ORIGINAL ARTICLES—ALIMENTARY TRACT

Endoscopic Ultrasound Does Not Accurately Stage Early Adenocarcinoma or High-Grade Dysplasia of the Esophagus

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This article has an accompanying continuing medical education activity on page e125. Learning Objectives—At the end of this activity, the learner should be able to recognize the importance of staging for esophageal adenocarcinoma, appreciate the limitations of endoscopic ultrasound to stage early cancer, and understand the potential role of endoscopic mucosal resection for staging.

See related article, Peters CJ et al, on page 1995 in *Gastroenterology*.

BACKGROUND & AIMS: Patients with esophageal high-grade dysplasia or mucosal esophageal cancer can be successfully treated by endoscopy. We performed a systematic review of the literature to determine whether endoscopic ultrasound (EUS) correctly predicts the T-stage of early esophageal cancers, compared with pathology specimens obtained by using endoscopic mucosal resection (EMR) or surgery. **METHODS:** Standard systematic review methods were used to perform reference searches, determine eligibility, abstract data, and analyze data. When possible, individual patient-level data were abstracted, in addition to publication-level aggregate data. **RESULTS:** Twelve studies had sufficient information to abstract and review for quality; 8 had individual patient-level data (n = 132). Compared with surgical or EMR pathology staging, EUS had T-stage concordance of 65%, including all studies (n = 12), but only 56% concordance when limited to individual patient-level data. Factors such as initial biopsy pathology (high-grade dysplasia vs early-stage cancer) did not appear to affect the concordance of staging between EUS and EMR/surgical staging. **CONCLUSIONS: EUS is not sufficiently accurate in determining the T-stage of high-grade dysplasias or superficial adenocarcinomas; other means of staging, such as EMR, should be used.**

Keywords: Endosonography; Esophageal Cancer; Barrett's Esophagus; Staging.

Adenocarcinoma of the esophagus (ECA) has the fastest rising prevalence of any malignancy in the Western world.[1] The vast majority of ECA arise from specialized intestinal metaplasia in the esophagus, so-called Barrett's esophagus.[2,3] Because surveillance of Barrett's esophagus is now recommended by specialty societies, endoscopists are discovering more high-grade dysplasia (HGD) and early malignancies that might be amenable to endoscopic therapy.[4–9]

The risk of lymph node involvement in esophageal adenocarcinoma correlates best with the depth of invasion.[10,11] Cancers that are confined to the mucosa have a risk of nodal involvement of less than 2%, whereas nodal involvement is present in 19% of patients with cancer that invades submucosa (T1sm).[12,13] Accurate pretreatment staging of cancer is necessary to determine the proper therapeutic modality for the individual patient. Tumor depth staging (ie, T-staging) is the primary determinant of whether a lesion might be completely resected endoscopically. Many studies of endoscopic resection therapy to date have used endoscopic ultrasound (EUS) to assess the depth of tumor invasion before resection. As such, an important clinical question is the accuracy of EUS in determining which histologic layers are involved. The purpose of this systematic review is to determine, in adults undergoing EUS for pretreatment staging of ECA, the accuracy of EUS in determining the depth of invasion of early esophageal cancers.

Methods

Literature Search and Eligibility Determination

Two gastroenterologists (A.G., R.A) and a medical librarian performed independent searches of the published literature to include MEDLINE, EMBASE, and OVID. The search was limited to English-language publications and to clinical trials and humans and included the following MeSH search terms: "endoscopic ultrasound," "Barrett's esophagus," "adenocarcinoma," "Barrett's esophagus and high grade dysplasia," "endoscopic ultrasound and high grade dysplasia or adenocarcinoma." The search was performed from January 1, 1980, to June 30, 2008. The year 1980 was chosen as the origin because EUS was not performed before this date. From the resultant search, the abstracts that contained "EUS" or "endoscopic ultrasound" were included for review. If no abstract was included, the article was retrieved for review. The reference lists of each of these publications were reviewed for articles that might have been missed on the initial search. Studies published only in abstract form, conference abstracts or symposium proceedings, and case reports were not eligible for inclusion. The retrieved articles were reviewed for eligibility by 3 gastroenterologists (P.Y., A.G., R.A.), one of whom is a trained endosonographer (P.Y.). To be included in the systematic

Abbreviations used in this paper: ECA, adenocarcinoma of the esophagus; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; HGD, high-grade dysplasia.

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review, the study participants had to (1) be 18 years old or older, (2) have undergone EUS for the pretreatment staging of early (stage T1m, T1sm, T2) esophageal adenocarcinoma, and (3) have undergone resection of the ECA so that definitive pathologic T-staging was available for comparison to the EUS staging. The staging of the resection specimen was considered the gold standard for comparison.

Data Extraction and Quality Scoring

Two unblended independent investigators (A.G., R.A.) extracted data from each of the publications by using a standardized and pretested data extraction form. Data elements extracted related to the primary outcome of interest included EUS staging results and surgical staging results. Data that might influence the interpretation or differential findings of the primary outcome were extracted and included study year, publication year, publication type, patient age, ultrasound frequency, criteria used for surgical intervention, length of Barrett's segment, presence of visible lesions, and prior Barrett's ablation therapy. There was a high degree of agreement between the 2 investigators. Conflicts were resolved by a third investigator (P.Y.) when necessary. A published assessment tool was used to evaluate the quality of the studies included in the review; however, given that all the studies were case series, there was little differentiation in quality, and thus, assessment of effect for study quality was limited.[14]

Statistical Analyses

Analyses were conducted by use of Stata Version 10 (StataCorp LP, College Station, TX). In addition to descriptive statistics on the included studies, meta-analysis was used to pool estimates and 95% confidence intervals of proportion of tumors correctly T-staged by using EUS compared with surgical or endoscopic mucosal resection (EMR) pathology staging, by using a random effects model by the method of DerSimonian and Laird.[15] Heterogeneity was assessed graphically by using forest plots and statistically by using the χ^2 test for heterogeneity and explored by the use of multiple subgroup analyses to determine any differences of estimates through stratification.[16,17]

For studies in which individual patient-level data were extractable, the dichotomous outcome of correct tumor staging was evaluated by using appropriate univariate methods for association with a particular covariate (eg, age, gender, visibility of lesions, tumor histology). A statistical significance level was set as $P < .05$ for all analyses.

Results Study Characteristics

Forty-four articles were retrieved for eligibility and reference list review. Thirty-two articles were excluded on the basis of not meeting the following eligibility criteria (Figure 1). Six of the articles were excluded for insufficient EUS data defined as the inability to correlate EUS, if provided, to either surgical or EMR pathology. Four of the studies evaluated more invasive carcinoma and were not pertinent to the clinical question.Three were equipment evaluations comparing different endoscopic arrays with new technology. Three were evaluations of patients with squamous cell carcinoma and did not pertain to our clinical question. One study by Murata et al[18] included 54 patients, 51 with squamous cell carcinoma and 3 labeled as others. Although the "other" cancers were likely ECA, this was not specifically documented, so the study was excluded. One case report, 1 photodynamic therapy article, and 1 restaging

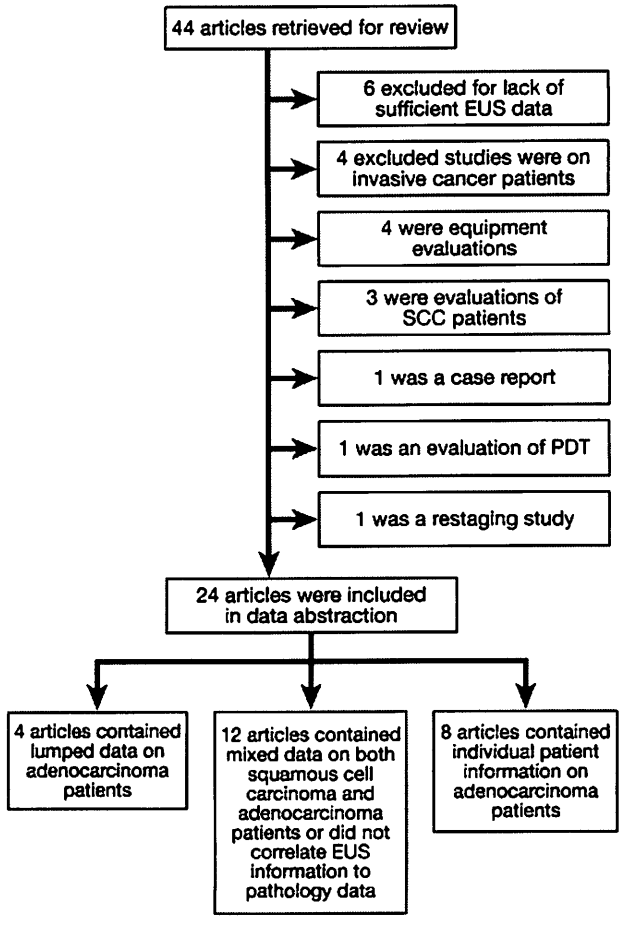

Figure 1. Schema for article selection and retrieval.

study were also not included. Twelve of the 24 articles included patients with squamous cell carcinoma. We attempted to contact the corresponding authors to ask for adenocarcinoma-only patient data, and only 1 author replied to say the data were not available in requested format, whereas the rest did not respond to our single query. The remaining 12 articles had sufficient information to abstract.[19-30] Of these 12 articles, 8 had patient individual information on 132 patients that could be abstracted. One article (Mino-Kenudson et al[24]) identified several lesions on each patient, so the highest grade lesion on pathology was used for analysis. Buskens et al[20] included patients who had nonendoscopically resectable tumors, so we only included patients with T-staging less than or equal to T2 for evaluation. In total, these 12 articles included data on 292 patients comparing EUS with surgical or EMR staging (Table 1).

Primary Outcome

Overall, when comparing the EUS staging with surgical or EMR pathology, EUS correctly predicted the T-stage of the target lesion with 67% accuracy (Figure 2, forest plot). There was significant heterogeneity between articles that could not be explained on the basis of study factors including publication year, quality, or percent of histology that was adenoma or HGD. On the basis of the individual patient-level analysis, the accuracy of correct staging was less at 56%. Differential accuracy of

Table 1. Articles Included for Review

Article	Year	Study dates	Study type and information source	Patient data reported	n	Patients with HGD at biopsy	Patients with nodules	No. EUS, same	No. EUS, high low
Buttar et al[30]	2001	1996–1999	CSP, nonsurgical candidates or refused surgery	Yes	17	0	N/A	9	8
Maish and DeMeester[23a]	2004	2001–2003	CSR, evaluation before surgery	Yes	7	0	7, entry criteria	2	3
Waxman et al[29]	2006	1996–1998	CSP, evaluation before surgery	Yes	9	7	7[b]	5	4
Nijhawan and Wang[25]	2000	1995–1998	CSNS, endoscopic treatment of lesions	Yes	25	5	25, entry criteria	13	12
Shami et al[28]	2006	2002–2004	CSNS, endoscopic treatment of HGD or intramucosal adenocarcinoma	Yes	25	12	18	9	8
Falk et al[21]	1994	1990–1991	CSNS, evaluation before surgery	Yes	9	9	3	4	5
Scotiniotis et al[27]	2001	1994–2000	CSR, evaluation before surgery	Yes	22	15	12	16	6
Mino-Kenudson et al[24]	2005	1998–2003	CSNS, nonsurgical candidates or refused surgery	Yes	18	5	18	8	6
Lopes et al[22c]	2007	1999–2005	CSR, endoscopic treatment for HGD	No	41	18	12	21	1
Prasad et al[26]	2007	1995–2004	CSR, evaluation before surgery	No	25	15	17	3	14
Barbour et al[19]	2007	1985–2003	CSR, evaluation before surgery, excluded T2 cancer and higher	No	76	0	N/A	51	25
Buskens et al[20d]	2004	1993–2001	CSR, evaluation before surgery	No	77	13	N/A	39	6

CS-NS, not specified case series; CSP, prospective case series; CSR, retrospective case series; N/A, not available.
[a]Two patients did not have preoperative EUS.
[b]Described as mucosal irregularities: erythema, erosion, flat nodule, nodular-appearing gastroesophageal junction, multiple superficial erosions.
[c]No EUS performed in patients with HGD.
[d]EUS performed in all patients; 30 did not report intramucosal and submucosal growth.

staging was not explained by patient gender, age, initial biopsy pathology, HGD, or early adenocarcinoma.

Discussion

Whereas providing therapy for early esophageal adenocarcinoma and HGD was previously the domain of the surgeon, these conditions are increasingly being treated endoscopically.[8,31-33] Traditionally, EUS has been performed prior for staging of esophageal adenocarcinoma and HGD. Recently, this practice has come into question because of questions regarding the accuracy of EUS staging of dysplasia and ECA confined to the mucosa.[34] The results of this systematic review further reinforce the concept that pretreatment EUS for HGD or mucosal esophageal adenocarcinoma is unnecessary and might in fact be misleading.

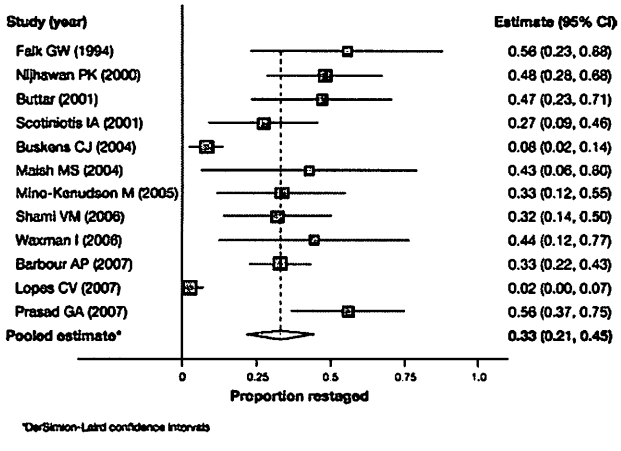

Figure 2. Forrest plot of staging accuracy. CI, confidence interval.

There are several factors that might help explain the relatively poor performance of EUS as a staging tool in early cancer. First, adenocarcinoma generally arises from Barrett's esophagus. Prior studies have shown altered esophageal wall anatomy in Barrett's esophagus, with thickening of the muscularis mucosa.[35] Moreover, duplication of the muscularis mucosa and musculofibrous anomaly in patients with Barrett's esophagus has been reported recently.[36,37] In some cases, this anomaly might lead to inaccurate cancer staging in histologic samples because the hypertrophic, redundant muscular layer might be mistaken for the muscularis propria. Because such duplication does not necessarily occur in a uniform fashion, it is possible that this phenomenon might contribute to inaccurate staging with EUS as well.

An additional factor that might lead to inaccurate staging is endoscopist experience. Studies have shown significant variation in the interpretation of endosonographic images, even among

expert endosonographers.[38-40] Staging small, superficial lesions is challenging, particularly in delineating the most superficial layers, which in Barrett's esophagus might be indistinct. We know that endoscopist experience and volume might affect performance in a number of domains.[41-43] The studies reviewed in our analysis are from expert centers; therefore, the 65% accuracy discovered in this systematic review likely represents that best-case scenario for the accuracy of endosonography in this setting.

It is important to differentiate the performance of EUS in the evaluation of HGD and early ECA from its performance in more advanced lesions. In the latter cases, the risk of lymph node metastasis is significantly higher, and optimal therapy hinges on accurate pretreatment staging. EUS with fine-needle aspiration has been shown in several studies to be up to 30% better than conventional computed tomography scanning for identifying malignant lymphadenopathy.[44,45] For these reasons, evidence-based guidelines on the use of EUS published recently in *Endoscopy* recommend its use for esophageal cancer TNM staging.[46]

EMR has recently emerged as an option for both staging and therapy of early Barrett's-related ECA.[47,48] Recently, EMR was compared with surgery in patients with mucosal ECA (stage 1a).[48] Results from this trial of 178 patients with a follow-up period of 43 months showed a cumulative mortality in the endoscopically treated group (17%) that was comparable to the surgically treated group (20%) ($P = .75$). Recurrent carcinoma was detected in 12% of patients in the endoscopically treated group, all of whom were successfully re-treated without impact on overall survival.

Our systematic review has several limitations that warrant mentioning. First, there is enough heterogeneity between the studies that a meta-analysis is not possible. This heterogeneity might be due to several factors including different proportions of mucosal and submucosal cancers within studies, different macroscopic tumor types, and location of some tumors at the gastroesophageal junction or cardia, which is a more difficult area to accurately image.[49] Second, in any such review, it is possible that salient articles were missed or were published in languages not spoken by the reviewers. Our rigorous adherence to prespecified search criteria should minimize this risk. Finally, relevant articles might have been published since the analysis that would alter its results. In repeating the search, several relevant articles that meet the a priori specification have been published since our review. The first was a retrospective study conducted in the United Kingdom at 2 tertiary care facilities with expertise in endosonography.[50] Examinations were conducted by using a radial endosonoscope. Fifty patients were included, all of whom had visible lesions in a Barrett's segment and underwent esophagectomy (n = 23), EMR (n = 17), or both (n = 6). For the detection of submucosal invasion, the most clinically relevant end point, EUS had a sensitivity of 66%. This is in keeping with our pooled analysis presented above and would not have changed the outcome of the systematic review. The second was published by Chemaly et al[51] and examined the use of miniprobe endosonography to differentiate T1m from T1sm lesion for both ECA and squamous cell carcinoma.[51] The staging accuracy of miniprobe EUS for the ECA subset was 70.6% and did not differ between the 2 probe frequencies (20 vs 30 MHz). Finally, repeat hand search before submission revealed an article by Pech et al[52] that likely would have been included for analysis.[52] This study of 100 consecutive patients with Barrett's esophagus and early adenocarcinoma found EUS examination to have perfect accuracy for differentiating T1 from >T1 lesions but a lower sensitivity and specificity for distinguishing T1m from T1sm tumors (89% and 27%, respectively). A recent study from this same group showed a sensitivity and specificity of 43% and 85%, respectively, for EUS staging of T1 lesions.[53] Inclusion of these studies would not have meaningfully altered our conclusions.

The optimal management of Barrett's-related HGD and early cancer remains a matter of debate. Methodical endoscopic evaluation with EMR of visible lesions remains the current standard. Although endosonography is useful for detecting nodal involvement, particularly in more advanced cancers, EUS for mucosal evaluation in early lesions has insufficient accuracy to warrant its inclusion in this process.

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Conflicts of Interest

The authors disclose no conflicts.