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[Diagnostic Test Accuracy Review]

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

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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.