1 vs T2.

Review: Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer
Test: 2 T1 vs T2

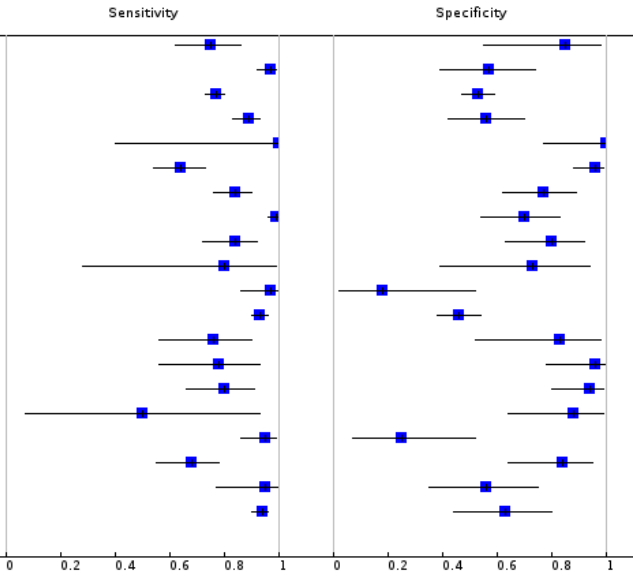
Study	TP	FP	FN	TN	Sensitivity	Specificity
Ahn 2009	64	4	3	0	0.96 [0.87, 0.99]	0.0 [0.0, 0.60]
Akahoshi 1991	37	7	3	14	0.93 [0.80, 0.98]	0.67 [0.43, 0.85]
Akahoshi 1998	61	2	5	5	0.92 [0.83, 0.97]	0.71 [0.29, 0.96]
Akashi 2006	161	6	3	24	0.98 [0.95, 1.00]	0.80 [0.61, 0.92]
Ang 2006	13	1	1	6	0.93 [0.66, 1.00]	0.86 [0.42, 1.00]
Barbour 2007	42	9	17	32	0.71 [0.58, 0.82]	0.78 [0.62, 0.89]
Bentrem 2007	41	8	21	63	0.66 [0.53, 0.78]	0.89 [0.79, 0.95]
Bhandari 2004	27	0	2	4	0.93 [0.77, 0.99]	1.00 [0.40, 1.00]
Bohle 2011	3	1	12	24	0.20 [0.04, 0.48]	0.96 [0.80, 1.00]
Botet 1991	4	1	0	7	1.00 [0.40, 1.00]	0.88 [0.47, 1.00]
Caletti 1993	5	0	2	5	0.71 [0.29, 0.96]	1.00 [0.48, 1.00]
Chen 2002	7	1	0	5	1.00 [0.59, 1.00]	0.83 [0.36, 1.00]
Dittler 1993	22	1	5	51	0.81 [0.62, 0.94]	0.98 [0.90, 1.00]
François 1996	7	0	1	4	0.88 [0.47, 1.00]	1.00 [0.40, 1.00]
Furukawa 2011	94	0	4	8	0.96 [0.90, 0.99]	1.00 [0.63, 1.00]
Ganpathi 2006	15	2	4	21	0.79 [0.54, 0.94]	0.91 [0.72, 0.99]
Garlipp 2011	11	2	16	65	0.41 [0.22, 0.61]	0.97 [0.90, 1.00]
Grimm 1993	28	2	10	54	0.74 [0.57, 0.87]	0.96 [0.88, 1.00]
Heye 2009	1	1	0	9	1.00 [0.03, 1.00]	0.90 [0.55, 1.00]
Hwang 2010	162	21	18	51	0.90 [0.85, 0.94]	0.71 [0.59, 0.81]
Hünerbein 1998	5	0	2	5	0.71 [0.29, 0.96]	1.00 [0.48, 1.00]
Hünerbein 2004	14	1	4	15	0.78 [0.52, 0.94]	0.94 [0.70, 1.00]
Javaid 2004	7	2	1	22	0.88 [0.47, 1.00]	0.92 [0.73, 0.99]
Kim 2007	179	10	1	9	0.99 [0.97, 1.00]	0.47 [0.24, 0.71]
Kutup 2012	11	4	15	52	0.42 [0.23, 0.63]	0.93 [0.83, 0.98]
Lok 2008	3	0	10	14	0.23 [0.05, 0.54]	1.00 [0.77, 1.00]
Mancino 2000	24	3	3	6	0.89 [0.71, 0.98]	0.67 [0.30, 0.93]
Massari 1996	12	2	0	12	1.00 [0.74, 1.00]	0.86 [0.57, 0.98]
Murata 1988	85	5	6	9	0.93 [0.86, 0.98]	0.64 [0.35, 0.87]
Nomura 1999	16	3	0	1	1.00 [0.79, 1.00]	0.25 [0.01, 0.81]
Pedrazzani 2005	6	1	2	21	0.75 [0.35, 0.97]	0.95 [0.77, 1.00]
Perng 1996	14	7	8	7	0.64 [0.41, 0.83]	0.50 [0.23, 0.77]
Polkowski 2004	4	0	5	11	0.44 [0.14, 0.79]	1.00 [0.72, 1.00]
Potrc 2006	2	0	9	37	0.18 [0.02, 0.52]	1.00 [0.91, 1.00]
Repiso 2010	5	0	5	6	0.50 [0.19, 0.81]	1.00 [0.54, 1.00]
Saito 1991	41	2	5	12	0.89 [0.76, 0.96]	0.86 [0.57, 0.98]
Shimizu 1994	72	1	8	9	0.90 [0.81, 0.96]	0.90 [0.55, 1.00]
Shimoyama 2004	21	1	0	15	1.00 [0.84, 1.00]	0.94 [0.70, 1.00]
Tan 2007	7	1	1	16	0.88 [0.47, 1.00]	0.94 [0.71, 1.00]
Tio 1989	10	1	3	17	0.77 [0.46, 0.95]	0.94 [0.73, 1.00]
Tsendsuren 2006	10	0	2	20	0.83 [0.52, 0.98]	1.00 [0.83, 1.00]
Tseng 2000	12	2	0	21	1.00 [0.74, 1.00]	0.91 [0.72, 0.99]
Wang 1998	19	3	8	28	0.70 [0.50, 0.86]	0.90 [0.74, 0.98]
Willis 2000	8	4	2	42	0.80 [0.44, 0.97]	0.91 [0.79, 0.98]
Zheng 2011	33	2	7	46	0.83 [0.67, 0.93]	0.96 [0.86, 0.99]
Ziegler 1993	20	2	2	30	0.91 [0.71, 0.99]	0.94 [0.79, 0.99]



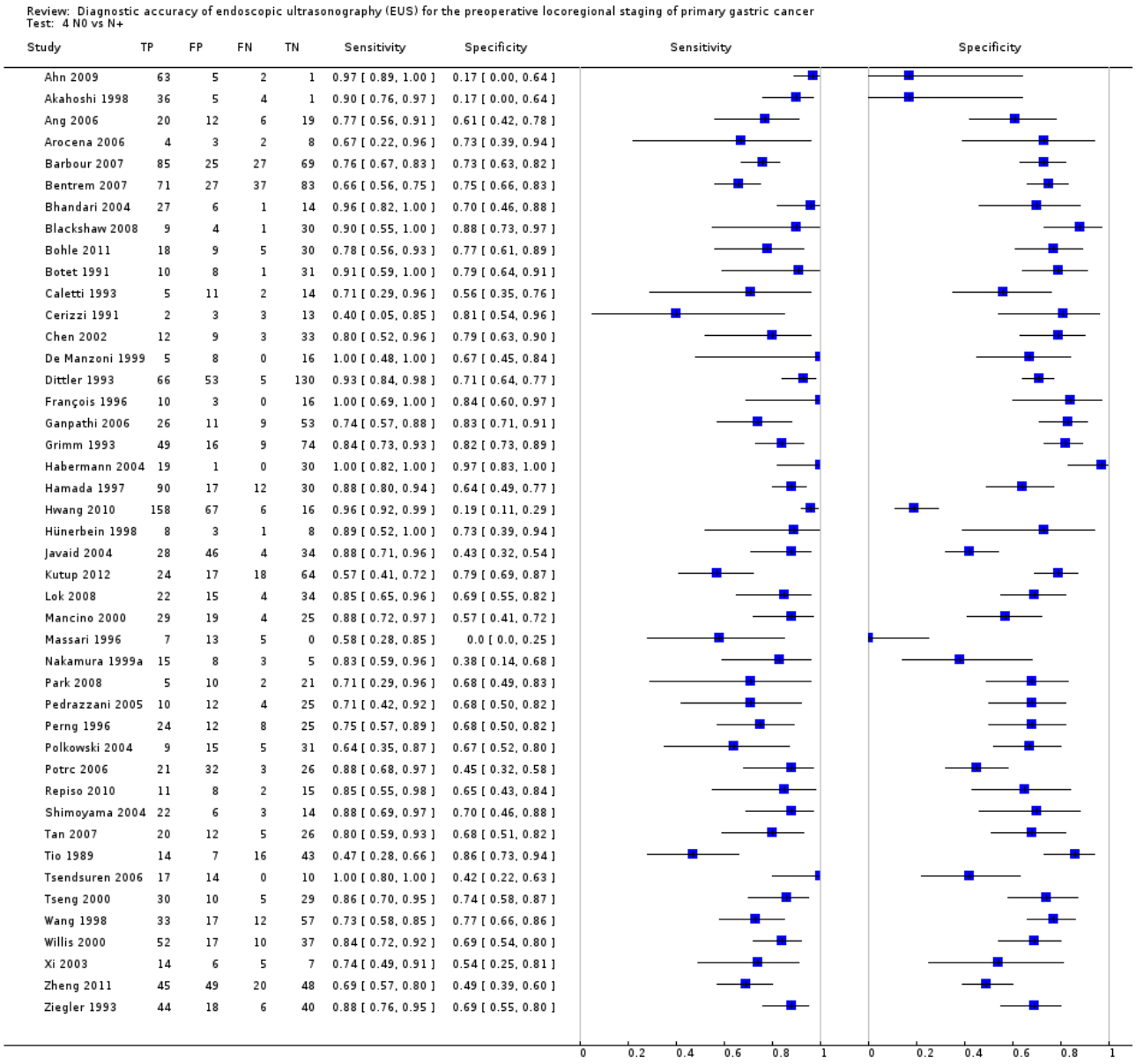
Test 3. T1a vs T1b.

Review: Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer
Test: 3 T1a vs T1b

Study	TP	FP	FN	TN	Sensitivity	Specificity
Akahoshi 1998	40	2	13	11	0.75 [0.62, 0.86]	0.85 [0.55, 0.98]
Akashi 2006	125	15	4	20	0.97 [0.92, 0.99]	0.57 [0.39, 0.74]
Choi 2010	487	139	147	157	0.77 [0.73, 0.80]	0.53 [0.47, 0.59]
Hizawa 2002	147	24	18	31	0.89 [0.83, 0.93]	0.56 [0.42, 0.70]
Hünerbein 2004	4	0	0	14	1.00 [0.40, 1.00]	1.00 [0.77, 1.00]
Kim 2007	70	3	40	67	0.64 [0.54, 0.73]	0.96 [0.88, 0.99]
Kim 2010	105	10	20	34	0.84 [0.76, 0.90]	0.77 [0.62, 0.89]
Mouri 2009	147	13	1	30	0.99 [0.96, 1.00]	0.70 [0.54, 0.83]
Murata 1988	47	7	9	28	0.84 [0.72, 0.92]	0.80 [0.63, 0.92]
Nomura 1999	4	3	1	8	0.80 [0.28, 0.99]	0.73 [0.39, 0.94]
Ohashi 1999	37	9	1	2	0.97 [0.86, 1.00]	0.18 [0.02, 0.52]
Okada 2011	344	85	25	72	0.93 [0.90, 0.96]	0.46 [0.38, 0.54]
Okamura 1999	22	2	7	10	0.76 [0.56, 0.90]	0.83 [0.52, 0.98]
Saito 1991	18	1	5	22	0.78 [0.56, 0.93]	0.96 [0.78, 1.00]
Shimizu 1994	37	2	9	32	0.80 [0.66, 0.91]	0.94 [0.80, 0.99]
Shimoyama 2004	2	2	2	15	0.50 [0.07, 0.93]	0.88 [0.64, 0.99]
Yamamoto 2012	56	12	3	4	0.95 [0.86, 0.99]	0.25 [0.07, 0.52]
Yanai 1997	48	4	23	21	0.68 [0.55, 0.78]	0.84 [0.64, 0.95]
Yanai 1999	21	12	1	15	0.95 [0.77, 1.00]	0.56 [0.35, 0.75]
Yoshida 2005	246	11	17	19	0.94 [0.90, 0.96]	0.63 [0.44, 0.80]



Test 4. N0 vs N+.



ADDITIONAL TABLES

Table 1. Subgroup and sensitivity analysis for T1 - T2 versus T3 - T4 gastric tumors

Variable	Category	Studies	Sensitivity (95% CI)	Specificity (95% CI)	P value*
Sample size	>100	18	0.89 (0.83 to 0.95)	0.90 (0.85 to 0.94)	0.46
	<100	32	0.83 (0.77 to 0.90)	0.91 (0.87 to 0.94)	
Year of publication	2000 or later	32	0.81 (0.75 to 0.88)	0.88 (0.84 to 0.91)	<0.01
	before 2000	18	0.91 (0.87 to 0.96)	0.94 (0.91 to 0.96)	

Table 1. Subgroup and sensitivity analysis for T1 - T2 versus T3 - T4 gastric tumors *(Continued)*

Country	Western	27	0.82 (0.75 to 0.89)	0.91 (0.87 to 0.94)	0.27
	Eastern	23	0.89 (0.84 to 0.94)	0.90 (0.86 to 0.94)	
EUS array	Radial	39	0.88 (0.84 to 0.93)	0.90 (0.87 to 0.93)	<0.01
	Linear	4	0.68 (0.40 to 0.96)	0.86 (0.73 to 1.00)	
Tumor site	Cardia only	6	0.70 (0.49 to 0.91)	0.90 (0.82 to 0.98)	0.12
	Any site	44	0.87 (0.83 to 0.91)	0.90 (0.88 to 0.93)	
Quality	High	45	0.86 (0.82 to 0.91)	0.90 (0.88 to 0.93)	0.59
	Low	5	0.78 (0.72 to 1.00)	0.90 (0.81 to 0.99)	

CI: confidence interval
EUS: endoscopic ultrasonography
*P values are from likelihood ratio test for model with and without the covariate, to identify diagnostic performance differences across variable categories.

Table 2. Subgroup and sensitivity analysis for T1 versus T2 gastric tumors

Variable	Category	Studies	Sensitivity (95% CI)	Specificity (95% CI)	P value*
Sample size	>100	5	0.97 (0.93 to 1.00)	0.73 (0.53 to 0.93)	0.01
	<100	41	0.81 (0.74 to 0.87)	0.91 (0.88 to 0.95)	
Year of publication	2000 or later	29	0.82 (0.74 to 0.90)	0.91 (0.87 to 0.96)	0.51
	before 2000	17	0.88 (0.80 to 0.96)	0.87 (0.80 to 0.95)	
Country	Western	22	0.71 (0.59 to 0.82)	0.94 (0.91 to 0.97)	<0.01
	Eastern	24	0.92 (0.88 to 0.96)	0.84 (0.77 to 0.91)	
EUS array	Radial	37	0.85 (0.79 to 0.91)	0.90 (0.85 to 0.94)	<0.01
	Linear	3	0.92 (0.77 to 1.00)	0.98 (0.93 to 1.00)	
Tumor site	Cardia only	5	0.91 (0.80 to 1.00)	0.89 (0.77 to 1.00)	0.59
	Any site	41	0.84 (0.77 to 0.90)	0.90 (0.86 to 0.94)	
Quality	High	41	0.85 (0.79 to 0.91)	0.89 (0.85 to 0.93)	0.39
	Low	5	0.79 (0.57 to 1.00)	0.96 (0.90 to 1.00)	

CI: confidence interval
EUS: endoscopic ultrasonography
*P values are from likelihood ratio test for model with and without the covariate, to identify diagnostic performance differences across variable categories.

Table 3. Subgroup and sensitivity analysis for T1a versus T1b gastric tumors

Variable	Category	Studies	Sensitivity (95% CI)	Specificity (95% CI)	P value*
Sample size	>100	8	0.90 (0.84 to 0.96)	0.67 (0.50 to 0.85)	0.49
	<100	12	0.85 (0.76 to 0.93)	0.79 (0.67 to 0.91)	
Year of publication	2000 or later	11	0.90 (0.84 to 0.95)	0.70 (0.55 to 0.85)	0.59
	before 2000	9	0.84 (0.75 to 0.94)	0.79 (0.66 to 0.93)	
Country	Western	1	1.00 (0.40 to 1.00)	1.00 (0.69 to 1.00)	N/A
	Eastern	19	0.88 (0.81 to 0.92)	0.73 (0.61 to 0.82)	
EUS array	Radial	18	0.89 (0.82 to 0.93)	0.72 (0.59 to 0.82)	N/A
	Linear	1	0.50 (0.07 to 0.93)	0.88 (0.64 to 0.99)	
Tumor site	Cardia region	1	0.50 (0.07 to 0.93)	0.88 (0.64 to 0.99)	N/A
	Any site	19	0.88 (0.82 to 0.92)	0.74 (0.61 to 0.83)	
Quality	High	18	0.84 (0.79 to 0.89)	0.75 (0.64 to 0.86)	0.05
	Low	2	0.98 (0.96 to 1.00)	0.64 (0.26 to 1.00)	

CI: confidence interval
EUS: endoscopic ultrasonography
*P values are from likelihood ratio test for model with and without the covariate, to identify diagnostic performance differences across variable categories.

Table 4. Subgroup and sensitivity analysis for N0 versus N+ gastric tumors

Variable	Category	Studies	Sensitivity (95% CI)	Specificity (95% CI)	P value*
Sample size	>100	12	0.83 (0.77 to 0.89)	0.65 (0.55 to 0.75)	0.90
	<100	32	0.84 (0.79 to 0.88)	0.67 (0.61 to 0.74)	
Year of publication	2000 or later	28	0.83 (0.79 to 0.88)	0.66 (0.59 to 0.73)	0.95
	before 2000	16	0.83 (0.76 to 0.89)	0.68 (0.58 to 0.77)	
Country	Western	24	0.80 (0.75 to 0.86)	0.72 (0.66 to 0.79)	0.04
	Eastern	20	0.86 (0.81 to 0.90)	0.59 (0.51 to 0.68)	
EUS array	Radial	35	0.84 (0.80 to 0.88)	0.66 (0.60 to 0.73)	0.11
	Linear	4	0.83 (0.69 to 0.98)	0.66 (0.46 to 0.86)	
Tumor site	Cardia region	6	0.86 (0.76 to 0.96)	0.76 (0.63 to 0.88)	0.27

Table 4. Subgroup and sensitivity analysis for N0 versus N+ gastric tumors *(Continued)*

	Any site	38	0.83 (0.79 to 0.87)	0.65 (0.59 to 0.71)	
Quality	High	41	0.83 (0.79 to 0.87)	0.67 (0.62 to 0.73)	0.57
	Low	3	0.88 (0.77 to 0.99)	0.56 (0.32 to 0.80)	

CI: confidence interval
EUS: endoscopic ultrasonography
*P values are from likelihood ratio test for model with and without the covariate, to identify diagnostic performance differences across variable categories.

APPENDICES

Appendix 1. Glossary

Clinical staging: the instrumental assessment of the extent of the primary tumor growth (T-stage), the status of the lymph nodes close to the primary tumor (N-stage) and the presence or absence of metastasis to distant organs (M-stage).

Computed tomography (CT) scan: a radiology diagnostic device that exploits the different ability of X-rays to go through body tissues (normal and pathologic) characterized by different density. The resulting image depicts the human body anatomy in the form of virtual transversal "slices" that enable the user to easily identify the relationship between organs (normal and diseased).

Distant staging: the definition of M-stage.

Endoscopy: medical procedure performed with a tube-like device called endoscope, which enables the operator to see the lumen of an hollowed organ (such as the stomach) by means of an optical channel.

Hepatic: adjective of the noun "liver".

Locoregional staging: the definition of T-stage and N-stage.

Magnetic resonance imaging (MRI): a radiology diagnostic device that exploits the different content of hydrogen proper of different human tissues and detected by means of strong magnetic fields. The resulting image depicts the human body anatomy in the form of virtual transversal "slices" that enable the user to easily identify the relationship between organs (normal and diseased).

Mucosa: the inner layer of hollowed organs such as the stomach, small bowel and large bowel.

Muscolaris propria: the intermediate layer of hollowed organs such as the stomach, small bowel and large bowel; contains the muscle fibers responsible for gastrointestinal movements.

Negative predictive value (NPV): a diagnostic accuracy measure that indicates the proportion of actually negative cases (e.g., healthy, or non-metastatic) among those classified as negative by a given diagnostic test. For instance, a 90% NPV means that among 100 cases classified as negative by a given test, 90 are actually negative.

Pathological staging: definition of T-stage, N-stage and M-stage by pathological examination of primary tumor, lymph nodes and distant metastasis, respectively.

Peritoneal: adjective of the noun "peritoneum".

Positive predictive value (PPV): a diagnostic accuracy measure that indicates the proportion of actually positive cases (e.g., diseased, or metastatic) among those classified as positive by a given diagnostic test. For instance, a 90% PPV means that among 100 cases classified as positive by a given test, 90 are actually positive.

Positron emission tomography (PET): a nuclear medicine diagnostic device that exploits the ability of some tissues (such as cancer and inflammatory tissues) to avidly uptake glucose. When the glucose is labeled with a positron-emitting tracer, PET can scan the human body to find areas that concentrate the tracer and thus can be considered suspicious.

Sensitivity: a diagnostic accuracy measure that indicates the proportion of positive (e.g., diseased, or metastatic) cases correctly classified by a given diagnostic test (it is also known as true positive rate). For instance, a 90% sensitivity means that the test correctly classifies 90 out of 100 cases known to be positive.

Serosa: the outer layer of hollowed organs such as the stomach, small bowel and large bowel. It is made of a membrane called peritoneum.

Specificity: a diagnostic accuracy measure that indicates the proportion of negative (e.g., healthy, or non-metastatic) cases correctly classified by a given diagnostic test (it is also known as true negative rate). For instance, a 90% specificity means that the test correctly classifies 90 out of 100 cases known to be negative.

Appendix 2. CENTRAL search strategy

EBM Reviews - Cochrane Central Register of Controlled Trials in OvidSP

1. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or adenocarcin$ or malig$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. (Digest$ or Gastr$ or gut or stomach$).mp.
3. 1 and 2
4. Neoplasm Staging/
5. Neoplasm Invasiveness/
6. Lymphatic Metastasis/
7. (lymph adj2 node adj2 metastasis).tw.
8. disease progression/
9. t-stag*.tw.
10. Stomach Neoplasms/
11. (gastric adj2 staging).tw.
12. or/4-11
13. Endosonography/
14. (endoscop* adj3 (ultrasound or ultrasonograph* or ultrasonic)).mp.
15. endosonograph*.mp.
16. EUS.ti,ab.
17. Diagnostic Imaging/
18. or/13-17
19. 3 and 12 and 18

Appendix 3. MEDLINE search strategy

Ovid MEDLINE(R)

1. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or adenocarcin$ or malig$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. (Digest$ or Gastr$ or gut or stomach$).mp.
3. 1 and 2
4. Neoplasm Staging/
5. *Lymphatic Metastasis/
6. (lymph adj2 node adj2 metastasis).tw.
7. disease progression/
8. t-stag*.tw.
9. Stomach Neoplasms/pa [Pathology]
10. (gastric adj2 staging).tw.
11. or/4-10
12. Endosonography/
13. (endoscop* adj2 (ultrasound or ultrasonograph* or ultrasonic)).tw.
14. EUS.ti,ab.
15. *Diagnostic Imaging/
16. Neoplasm Invasiveness/us [Ultrasonography]
17. Peritoneal Neoplasms/us [Ultrasonography]
18. Abdominal Neoplasms/us [Ultrasonography]
19. Stomach Neoplasms/us [Ultrasonography]
20. or/12-19

21.3 and 11 and 20

Appendix 4. EMBASE search strategy

Embase in OvidSP

1. (carcin$ or cancer$ or neoplas$ or tumour$ or tumor$ or adenocarcin$ or malig$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2. (Digest$ or Gastr$ or gut or stomach$).mp.
3. 1 and 2
4. *cancer staging/
5. *lymph node metastasis/
6. (lymph adj2 node adj2 metastasis).tw.
7. *disease course/
8. t-stag*.tw.
9. stomach tumor/co [Complication]
10. (gastric adj2 staging).tw.
11. or/4-10
12. endoscopic echography/
13. (endoscop* adj3 (ultrasound or ultrasonograph* or ultrasonic)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. EUS.ti,ab.
15. *diagnostic imaging/
16. cancer infiltration/di, dm, th [Diagnosis, Disease Management, Therapy]
17. *cancer invasion/di, dm, th [Diagnosis, Disease Management, Therapy]
18. exp abdominal tumor/di [Diagnosis]
19. stomach tumor/di [Diagnosis]
20. or/12-19
21. 3 and 11 and 20

Appendix 5. QUADAS-2

Questions (in bold) were used to score studies as at high or low or unclear risk of bias or with high or low or unclear applicability concerns.

Domain 1: Patient Selection

Risk of Bias: Could the selection of patients have introduced bias?

Signaling question 1: Was a consecutive or random sample of patients enrolled?

Signaling question 2: Was a case–control design avoided? (yes versus no)

Signaling question 3: Did the study avoid inappropriate exclusions? (For example, large primary tumors that do not allow to technically perform EUS, ulcerated primary tumors, or doubtful findings)

Applicability concern: Are there concerns that the included patients and setting do not match the review question?

Domain 2: Index Test

Risk of Bias: Could the conduct or interpretation of the index test have introduced bias?

Signaling question 1: Were the index test results interpreted without knowledge of the results of the reference standard? (yes versus no)

Signaling question 2: If a threshold was used, was it prespecified? (For example, definition of T and N categories.)

Applicability concern: Are there concerns that the index test, its conduct, or its interpretation differ from the review question?

Domain 3: Reference Standard

Risk of Bias: Could the reference standard, its conduct, or its interpretation have introduced bias?

Signaling question 1: Is the reference standard likely to correctly classify the target condition? (That is, is the pathology examination performed according to the worldwide accepted standards, so to guarantee that the target condition can be correctly classified? For instance, the description of the pathology methods were used to assess whether or not a risk of bias exists for this item.)

Signaling question 2: Were the reference standard results interpreted without knowledge of the results of the index test? (yes versus no)

Applicability concern: Are there concerns that the target condition as defined by the reference standard does not match the question?

Domain 4: Flow and Timing

Risk of Bias: Could the patient flow have introduced bias ?

Signaling question 1: Was there an appropriate interval between the index test and reference standard? (Since the disease can progress since the index test is performed, a time interval between EUS and the pathology evaluation longer than two months was considered a potential source of bias.)

Signaling question 2: Did all patients receive the same reference standard? (yes versus no)

Signaling question 3: Were all patients included in the analysis? (high risk: 5 or more patients)

CONTRIBUTIONS OF AUTHORS

Simone Mocellin: study design and coordination, literature search, data collection and management, statistical analysis, manuscript writing.

Sandro Pasquali: literature search, data collection and management, manuscript writing.

DECLARATIONS OF INTEREST

The review authors declare no conflict of interest.

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Internal sources

- None, Other.

External sources

- None, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

Endosonography [*standards]; Lymphatic Metastasis; Neoplasm Staging [methods]; Preoperative Care; Randomized Controlled Trials as Topic; Stomach Neoplasms [*diagnostic imaging] [pathology]

MeSH check words

Humans