

Endoscopic Ultrasound Estimates for Tumor Depth at the Gastroesophageal Junction Are Inaccurate: Implications for the Liberal Use of Endoscopic Resection

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Background. Endoscopic resection is increasingly utilized for treating early stage esophageal cancer, and endoscopic ultrasound (EUS) frequently guides treatment selection. Studies report greater than 80% sensitivity and 90% specificity, but our experience suggests less accuracy at the gastroesophageal (GE) junction. The objective of this study is to determine the accuracy of EUS for depth of GE junction cancer and the potential treatment implications.

Methods. A retrospective review of a prospective database was performed for patients from 1995 to 2014 with GE junction esophageal cancer that underwent EUS staging and resection (surgical or endoscopic) without neo-adjuvant therapy. Patient, tumor, EUS, and pathologic characteristics were examined.

Results. For the 181 patients that met criteria, the median age was 66 years, 17% were female, 91% white, and 98% had adenocarcinoma. Concordance between EUS (u

T and pathologic (p) T was 48%, with 23% under-staged and 29% over-staged. The EUS was accurate in the following: uT0 6% (1 of 18); uT1a 56% (23 of 41); uT1b 58% (41 of 71); uT2 10% (2 of 21); and uT3 70% (21 of 30). Inaccurate EUS depth had potential to lead to over-treatment in 38% (27 of 71) of uT1b and 76% (16 of 21) of uT2. In 50% of pT1a tumors, EUS depth was T1b or greater. Logistic regression revealed tumor length (continuous variable) to be associated with inaccurate uT ($p = 0.016$). Accurately staged tumors were significantly longer than inaccurately staged tumors (2.7 vs 1.7 cm, $p = 0.011$).

Conclusions. Early to intermediate GE junction tumors are frequently over-staged. This highlights the importance of diagnostic endoscopic resection for determining accurate tumor depth and selecting correct therapy.

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Esophageal cancer is an aggressive malignancy that frequently presents at an advanced stage. In the United States the incidence of esophageal cancer continues to rise, with approximately 18,000 new cases and 15,000 deaths per year [1]. The last 2 decades have seen the implementation of multimodality therapy to improve cure rates and disease-free survival. However, the prognosis of this cancer remains grim, with low 5-year survivals.

Staging is a key component to directing treatment for esophageal cancer because surgical and medical therapy varies significantly for locally limited, locally advanced,

and metastatic disease. Selecting appropriate treatment based on staging significantly impacts quality of life, morbidity, and mortality. Some centers advocate the treatment of locally limited (T1aN0M0) esophageal cancer by endoscopic resection with close follow-up, while surgical or multimodality therapy is employed for locally advanced cancers [2-4].

While computed tomography and positron emission tomography scan are utilized in staging, endoscopic ultrasound (EUS) is considered the standard for determining tumor depth, which often differentiates locally limited from locally advanced esophageal cancer [5]. Studies report sensitivity and specificity of EUS for tumor depth in early esophageal cancer as greater than 80% and 90%, respectively [6]. Some studies suggest the accuracy of EUS for determining tumor depth of esophageal tumors at the gastroesophageal (GE) junction may not be this high [7-11]. The objective of this study is to determine the accuracy of EUS for tumor depth of GE junction esophageal cancer by comparing EUS with pathologic tumor depth.

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Acronyms and Abbreviations

EMR	= endoscopic mucosal resection
EUS	= endoscopic ultrasound
GE	= gastroesophageal
pT	= pathologic tumor depth
uT	= EUS tumor depth

Material and Methods

Approval was granted by the MD Anderson Cancer Center Institutional Review Board for this study. We performed a retrospective review of a database of 2,413 patients who underwent esophagectomy (2,189) or endoscopic mucosal resection (EMR; 224) between January 1995 and January 2014. Inclusion criteria for this study were the following: (1) patients undergoing esophagectomy or EMR for primary adenocarcinoma or squamous cell carcinoma of the GE junction only; (2) no preoperative chemotherapy or radiation; (3) no previous esophagectomy; and (4) preoperative EUS tumor depth and pathologic tumor depth data available. A total of 181 patients met these criteria (100 esophagectomy patients, 81 EMR patients). The patient selection flow diagram is shown in Figure 1. Because this is a study to examine tumor depth, we did not include lymph node status in the results. Of 181 patients, 114 underwent esophagectomy. Lymph node data were not available for 1 patient. Pathologic lymph node status was N0 = 73, N1 = 20, N2 = 11, and N3 = 9.

The GE junction esophageal tumors had the epicenter no more than 5 cm above or 2 cm below the GE junction. Carcinoma in situ (T_{is}) was considered as T0 as we would expect EUS findings to be similar to T0. All patients had EUS and resection (esophagectomy or EMR) performed at 1 institution, and all pathologic specimens were reviewed at this institution. Pathologic staging is based on American Joint Committee on Cancer 7th edition guidelines, with invasion into duplicated muscularis mucosae considered as T1a. Ninety-two percent of patients were resected to negative margins. For EMR patients, only the deep margin was assessed for being positive or negative as most EMR were done in piece-meal, and positive radial margins would not necessarily reflect incomplete resection. All endoscopy reports were reviewed and in all cases the tumor was felt to be completely resected radially by the endoscopist.

The EUS procedures were performed by 4 gastroenterologists at MD Anderson Cancer Center. All have advanced training and see these cases regularly, in the last several years performing more than 1,000 per year. This experience has increased over time as EUS was a relatively new modality in the 1990s. Typically, tumor depth is assessed with a radial echo endoscope (5 to 12 MHz), but the linear scope is used occasionally based on operator preference. Miniproboscopes (10/12 and 20 MHz) are used rarely, usually for small or flat lesions.

We analyzed demographics, EUS depth, pathologic depth, and survival. The EUS inaccuracy was determined by comparing tumor depth on EUS to tumor depth on

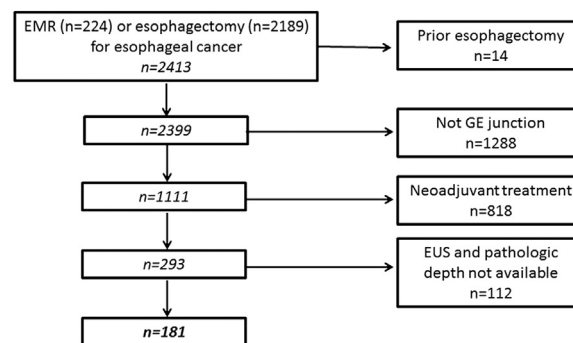


Fig 1. Flow chart demonstrating patient selection for this study. (EMR = endoscopic mucosal resection; EUS = endoscopic ultrasound; GE = the gastroesophageal.)

pathology. For statistical analysis, Kaplan-Meier survival curves were constructed based on EUS and pathologic stages. A logistic regression was performed to determine how presence of Barrett's esophagus, tumor length (continuous variable), and pathologic tumor depth relate to EUS accuracy. For this analysis pT0, pT1a, and pT1b tumors were lumped, and pT2, pT3, and pT4 tumors were lumped. Variables were not chosen based on univariate analysis. The Mann-Whitney *U* test determined if average length of accurately staged tumors was different from inaccurately staged tumors. Values were considered to be statistically significant if the *p* value was less than 0.05.

Results*Patient and Pathologic Characteristics*

There were 181 patients with GE junction esophageal cancer that underwent resection by esophagectomy (n = 100) or EMR (n = 81) and that did not have neo-adjuvant treatment. The median age was 66 years (range, 40 to 86), 91% of patients were white, and 17% were women.

Adenocarcinoma of the GE junction was present in 98% of patients, and 2% were squamous cell cancer. Tumors were well differentiated in 5%, moderately differentiated in 54.7%, poorly differentiated in 36.5%, undifferentiated in 0.6%, and could not be assessed in 3.3%.

Endoscopic Ultrasound Accuracy

We examined how EUS tumor depth (uT) correlated with pathologic tumor depth (pT). The number of patients with each tumor depth as determined by both EUS and pathology are shown in Table 1. We also examined if patients had uT that correlated with pT on an individual basis, and found that EUS was accurate in only 48% (88 of 181) of cases. Accurate EUS staging occurred in 5.6% (1 of 18) of patients with uT0, 56.1% (23 of 41) of patients with uT1a, 57.7% (41 of 71) of patients with uT1b, 9.5% (2 of 21) of patients with uT2 lesions, and 70% (21 of 30) of patients with uT3 lesions (Fig 2).

Additionally, we analyzed the circumstances in which uT was deeper or less deep than pT. Patients were under-staged 23% (42 of 181) of the time, and were over-staged

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