Review Article

The Role of EUS in Staging of Gastric Cardiacancer: A Meta-Analysis and Systematic Review

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Abstract

Background

Prognosis and treatment in patients with Gastric Cardia Cancers (GCC) depends on the TNM staging. The published data on accuracy of Endoscopic Ultrasound (EUS) for TNM staging in GCC patients has been variable.

Aim

To evaluate the accuracy of EUS in TNM staging of GCC cancers.

Method

Study Selection Criteria: Only EUS studies with staged gastric cardia cancers thatwere eventually confirmed by surgery were selected. EUS criteria used for T staging were: T1- the tumor invades the lamina propria or submucosa but does not invade the muscularispropria, T2- the tumor invades but does not extend beyond the muscularispropria, T3- the tumor invades the periesophageal tissues but does not invade adjacent organs, and T4- the tumor invades adjacent structures. EUS criteria used for nodal invasion were: larger than 1 cm, hypoechoic, and round instead of elliptical. Only studies from which a 2 X 2 table could be constructed for true positive, false negative, false positive and true negative values were included.

Data collection & extraction: Articles were searched in Medline, Pubmed, Ovid journals, Cumulative index for nursing & allied health literature, International pharmaceutical abstracts, old Medline, Medline nonindexed citations, and Cochrane control trial registry. Two reviewers independently searched and extracted data into an abstraction form. The differences were resolved by mutual agreement. 2 X 2 tables were constructed with the data extracted from each study.

Statistical Method: Meta-analysis for the accuracy of EUS was analyzed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratio. Pooling was conducted by both the Mantel-Haenszel method (fixed effects model) and by the DerSimonian Laird method (random effects model). The heterogeneity of studies was tested using Cochran's Q test based upon inverse variance weights.

Results

Seven studies were chosen which met the inclusion criteria in this analysis.

Conclusion

EUS has excellent sensitivity and specificity in accurately diagnosing T stage in a patient with GCC. EUS performs better with advanced disease (T4) than early disease (T1). Theexcellent sensitivity and specificity of EUS in evaluating N (nodal) stage of gastric cardia cancers also allows for accurate staging and planning of therapy. EUS should be strongly considered for staging of GCC.

INTRODUCTION

Gastric cancer is one of the leading causes of cancer worldwide with 989,600 new cases and an estimated 738,000 deaths in 2008 alone [1]. It accounts for 8% of the total cancer cases and nearly 10% of the cancer related deaths [1]. Epidemiologically, it is twice as common in males as compared to females, with higher incidence reported from Asia and Eastern Europe. In the United States, the data from Surveillance Epidemiology and End Results (SEER) note an estimated total of 21,600 new cases diagnosed with 11,000 deaths. The observed incidences of combined Esophageal Adenocarcinoma (EAC) and Gastric Cardia Cancers (GCC) between the years 1973 and 2009 show an increase by 400% in the United States [2].

Histologically, gastric cancer is classified into two distinct

types. These include intestinal (well differentiated) and diffuse types (poorly differentiated) with a heterogeneous histology and molecular profile [3,4]. Intestinal type adenocarcinoma is found organized into glandular structures whereas the diffuse type tends to lack the typical gland formation and often infiltrates the gastric wall (linitisplastica). There has been substantial progress in our understanding of pathobiology of the adenocarcinomas of the distal esophagus and the gastric cancers. Mid and distal gastric cancers have been linked to late complications of *H.pylori* associated chronic superficial gastritis and atrophic gastritis in addition to host and environmental factors [5,6]. While gastroesophageal reflux is a greater risk factor for esophageal adenocarcinoma [7], both reflux and H.pylori infection have been associated with gastric cardia cancer [8].

Tumors originating within the proximal stomach i.e. within 5 cm from the EGJ and extending into distal esophagus are now categorized and treated as esophageal cancers as described by American Joint Committee on Cancer (AJCC 7th edition) [9]. If the proximal stomach cancer does not invade the EGJ, then it is classified as gastric cancers and is treated as such.

Accurate clinical staging is essential in planning appropriate treatment in patients with gastric cardia cancer. Surgical and chemoradiotherapy decisions are based upon accurate staging of the gastric cardia cancer. Additionally, neoadjuvant chemoradiotherapy has been shown to improve overall survival compared with surgery alone in patients with esophageal cancer [10]. Our previously analyses showed excellent diagnostic accuracy of EUS in T and N stage of esophageal and gastric cancers [11,12]. Despite the previously published meta-analysis on accuracy of EUS for gastric cancer, the question remains in the setting of cardia cancers. Given the location of the cardia cancers with EUS technology, the positioning and accessibility could make it difficult to achieve good acoustic coupling to interpret the images acquired during endosonography. The aim of this meta-analysis is to assess the diagnostic accuracy of EUS in staging gastric cardia cancers.

METHODS

Study selection criteria

Studies evaluating the use of EUS to assess T and N stage were selected. From this pool, only studies from which a 2 X 2 table could be constructed for true positive, false negative, false positive and true negative values were included.

Data collection & extraction

Articles were searched in MEDLINE (through PubMed, an electronic search engine for published articles and Ovid), Pubmed, Ovid Journals, EMBASE, Cumulative Index for Nursing & Allied Health Literature, ACP Journal Club, DARE, International Pharmaceutical Abstracts, old Medline, Medline non-indexed citations, OVID Healthstar, and Cochrane Central Register of Controlled Trials & Database of Systematic Reviews(CENTRAL). The search was performed from January 1966 to January 2012. The terms used for search were endoscopic ultrasound, EUS, ultrasound, endosonography, pancreatic mass, neuroendocrine tumors, sensitivity, specificity, positive predictive value, and negative predictive value. Study authors were contacted when

the required data could not be determined from the publications. Two by two tables were constructed with the data extracted from each study. Two authors (SP and DM) independently searched and extracted the data using an abstraction form. Any differences were resolved by mutual agreement. The agreement between reviewers for the collected data was quantified using the Cohen's κ [13].

Quality of Studies

Clinical trials designed with control and treatment arms can be assessed for quality of the study. A number of criteria have been used to assess the quality of a study (e.g. randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome) [14]. There is no consensus on how to assess studies designed without a control arm. Hence, these criteria do not apply to studies without a control arm [14]. Therefore, for this meta-analysis and systematic review; studies were selected based on completeness of the data and inclusion criteria. Completeness was defined as data available for true positive, false negative, false positive and true negative values of the diagnostic test (EUS). Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS) criteria has been proposed to evaluate quality of diagnostic studies [15,16]. This was used to evaluate the studies on 14 items described in the QUADAS criteria.

RESULTS

Initial search revealed 2250 reference articles. 326 articles relevant articles were selected and reviewed. Data was extracted from studies [17-23], which met the inclusion criteria (Figure 1). During the time periods of 1990 to 1999 there were 3 studies which met the inclusion criteria. Four studies met the inclusion criteria for the time period between 2000 to 2006. T staging for gastric cardia cancers is shown in Table 1. Pooled estimates for these time periods are shown in Table 2. All the pooled estimates, calculated by fixed and random effect models, were similar. The p for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.05.

Accuracy of EUS for T staging in Gastric Cardia cancers

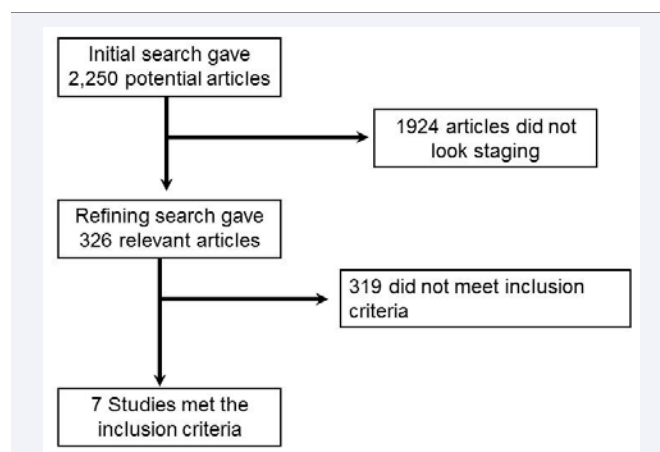Pooled sensitivity and specificity of T1 staging for gastric

Figure 1 Flow diagram.

Table 1: Shows the accuracy of EUS with confidence intervals to diagnose T stages in Gastric Cardia cancer patients.

	Pooled Sensitivity	Pooled Specificity	Pooled+LR	Pooled-LR	Pooled DOR
T1	90.0%(83.2-94.7)	99.1%(97.3-99.8)	37.3(16.3-85.2)	0.1(0.1-0.2)	370.8(128.6-1068.9)
T2	73.3%(63.8-81.5)	93.4%(90.3-95.7)	9.8(5.4-17.8)	0.3(0.2-0.6)	37.6(11.9-118.1)
T3	86.5%(79.8-91.7)	91.2%(87.5-94.0)	8.9(4.8-16.3)	0.2(0.1-0.4)	83.3(26.2-264.2)
T4	91.8%(81.9-97.3)	98.3%(96.4-99.4)	25.1(12.8-49.4)	0.1(0.1-0.2)	215.3(71.8-645.8)

Table 2: Pooled diagnostic accuracy estimates of EUS for different time periods with 95 % confidence intervals.

Time period	No of Studies	Pooled Sensitivity	Pooled Specificity	Pooled +LR	Pooled - LR	Pooled DOR
1990-2000	3	77.8%(65-87.3)	92.7%(80.1-98.5)	7.2(2.8-18.2)	0.28(0.11-0.71)	36.2(10.3-127.5)
2001-2008	4	81.3%(74.3-87.0)	73.6%(65.8-80.5)	3.0(2.0-4.6)	0.28(0.19-0.38)	12.6(7.2-22.0)

LR+ - Positive Likelihood Ratio
LR- - Negative Likelihood Ratio
DOR – Diagnostic Odds Ratio

cardia cancer was 90% (83.2-94.7) and 99.1% (97.3-99.8), respectively. T2 staging for GCC had a pooled sensitivity and specificity of 73 % (63.8-81.5) and 93.4% (90.3-95.7), respectively. T3 staging for GCC had a pooled sensitivity of 86.5% (79.8-91.7) and specificity of 91.2% (87.5-94.0), respectively. T4 staging for GCC had a pooled sensitivity and specificity of 91.8% (81.9-97.3) and 98.3% (96.4-99.4), respectively. 23

Accuracy of EUS for N staging

Pooled sensitivity of EUS in diagnosing nodal involvement of gastric cardia cancers was 80% (95% CI: 74.4-85.3). EUS had a pooled specificity of 77.8% (95% CI: 71.2 – 83.5) for nodal involvement. The positive likelihood ratio of EUS was 3.7 (95% CI: 2.4 - 5.8) and negative likelihood ratio was 0.3 (95% CI: 0.2 - 0.4). The diagnostic odds ratio, the odds of having nodal metastasis in positive as compared to negative EUS studies was 14.9 (95% CI: 8.9 - 24.9). All the pooled estimates calculated by fixed and random effect models were similar.

DISCUSSION

EUS has revolutionized our ability in diagnosing and staging of luminal upper gastrointestinal tract cancers since it's introduction in early 1990's. Additionally it has the distinct advantage over the cross sectional imaging in identifying different layers of the stomach with the potential for more accurate T stage. Gastric cardia cancers for one have gained interest recently because of raising incidence along with distal esophageal adenocarcionoma, possibly because of shared histologic origin including short segment Barrett's esophagus. Curative intent with total gastrectomy with regional lymph node dissection is the treatment of choice in early stage disease. D2 Lymph node dissection is recommended over D1 in high volume centers in the United States despite previously published randomized trials showing no survival benefit and an added increase in morbidity in the former group [24-27]. Accurate pretreatment tumor staging could assist in correctly selecting patients for surgical cure if clinical staging closely resembles that of true pathologic stage, especially when at an early stage. If this could be achieved with EUS as a staging modality, it could be extremely useful in appropriate identification of surgical candidates. Additionally, prognosis and survival in gastric cancers is stage specific with

improved survival is noted in early stage disease i.e. negative lymph node and tumor depth [28]. Typically, locoreginal staging with specific information regarding the T and N stage is undertaken when there is no clear evidence of metastasis as demonstrated by CT or integrated PET scan. Our current analysis on diagnostic accuracy of EUS for gastric cardia cancers shows excellent pooled sensitivity and specificity for both T and N stage disease when compared to the reference standard, which is final pathologic specimen.

From our current analysis T stages has a pooled sensitivity ranges between 73% to >90% with relatively modest sensitivity for T2 stage. The higher diagnostic accuracy for T1 stage would mean selecting patients for endoscopic mucosal resection and avoiding surgery, which carries risk and added complications. EUS does perform better with more advanced disease (T3, T4) than early disease (T2). The notably modest sensitivity for T2 could be due to overstaging and could result from peritumor inflammation. Given these findings for the T2 stage of the disease, patient's treatment decision for or against curative surgery will likely not be made on these findings. Specificity of T staging is > 90% in all instances, with 99% specific in advanced (T4) disease. EUS has a very high diagnostic odds ratio for each particular stage. For example, if EUS says that a patient has advanced T4 disease, then that patient is 215 times likely to have that stage of disease. The diagnostic odds is an important factor when deciding further treatment options and prognosis in order to confidently give the patient accurate information. Nodal staging by EUS has modest sensitivity approaching of 81%. Pooled specificity for N staging was around 77%. Addition of FNA for confirmation could significantly improve sensitivity and specificity of nodal status.

A major limitation in our current analysis is inclusion of studies that had low to moderate quality of evidence and were small and retrospective in nature, which could increase the likelihood of selection bias.

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

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