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The Impact of Endoscopic Ultrasound Findings on Clinical Decision-making in Barrett's Esophagus with High-Grade Dysplasia or Early Esophageal Adenocarcinoma

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Abstract

Background & Aims—The clinical utility of endoscopic ultrasound (EUS) for staging patients with Barrett's esophagus (BE) and high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) prior to endoscopic therapy is unclear.

Methods—Retrospective analysis of patients with HGD or IMC referred to an American medical center for endoscopic treatment between 2004 – 2010. All patients had pre-treatment staging by EUS. We examined the frequency that EUS findings consistent with advanced disease (tumor invasion into the submucosa, lymph node involvement, or regional metastasis) led to a change in management. The analysis was stratified by nodularity and pre-EUS histology.

Results—135 patients with HGD (n=106, 79%) or IMC (n=29, 21%) had staging by EUS (79 non-nodular, 56 nodular). Pathologic lymph nodes or metastases were not found by EUS. There were no endosonographic abnormalities noted in any patient with non-nodular mucosa (0/79). Abnormal EUS findings were present in 8/56 patients (14%) with nodular neoplasia (5 IMC, 3 HGD). EMR was performed in 44 patients with a nodule, with 13% (6/44) having invasive cancer. In nodular neoplasia, the EUS and EMR were abnormal in 24% (5/21) and 40% (6/15) of those with IMC and 9% (3/35) and 0% (0/29) of those with HGD, respectively.

Conclusions—EUS did not alter management in patients with non-nodular HGD or IMC. Because the diagnostic utility of EUS in subjects with non-nodular BE is low, the value of performing EUS in this setting is questionable. For patients with nodular neoplasia, resection of the nodule with histologic examination had greater utility than staging by EUS.

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Keywords

EUS; Barrett; dysplasia; utility

Background & Aims

In the last decade, endoscopic therapies have emerged as effective, well-tolerated, and safe alternatives to esophagectomy for carefully selected patients with Barrett's esophagus (BE) and dysplasia or early esophageal adenocarcinoma.(1-3) Neoplasia limited to the mucosa and superficial submucosa (sm1) rarely spreads to regional lymph nodes, while 20% of sm2 tumors and more than 50% of sm3 tumors metastasize.(4, 5) Endoscopic techniques reliably cure tumors limited to the mucosa, while esophagectomy is favored for extension to the deep submucosa. For this reason, pre-treatment staging is critical to selection of optimal therapy.

The utility of endoscopic ultrasound (EUS) as a staging tool for superficial esophageal neoplasia is unclear. Proponents cite its superiority to alternative staging tools such as helical computed tomography for delineating depth of tumor invasion and the presence of pathologic lymph nodes.(6) EUS may avoid understaging and insufficient treatment of advanced disease. However, EUS may have limited accuracy for superficial esophageal neoplasia. One meta-analysis demonstrated just 65% concordance of EUS with endoscopic mucosal resection (EMR) or surgical pathology for tumor staging.(7) A second study demonstrated improper treatment in 16.5% of patients due to EUS misdiagnosis.(8) The accuracy of EUS in nodular versus non-nodular BE was not assessed in either study.

EUS is still routinely performed in many medical centers to evaluate depth of infiltration and the presence of lymph nodes prior to endoscopic therapy. This is often done with concurrent targeted EMR for nodular lesions, and as a lone staging tool for non-nodular BE. There is a paucity of literature on the utility of EUS for pretreatment staging at American medical centers. Additionally, the utility of EUS for pre-treatment staging of nodular versus non-nodular BE has not been adequately examined. The aim of this retrospective study was to evaluate how frequently EUS changed the management approach to patients with early esophageal neoplasia (nodular versus non-nodular). Based on clinical experience, we hypothesized that EUS would infrequently impact clinical decision-making.

Methods

Data collection and patient eligibility criteria

We performed a retrospective study of adult patients with BE and confirmed high-grade dysplasia (HGD) or intramucosal carcinoma (IMC) who had EUS prior to undergoing endoscopic therapy at University of North Carolina (UNC) Hospitals. To identify all such subjects at our institution, we searched our electronic endoscopic database (ProvationMD, Wolters Kluwer, Minneapolis, MN) from December 1, 2004 through November 1, 2010 using the following terms: upper EUS, Barrett, esophageal adenocarcinoma, cancer, carcinoma in situ, dysplasia, ablation, photodynamic therapy, thermal, YAG laser. We also searched for procedure codes for EGD with EUS (43231, 43237, 43259) or EUS and fine needle aspiration (43242).

Each subject was reviewed by one of two investigators (WB, AR) using the electronic medical record (WebCIS, University of North Carolina Health Care System) to determine eligibility for inclusion. All institutional health information plus imported external records were reviewed. Subjects were excluded if they did not have Barrett's esophagus with HGD or IMC, never had an EUS, or the EUS was performed for an indication other than pre-ablation staging (such as staging of known invasive adenocarcinoma).

Pertinent data were extracted from clinical, endoscopy, and pathology reports for each subject, including: demographic information (age, gender, race, body mass index), pre-EUS histology, endoscopic (Prague C and M class, presence of ulcer, esophagitis or nodule) and EUS findings (depth of tumor invasion or lymph nodes), fine needle aspiration results (when performed), pathology after endoscopic mucosal resection (EMR) or surgery, and treatment outcome (endoscopic therapy, esophagectomy, chemoradiation, or hospice care). To standardize methodology, the first ten subjects were reviewed by both investigators jointly with discrepancies in data collection resolved by consensus. For additional quality control, every 20th study subject was reviewed independently by both investigators to assess inter-rater agreement.

Histologic grade of BE with dysplasia was determined by review of original pathology reports. In all cases, review by a second expert gastrointestinal pathologist was performed as part of their routine care, and if findings discordant, by an additional expert gastrointestinal pathologist for categorization. Focal dysplasia was defined as dysplasia occurring in a single biopsy during any given endoscopic procedure, while multifocal dysplasia was dysplasia noted in more than one biopsy location from any given procedure.

Endoscopic, EUS, and EMR evaluation

All patients underwent upper endoscopy at our center with Prague M and C criteria established, and the macroscopic presence of ulcer, nodule or other mucosal abnormality recorded.(9) Prague M length was defined as the maximum length of the Barrett's segment, from the top of intestinal metaplasia to the top of the gastric folds. Prague C length was defined as the maximum circumferential length of the Barrett's segment beginning at the top of the gastric folds. Disruption of the mucosal barrier with discernable depth was noted as an ulcer (Paris classification 0-III) while contoured irregularity and elevation of the mucosa without breaks was noted as nodularity (Paris classification 0-I, 0-IIa).(10) Nodules were defined by endoscopic, not endosonographic, criteria.

EUS was performed on the same day as the upper endoscopy with a 7.5-MHz radial-scanning echoendoscope (Olympus GF-UE160) to detect depth of tumor invasion and any lymphadenopathy. Higher ultrasound frequencies, mini-probes, and modified balloons were not used during the exam. All EUS exams were performed by one of three echoendoscopists, each with greater than 300 upper EUS exams performed. T staging was performed with EUS using standard EUS definitions based on the TNM classification system: T1, invasion up to the third layer (submucosal layer); T2, invasion into but not through the fourth wall layer (muscularis propria); T3, invasion beyond the fourth wall layer into the adventitia; T4, invasion of adjacent structures, i. e., pleura, aorta, lung.(8, 11) Fine needle aspiration was performed with a linear-scanning echoendoscope (Olympus GF-

UC140P) if lymph nodes exhibited at least two of the following EUS criteria: diameter greater than 1 cm, round shape with discrete margins, and hypoechoic texture. Lymph nodes were considered positive if fine needle aspiration confirmed histologic evidence of adenocarcinoma

EMR was performed for resection of nodular disease (Paris 0-I, 0-IIa) using either the Olympus 18 mm oblique cap kit (Olympus America, Center Valley, PA), or the Duette device (Cook Medical, Winston-Salem, NC). All EMR's performed with the Olympus system were performed after submucosal injection of saline, while Duette EMR was performed without prior injection. Narrow band imaging was performed during endoscopic evaluation, however EMR of non-nodular mucosa was not performed.

Outcome measurement and statistical analysis

The treatment strategy for each patient was determined by pre-ablation T- and N-staging. EUS was performed first for all patients being considered for endoscopic therapy. If EUS revealed invasion into the submucosa or histologically-confirmed nodal spread, endoscopic therapy was considered contraindicated by EUS criteria, and the patient was considered for surgery or palliative modalities. If the EUS was normal, patients with nodular mucosa (Paris 0-I, 0-IIa) had EMR to evaluate for submucosal or lymphovascular invasion (contraindications to endoscopic therapy by EMR criteria). Patients with a contraindication to curative endoscopic therapy by EUS or EMR were considered for surgery, chemoradiation, palliative (non-curative) endoscopic therapy, or hospice care. If pre-ablation staging did not reveal a contraindication, patients were treated with curative intent by one of four endoscopic ablation modalities: radiofrequency ablation (RFA), cryotherapy, photodynamic therapy (PDT), or argon plasma coagulation (APC).

The primary outcome of this study was the frequency that patients were excluded from endoscopic therapy based on EUS findings. Given our practice to perform EMR only for nodular mucosa, we stratified our analysis by whether the patient had flat or nodular mucosa, to delineate the utility of EUS for these subgroups. We also report the rate of disagreement between EUS findings and available pathology (surgical or EMR) as a measure of the frequency that EUS provided inaccurate and potentially misleading pretreatment staging information. However, this study was not designed to assess the accuracy of EUS for staging in this setting, as multiple studies have assessed accuracy of EUS in superficial esophageal neoplasia.(7, 8, 12-14)

For statistical analysis, patient characteristics were described using medians for continuous variables (unless otherwise stated) and proportions for categorical variables. Inter-rater agreement for data extraction was calculated using Cohen's kappa coefficient. All statistical tests were performed using Stata v. 11.1 (StataCorp LP, College Station, TX). This study was approved by the UNC Institutional Review Board.

Results

The initial search of our endoscopic database identified 275 potential subjects. One hundred forty were excluded for the following reasons: 9 did not have Barrett's with high-grade

dysplasia or intramucosal carcinoma, 37 did not have an EUS, and 94 had an EUS for an indication other than clinical staging before intended endoscopic therapy (i.e. staging of known invasive adenocarcinoma). The remaining 135 patients were included for analysis. Inter-rater agreement for data extraction was 94% overall. Cohen's kappa coefficient was excellent at 0.89 ($p < 0.0001$).

The median age of subjects was 65 years old (interquartile range: 58 - 74) (Table 1). Most subjects were white (98%) and male (83%). Median body mass index was 29 kg/m² (IQR: 25 - 34). A pre-procedure diagnosis of high-grade dysplasia (70% focal, 9% multifocal) was more common than intramucosal carcinoma (21%). There were no complications attributable to EUS or EMR during the study.

Patients with abnormal EUS Findings

Figure 1 demonstrates the testing and treatment of subjects in the cohort. EUS identified 8 patients (6%) with evidence of tumor progression into or beyond the submucosa (2 submucosa, 3 muscularis propria, 3 adventitia). There were no cases of lymph node involvement or distant metastases identified by EUS, and none of these 8 patients had FNA. The median age was 65.5 years old, 6/8 were male, 38% had pre-treatment HGD (3/8) and 62% had IMC (5/8) (Table 2). The patients were treated with esophagectomy (5), chemoradiation (2), and hospice care (1). Surgical pathology was available for 4 of 5 patients who underwent esophagectomy and demonstrated 2 subjects with and 2 without lymph node involvement. Therefore, EUS missed lymph node involvement in at least 25% of the eight patients (50% of those with surgical pathology available).

Two of eight subjects with abnormal EUS findings were overstaged by EUS (surgical pathology negative for submucosal invasion and lymph node involvement). Both cases were staged by EUS as extending into the muscularis propria with no lymph node involvement. In both cases, esophagectomy was performed.

Patients with normal EUS findings

There were 127 of 135 patients with normal EUS findings: no submucosal invasion, no histologically-proven lymph node involvement, and no evidence of regional metastasis. The median age of this group was 64.4 years, 83% were male (106/127), 81% had HGD (103/127) and 19% had IMC (24/127). Among this group, five patients had lymph nodes with endosonographic characteristics as described above that prompted fine-needle aspiration. The nodes were all locoregional with sizes of 7, 10, 10, 15, and 30 mm. Four had distinct margins and the fifth was hypoechoic and round. All five cases had adequate cytology revealing benign tissue. All five patients had endoscopic therapy (4 RFA, 1 PDT) and were disease free 6 months after treatment.

There were 44 patients who had a diagnostic EMR for nodular mucosa in whom the EUS was negative. The median age of these patients was 68.5 years, 84% were male (37/44), 66% had HGD (29/44) and 34% had IMC (15/44). Among those who had EMR, histology on EMR specimen differed from pre-EMR histology in 28/44 cases (64%); EMR revealed more advanced histology than previous cold biopsies in 16/44 patients (36%), of which 6/44 (13%) demonstrated cancer invasive into the submucosa.

The median age of patients with invasive carcinoma on EMR was 54.5 years and all 6 were men with IMC histology before the EMR (Table 3). In each case, the EUS showed tumor confined to the mucosa without lymph node involvement. In these 6 patients whose depth of tumor invasion was understaged by EUS, inappropriate endoscopic therapy was averted because diagnostic EMR identified local tumor extension. These six patients were treated with esophagectomy (2), chemoradiation (2), and hospice care (2). The remaining 38 patients who had EMR did not have submucosal invasion. In this population, the median age was 70 years, 82% were male (31/38), 76% had HGD (29/38) and 24% had IMC (9/38). After negative staging by both EUS and EMR, these patients were all treated with endoscopic therapy: 35 RFA, 1 cryotherapy, 1 PDT, and 1 APC.

EMR was not performed on 83 patients who had a normal EUS. The median age was 63.9 years, 83% were male (69/83), 89% were HGD (74/83) and 11% were IMC (9/83). Non-nodular mucosa was present in 79 of 83 but 4 had nodular mucosa. In these 4, 3 subjects were treated with ablation without resection (2 PDT, 1 RFA) early in our experience, and 1 subject had unsuccessful EMR (non-lifting mucosa) followed by esophagectomy revealing HGD. The three subjects with ablation without resection of the nodule were disease free 6 months after treatment initiation. After negative staging by EUS, the 83 patients were treated with endoscopic therapy: 69 RFA, 9 cryotherapy, and 4 PDT. As previously noted, one patient who had unsuccessful EMR opted for esophagectomy.

EUS and EMR findings by mucosal nodularity

Figure 2 demonstrates the testing and treatment of subjects in the cohort stratified by whether they had nodular or non-nodular mucosa. Non-nodular mucosa was present in 79 upper endoscopies (59%), predominantly consisting of HGD (71/79, 90%) more than IMC (8/79, 10%). All 79 underwent pre-treatment staging by EUS. There were no endosonographic abnormalities noted in any of the 79 patients with non-nodular mucosa. None of the 79 patients with non-nodular mucosa underwent EMR, and therefore all patients with non-nodular mucosa ultimately proceeded with endoscopic treatment. There were no occurrences of invasive carcinoma among patients with non-nodular dysplasia and negative EUS during 6 months after treatment. EUS findings did not alter the treatment strategy in any patients with non-nodular mucosa.

Visible nodularity was identified in 56 upper endoscopies (41%), and most had a pre-treatment diagnosis of HGD (35/56, 62%) as compared to IMC (21/56, 38%). All 56 underwent pre-treatment staging by EUS, and 8 had endosonographic evidence of submucosal invasion (14%). IMC (5/8, 63%) was more common than HGD (3/8, 37%) among those with nodular mucosa and abnormal EUS findings, while HGD (29/44, 66%) predominated over IMC (15/44, 34%) if the EUS was normal.

Among patients with nodular mucosa and a normal EUS, diagnostic EMR was performed in 44 of 48 patients (92%). As previously described, 4 patients early in our experience did not have EMR. Invasive carcinoma was found in 6 of 44 patients with nodular mucosa and a negative EUS, or 14% of such patients who had an EMR (6/44). All 6 patients had IMC. In contrast, HGD (29/38, 76%) was more prevalent than IMC (9/38, 24%) among the 38 patients with nodular mucosa that did not have invasive carcinoma on their EMR specimen.

EUS and EMR evidence of invasive carcinoma was most common in patients with both a pre-treatment diagnosis of IMC as well as nodular mucosa. Among patients with nodular IMC, the EUS and EMR demonstrated invasion in 24% (5/21) and 40% (6/15), respectively. By comparison, the EUS and EMR had invasion in 9% (3/35) and 0% (0/29) of patients with nodular HGD, respectively. EUS demonstrated superficial disease in all patients with non-nodular neoplasia (8 IMC, 71 HGD). Overall, clinically relevant staging abnormalities were found on either EUS or EMR in 52% (11/21) with nodular IMC and 9% (3/35) with nodular HGD. Of note, the 2 cases of overstaging by EUS and 6 cases of understaging by EUS all occurred in patients with nodular IMC.

Discussion

In this study of 135 consecutive patients at an American medical center with early esophageal neoplasia who had EUS for pre-treatment staging, we found that none of the 79 cases of non-nodular BE had a change in their clinical management as a result of EUS. Therefore, in this center, using practices consistent with currently recommended guidelines(15), EUS in subjects with non-nodular BE added no clinical utility. Tumor invasion into the submucosa detected by EUS or EMR was only found in patients with nodular disease, and all patients with an EUS or EMR contraindication to ablation had nodular Barrett's.

In subjects with nodular disease, EMR provided more useful information than did EUS. In six cases, if EMR had not been performed, EUS would have understaged the disease. Additionally, two of the eight cases with EUS findings suggesting invasion were overstaged by EUS, resulting in esophagectomy of two subjects with lesions that may have been amenable to endoscopic therapy. Because our understanding of the utility of EUS in the staging of superficial esophageal neoplasia was evolving over the time period of this retrospective study, these early cases did not undergo EMR. Currently, all such subjects with nodular disease at our institution receive EMR regardless of EUS findings on depth of invasion, presumably increasing the likelihood that these two subjects would have been correctly staged.

A major finding of the current study is that in no subject with non-nodular dysplastic BE or non-nodular IMC did the EUS yield a finding that either suggested invasive cancer or led to a change in the plan of care. All such subjects ultimately received endoscopic therapy. Confinement of neoplasia to the mucosa in subjects with non-nodular BE is supported by prior, smaller series.(12, 16, 17) Therefore, EUS appears to be of limited benefit for tumor staging in non-nodular dysplastic BE, and based on these data is no longer routinely obtained at our institution. EUS also did not identify either of the 2 subjects subsequently demonstrated to have lymph node involvement in our study. If non-nodular Barrett's with HGD or IMC is limited to the mucosa, then 2% or less can be expected to have lymph node involvement based upon surgical resection specimens.(5) In contrast to EUS staging of advanced esophageal cancer, staging of early esophageal neoplasia may be significantly less accurate.(18) For example, in a study by Buskens et al, correlating EUS and surgical findings for mucosal neoplasia (HGD/IMC) or submucosal cancers (T1sm), 27/38 (71%) were accurately staged as N0.(13) The remaining 11/38 (29%) were N1 by EUS and N0 by

pathology (6) or N0 by EUS and N1 by pathology (5). In other words, EUS missed all cases of lymph node involvement in that study and overstaged 16% for HGD and early cancer. Although identification of tumor involvement of lymph nodes would presumably alter a patient's management, prognosis in subjects with N1 disease is poor regardless of treatment modality, with a median survival of 36 months and 5 year survival of 34% despite esophagectomy or chemoradiation.(19)

Our results are consistent with prior observations that nodular Barrett's is best staged by EMR rather than EUS. In our study, 25% of the patients (2/8) with submucosal invasion by EUS were overstaged and treated with esophagectomy when endoscopic therapy may have sufficed. Four of the eight did not have surgical pathology available, making 25% a conservative estimate. Similarly, overstaging by EUS led to unnecessary esophagectomy in 17% (2/12) subjects in a series by Thomas et al, and 17% (1/6) of those in the series by Scotinotis and colleagues.(12, 16) Similar findings have been observed by others, and nodularity may cause difficulty in discerning sonographic layers.(20) Because EMR of nodular BE is generally performed prior to ablative therapy, EMR has both a diagnostic and therapeutic role in these subjects, and would be necessary as a therapeutic maneuver in most subjects even if EUS staging were highly accurate.

A recent series from a European tertiary medical center (Amsterdam Medical Center, the Netherlands) similarly called into question the utility of EUS for pre-treatment staging.(21) In that series by Pouw et al, EUS demonstrated significant errors in under- and over-staging disease. Similar to our study, pre-treatment staging was best performed with EMR rather than EUS. In contrast to our study, all patients in that series had some focal mucosal irregularity leading to EMR. Patients without a mucosal irregularity were excluded, and the utility of EUS in subjects without mucosal irregularity was not assessed in that study. We present our entire experience with EUS for pre-treatment staging and found that the majority of our subjects had non-nodular disease. In most American centers, subjects with non-nodular disease would not undergo EMR, because widescale EMR in the setting of non-nodular neoplastic BE is associated with an unacceptably high rate of stricturing, and confers no additional efficacy compared to RFA treatment alone.(22) For this reason, EUS is frequently performed for pre-treatment staging of non-nodular neoplasia. In our study of 79 patients with non-nodular disease encompassing nearly 6 years of experience, EUS did not ever alter management and therefore did not provide any utility for pre-treatment staging.

A major strength of our study is that it addresses the utility of EUS for non-nodular neoplastic mucosa, the most common clinical setting in subjects with high-grade dysplasia. (1) Additional strengths of the study include the large number of patients studied, with very little missing data; this is the largest series to date addressing this topic. Data were collected from a fully electronic medical record and endoscopic database. Inter-rater reliability was assessed and was high. Our findings were in agreement with those seen in smaller series and in European series, adding to the external validity of the results. The echoendoscopist was not blinded to relevant clinical information (ie pre-treatment histology or endoscopy findings) prior to performing the EUS. As a result, our findings most accurately reflect the utility of EUS for pre-treatment staging in a "real world" setting. The study is limited by its retrospective and single-center design. Although this series is large relative to prior studies,

there were relatively few study subjects with a contraindication to endoscopic treatment. As a result, multivariable modeling for risk factors associated with contraindication to endoscopic therapy was not feasible and some of the findings need to be interpreted with caution. For example, only 8 of the patients with non-nodular mucosa had IMC histology – most subjects with IMC also had mucosal irregularity. Although EUS findings were negative in all 8 patients, the small number of non-nodular IMC patients limits our ability to draw conclusions on the utility of EUS in subjects with non-nodular IMC. Next, while some clinical follow-up is available on all patients, given the referral nature of our practice, we are unable to comment on the long-term outcomes of the majority of subjects with non-nodular disease managed with only endoscopic ablation. Therefore, we cannot say whether EUS provided the “right” answer in such patients; we can only say that it did not alter in any way their management using currently acceptable treatment algorithms.⁽¹⁵⁾ Finally, our study is limited to conventional 7.5-MHz EUS and therefore we cannot comment on the utility of higher frequency EUS (10 – 12 MHz) for pre-treatment staging.

In assessing the impact of endoscopic ultrasound findings on clinical decision-making in BE, we found that EUS did not change management in any subjects with non-nodular BE mucosa. Taken with the exceptionally low risk of lymph node spread in subjects with a pre-procedure diagnosis of non-nodular HGD, EUS has limited utility for staging non-nodular BE. In such patients, it would be reasonable to proceed with endoscopic therapy after only a careful endoscopic examination. Although not evaluated in this study, there may also be a role for EMR of non-nodular mucosa with abnormalities detected by narrow band imaging or other advanced imaging modalities, or as definitive treatment for short segment disease.,^(23, 24) We also found that submucosal invasion occurred only in the setting of nodular BE. Considering the poor performance of EUS for tumor staging nodular disease, EMR is the staging tool of choice for nodular BE. The main advantage in combining EUS with EMR is to evaluate for pathologic lymph nodes. However, in subjects with non-nodular dysplastic BE, the benefit of EUS for pathological lymph node detection is questionable given the rare incidence of N1 disease in such subjects, the imperfect accuracy of EUS for detection of pathological lymph nodes, and the poor prognosis of N1 disease regardless of T stage at diagnosis.

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Abbreviations

HGD	High-grade dysplasia
IMC	intramucosal carcinoma
EUS	endoscopic ultrasound
EUS-FNA	endoscopic ultrasound with fine-needle aspiration
EMR	endoscopic mucosal resection

Figure 1. Testing outcomes with EUS and EMR and subsequent treatment

Abnormal EUS indicates submucosal invasion or beyond, nodal spread, or metastasis.

Abnormal EMR indicates submucosal invasion or beyond on pathologic interpretation.

Figure 2. Testing and treatment outcomes with EUS and EMR stratified by mucosal nodularity HGD, high-grade dysplasia; IMC, intramucosal carcinoma; RFA, radiofrequency ablation; Cryo, cryotherapy; PDT, photodynamic therapy; APC, argon plasma coagulation. Abnormal EUS indicates submucosal invasion or beyond, nodal spread, or metastasis. Abnormal EMR indicates submucosal invasion or beyond on pathologic interpretation.

Table 1
Characteristics of the study population (n=135)

Characteristic	Median (IQR) or n (%)
Age in years	65 (58 – 74)
Body mass index (BMI) in kg/m ²	29 (25 – 34)
Male	112 (83%)
White	132 (98%)
Pre-EUS Histology (n=135)	
HGD	106 (79%)
IMC	29 (21%)
Prague M length (cm)	5 (2 – 7)
Prague C length (cm) [#]	1.5 (2.8)
Ulcer/esophagitis present on EGD	11 (8%)
Nodule present on EGD	56 (41%)
Histology of EMR specimen (n=44)	
LGD	9 (20%)
HGD	16 (36%)
IMC	13 (30%)
Invasive carcinoma	6 (14%)
Depth of Invasion of Neoplasia on EUS (n=135)	
Mucosa	127 (94%)
Submucosa/Muscularis	5 (4%)
Adventitia	3 (2%)
Extra-esophageal invasion	0
Fine needle aspiration performed during EUS (n=135)	5 (4%)
Benign cytology on fine needle aspiration (n=5)	5 (100%)

[#] Mean and standard deviation reported rather than median. Median length was 0 cm.

Table 2
Outcome of cases with local tumor invasion by endoscopic ultrasound

Age/Gender	Pre-EUS Histology	Depth of Tumor (EUS)	Treatment	Follow up pathology
59 F	IMC	Adventitia	Esophagectomy	Surgical pathology: carcinoma invading adventitia, 2/24 LNs (+)
64 M	IMC	Muscularis propria	Esophagectomy	Surgical pathology: IMC (lamina propria), 0/33 LNs (+)
66 M	HGD	Adventitia	Esophagectomy	Surgical pathology: carcinoma invading peri-esophageal soft tissue, 6/21 LNs (+)
79 M	IMC	Muscularis propria	Esophagectomy	Surgical pathology: IMC (lamina propria), 0/12 LNs (+)
69 M	IMC	Submucosa	Esophagectomy	Performed at outside institution. Records not available.
58 M	HGD	Submucosa	Chemoradiation	Biopsy: suggestive of invasive carcinoma
65 F	HGD	Adventitia	Chemoradiation	Biopsy: suggestive of invasive carcinoma
72 M	IMC	Muscularis propria	Hospice	Biopsy: suggestive of invasive carcinoma

Table 3
Outcome of cases with local tumor invasion on histology obtained by endoscopic mucosal resection

Age/Gender	Pre-EUS Histology	Depth of Tumor (EUS)	EMR Specimen Findings	Treatment	Follow up pathology
58 M	IMC	Mucosa	Moderately differentiated adenocarcinoma into submucosa to margin.	Esophagectomy	Surgical pathology: carcinoma invading muscularis propria, 0/24 LNs (+)
51 M	IMC	Mucosa	Invasive adenocarcinoma suspicious for lymphovascular invasion.	Esophagectomy	Performed at outside institution. Records not available.
74 M	IMC	Mucosa	Moderately differentiated adenocarcinoma into muscularis mucosa to margin.	Palliative ablation	N/A
76 M	IMC	Mucosa	Invasive moderately differentiated adenocarcinoma.	Palliative ablation	N/A
44 M	IMC	Mucosa	Invasive adenocarcinoma to margin.	Hospice	N/A
51 M	IMC	Mucosa	Invasive adenocarcinoma.	Hospice	N/A