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Endoscopic Ultrasound Errors in Esophageal Cancer

Gregory Zuccaro, Jr., M.D.,Thomas W. Rice, M.D., John J. Vargo, M.D., John R. Goldblum, M.D., John A. Dumot, D.O., David J. Adelstein, M.D., Patricia A. Trolli, R.N., and Eugene H. Blackstone, M.D.
Departments of Gastroenterology; Thoracic and Cardiovascular Surgery; Anatomic Pathology; Hematology and Oncology; and Biostatistics and Epidemiology, Cleveland Clinic, Ohio

BACKGROUND: Previous assessments of endoscopic ultrasound (EUS) classification of esophageal cancer are dominated by symptomatic patients with advanced stage disease. Fewer data exist on EUS errors in a cohort balanced between early and advanced disease.

PURPOSE: Assess EUS errors in classification of esophageal cancer in a more balanced cohort, and identify clinical and tumor characteristics associated with EUS errors.

METHODS: A total of 266 patients underwent EUS and esophagectomy without preoperative chemoradiotherapy. *Pathologic classification of disease extent*: 108 (41%) tumors were confined to the esophageal wall (pTis-pT2, pN0, pM0); 158 (59%) were advanced beyond (pT3-pT4, pN1, or pM1). Logistic regression analysis was performed to identify correlates of error in T classification and disease extent using 10 clinical and tumor characteristics (gender, age, dysphagia, weight loss, tumor length, location, traversability, morphology, histopathologic type, and histologic grade).

RESULTS: EUS erroneously predicted pathologic T (pT) in 119 patients (45%). When T classification was dichotomized into tumors whose depth of invasion was not beyond the muscularis propria (pTis-pT2) and those beyond (pT3-pT4), errors occurred in 42 patients (16%). EUS erroneously predicted N classification in 67 patients (25%), and was insensitive to the presence of distant metastases. EUS misclassified disease extent in 40 patients (15%). Logistic regression analysis indicated that weight loss and tumor length were the only clinical and tumor characteristics correlated with EUS errors; more weight loss was associated with decreased odds of misclassification, while the odds of misclassification were four to six times greater for intermediate length tumors than for shorter tumors.

CONCLUSIONS: EUS errors, particularly in predicting pT, are more frequent than previously reported. Weight loss and tumor length are the only clinical and tumor characteristics correlated with EUS errors.

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INTRODUCTION

For patients with esophageal cancer, endoscopic ultrasound (EUS) has become the principal tool for determining cT (clinical assessment of depth of tumor invasion) and cN (clinical assessment of regional lymph node status) classifications, and directs stage-based therapy. However, most published experiences assessing value of EUS have been in symptomatic patients with advanced stage disease (1–7). Fewer data exist on EUS errors in a cohort of esophageal cancer patients balanced between early and advanced disease. With Barrett's surveillance programs and more frequent endoscopic screening of chronic GERD, esophageal cancer patients now present at earlier and varied stages of disease. Therefore, the purposes of this study were to (i) assess errors in EUS classification of esophageal cancer in a more balanced patient cohort and (ii) identify factors associated with EUS errors.

METHODS

Patients

From June 1987 through November 2001, 1,058 patients were seen at the Cleveland Clinic Foundation with a diagnosis of esophageal cancer. Of these, 266 patients had EUS followed immediately by esophagectomy, without induction chemoradiotherapy, allowing direct comparison between clinical TNM classification (cTNM) and pathologic TNM classification (pTNM) (8). Data were entered into the prospective esophageal surgery registry. The institutional review board has approved research based on data contained in this registry. The clinical, endoscopic, and histopathologic tumor characteristics of the patients are summarized in Table 1.

Clinical TNM Classification

Patients received sedation with an intravenous narcotic and benzodiazepine. First, standard upper endoscopy was

Table 1. Clinical and Tumor Characteristics

Variable	N	% of 266
Clinical		
Males	228	86
Weight loss (N = 261)	109	42
Dysphagia (N = 262)	158	60
Endoscopy		
Tumor length		
0–2 cm	93	35
3–4 cm	96	36
>4 cm	77	29
Tumor location		
Proximal esophagus	1	0.4
Mid esophagus	36	14
Distal esophagus	152	57
Gastroesophageal junction/cardia	76	29
Unknown	1	0.4
Nontraversable	60	23
Tumor morphology		
Exophytic	166	63
Nodular	58	23
Submucosal	19	7
Indeterminate	23	9
Pathology		
Histopathologic type		
Adenocarcinoma	226	86
Squamous	36	14
Adenosquamous	3	1.1
Leiomyosarcoma	1	0.4
Histologic grade		
Well	51	19
Moderate	95	36
Poor	120	46

performed, followed by endosonography with the available Olympus echoendoscope at that time (primarily the EU-M2, EU-M3, and EU-M20). Clinical classification of depth of tumor invasion (cT) was as follows: nonvisualization of tumor, cT0; invasion up to the third ultrasound layer, cT1; invasion limited to fourth ultrasound layer, cT2; invasion beyond the fourth ultrasound layer, cT3; and invasion of adjacent structures, cT4. Clinical classification of depth of tumor invasion was routinely assessed using the 12 mHz frequency setting. Sixty patients (23%) had tumors unable to be traversed with a standard endoscope; of these, 24 (40%) underwent dilation to facilitate a complete EUS exam, 20 (33%) were studied using the 7.9 mm over-the-wire MH-908 blind probe without dilation, and 16 (27%) were evaluated only by passing the echoendoscope to the proximal end of the tumor. Clinical classification of regional lymph node status (cN) and distant metastases (cM) was as follows: no evidence of disease, cN0 or cM0, respectively; evidence of disease, cN1 or cM1, respectively. Classification of regional lymph nodes was accomplished using established criteria of size, shape, border, and texture, and was routinely assessed using the 7.5 mHz setting (9).

Esophagectomy

Esophagectomy with thoracotomy and 2-field lymphadenectomy was performed in 177 patients (67%), transhiatal esophagectomy and lymph node sampling in 86 patients (32%), and laparotomy and lymph node sampling in 3 patients (1%) (10–12).

Table 2. pTNM and Disease Extent

Disease Extent and pTNM	N	% of 266
Tumor confined to esophageal wall		
pTisN0M0	19	7.1
pT1N0M0	72	27
pT2N0M0	17	6.4
Total	108	41
Tumor advanced beyond esophageal wall		
pT3N0M0	25	9.4
pT4N0M0	2	0.8
pT1N1M0	9	3.4
pT2N1M0	8	3.0
pT3N1M0	87	33
pT4N1M0	3	1.1
pT1N0M1	1	0.4
pT2N1M1	1	0.4
pT3N1M1	22	8.3
Total	158	59

Pathologic TNM

Pathologic TNM data are shown in Table 2. Pathologic TNM (pTNM) was categorized according to the AJCC TNM system (8). Pathologic T classification was Tis in 19 (7%), T1 in 82 (31%), T2 in 26 (10%), T3 in 134 (50%), and T4 in 5 (2%). Since clinical decisions may be made on this basis, T classification was also dichotomized into tumors whose depth of invasion was not beyond the muscularis propria (pTis-pT2) and those beyond (pT3-pT4), 127 (48%) were pTis-pT2, and 139 (52%) were pT3-pT4. Pathologic N classification was N0 in 136 (51%), N1 in 130 (49%). Twenty-four patients (9%) were pM1. "Disease extent" was defined as confined to the esophageal wall (pTis-pT2, N0, M0) or advanced beyond (pT3-pT4, N1, or M1); 108 tumors (41%) were confined to the esophageal wall, and the remaining 158 (59%) advanced beyond.

Data Analysis

EUS ERRORS. The diagnostic efficacy of EUS to identify T3–4 tumors, N1 tumors, M1 tumors, and advanced disease was assessed by calculating sensitivity, specificity, positive and negative predictive value, and overall misclassification. Pathologic findings were the gold standard. Using advanced disease to illustrate, sensitivity is the ability of EUS to identify advanced disease among patients who have advanced disease. Specificity is the ability of EUS to identify limited disease among patients who have limited disease. Positive predictive value is the percentage of patients who have advanced disease among those predicted to have advanced disease by EUS. Negative predictive value is the percentage of patients who have limited disease among those predicted to have limited disease by EUS. Overall misclassification is the total percentage of patients misclassified by EUS, and is also referred to

in this manuscript as "inefficiency." Exact 95% confidence intervals were calculated for each measure of diagnostic efficacy.

Characteristics Associated with Misclassification

Ten clinical and tumor characteristics were assessed as potential correlates of error in classification of dichotomized T, and error in classification of disease extent: gender, age, dysphagia, weight loss, tumor length, location, traversability, morphology, histopathologic type, and histologic grade. Stepwise logistic regression analysis was used to identify multivariable correlates of each outcome. $p < 0.10$ was used to allow variables to enter the model, while $p < 0.05$ was required to retain variables in the final model. Model-based probabilities of misclassification were calculated for each combination of variables in the final model. There was some concern that use of three types of echoendoscope over the course of the study might have had an impact on the study findings. To address this concern, a variable was created for the timing of each operation relative to the first surgery in this series and this timing variable was added to each of the final models. The timing variable was not significant in either model and it also did not impact the previous findings (results not shown).

RESULTS

EUS Errors

OVERALL T CLASSIFICATION. EUS erroneously predicted pT in 119 patients (45% inefficiency) (Table 3). EUS classification of pT3 was incorrect in 23 cases (17%); only for pT3 was cT correct more frequently than it was incorrect. Both over- and underclassification occurred for pT1 tumors, with overclassification more frequent, including 8 (10% of total pT1) erroneously classified as cT3 (invasion beyond the fourth ultrasound layer). Most errors for pT2 were overclassification. Though the numbers are small, EUS underclassified pT4 in four cases (80%).

DICHOTOMIZED T CLASSIFICATION, N CLASSIFICATION, M CLASSIFICATION, AND DISEASE EXTENT. The diagnostic accuracy for EUS identification of pT3-pT4 (invasion of the primary tumor beyond the muscularis propria), N1 disease (regional lymph node metastases), M1 disease (distant metastases), and disease extent (tumor extends beyond the esophageal wall; *i.e.*, pT3-T4, N1, or M1) are depicted in Tables 3 and 4. EUS erroneously classified dichotomized T in 42 patients (16% error), 23 were overclassified, and 19 underclassified. Using radial technology only, EUS was relatively insensitive for the presence of N1 disease, but with high specificity, and an overall error rate of 25%. EUS was completely insensitive to the presence of distant metastases. EUS demonstrated good sensitivity to the presence of advanced disease. Overall, EUS erroneously predicted disease extent in 40 patients (15% inefficiency); 16 patients were overclassified, 24 underclassified.

Characteristics Associated with Misclassification

DICHOTOMIZED T CLASSIFICATION. Of the ten variables examined, only weight loss and tumor length were found to be associated with misclassification errors in dichotomized T classification (Table 5). Compared to patients with short tumors (0–2 cm), the odds of misclassification were almost six times greater among patients with intermediate-length tumors (3–4 cm) and almost four times greater among patients with long tumors (>4 cm). The probability of misclassification was as high as 30% among patients with 3–4 cm tumors and no weight loss; in contrast, those with 3–4 cm tumors and a 50 pound weight loss had only a 3.1% probability of misclassification (Fig. 1).

DISEASE EXTENT. Of the ten variables examined, only weight loss and tumor length were found to be associated with misclassification errors in disease extent (Table 6). Compared to patients with short tumors (0–2 cm), the odds of erroneous

Table 3. cTNM *versus* pTNM

	pTNM											
cTNM	**pTis**	**pT1**	**pT2**	**pT3**	**pT4**	**pN0**	**pN1**	**pM0**	**pM1**	pLIM	pADV	Total
cTO	13	16	0	1	0							30
cTis	0	4	0	0	0							4
cT1	3	24	1	2	0							30
cT2	2	30	11	15	1							59
cT3	1	8	14	111	3							137
cT4	0	0	0	5	1							6
	19	**82**	**26**	**134**	**5**							**266**
cNO						122	53					175
cN1						14	77					91
						136	**130**					**266**
cMO								241	24			265
cM1								1	0			1
								242	**24**			**266**
cLIM										92	24	116
cADV										16	134	150
Total										**108**	**158**	**266**

LIM = limited to wall; ADV = advanced through wall.

Table 4. Diagnostic Efficacy of EUS

Pathologic Finding	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall Error (%)
T3–4	86 (79–92)	82 (74–88)	84 (77–90)	85 (77–90)	16 (12–21)
N1	59 (50–68)	90 (83–94)	85 (76–91)	70 (62–76)	25 (20–31)
M1	0 (0–14)	99 (98–100)	0 (0–98)	91 (87–94)	9 (6–14)
Advanced disease	85 (78–90)	85 (77–91)	89 (83–94)	79 (71–86)	15 (11–20)

classification were over four times greater among patients with intermediate-length tumors (3–4 cm) and almost twice as great among patients with long tumors (>4 cm). The probability of misclassification was as high as 32% among patients with 3–4 cm tumors and no weight loss; in contrast, the probability of misclassification was <2% among patients with 3–4 cm tumors and 50 pound weight loss (Fig. 2).

DISCUSSION

EUS Errors

Assessments of the diagnostic performance of imaging modalities suffer from important biases in study design (13). For EUS evaluation of esophageal cancer, one of the most important is *work-up bias*. In an attempt to obtain a gold standard pathologic classification after EUS, patients receiving induction chemoradiotherapy prior to surgery are not included; because referent values are then based upon only a selected portion of the patient population, work-up bias artificially inflates sensitivity and depresses specificity. Another is s*pectrum bias,* because only patients who were operable were sent for EUS; those with distant metastatic disease, or with comorbid conditions rendering them nonoperative candidates were not offered EUS. *Clinical review bias* is also present, because echoendoscopists were aware of clinical data and endoscopic findings prior to their interpretation of EUS images.

Nevertheless, ours and earlier studies possess the positive attribute of having esophagectomy immediately following EUS, so that a gold standard pathologic classification is available. Vasquez-Sequeiros and colleagues from the Mayo Clinic recently reported on 125 patients who underwent EUS evaluation for esophageal cancer, only 29 of whom underwent esophagectomy immediately after EUS (14). These authors introduced two pseudo-gold standards for N and M classification. One is the use of EUS with fine needle aspiration (EUS/FNA), a technological advancement of EUS, as a surrogate for pathologic classification. This is a questionable gold standard particularly for evaluating peritumor nodes, because unrecognized passage of the needle through an edge of the primary tumor is possible. The second was the use of pathologic classification from esophagectomy after chemoradiotherapy, making the assumption that a pN1 lymph node that had been downstaged to pN0 by chemoradiation can always be distinguished from a pN0 node that was never downstaged. So we are now asked to accept *three* "gold standards" for EUS classification of esophageal cancer: pathologic classification immediately after EUS, EUS/FNA, and pathologic classification after chemoradiation. This is called *verification bias* by Kelly and colleagues (13). In summary, we submit that far less is known of the true efficiency of EUS in classification of esophageal cancer than is believed!

Table 5. Characteristics Associated with Misclassification of Dichotomized pT

Characteristic	Odds Ratio	95% CI	*p*
Weight loss (per 5 pound increase)	0.77*	0.61–0.97	0.02
Tumor length			
0–2 cm	1.0		
3–4 cm	5.6	2.1–15	<0.001
>4 cm	3.6	1.2–10	0.02

*More weight loss is associated with decreased odds of error.
CI: confidence interval.

T CLASSIFICATION. According to previous series, EUS erroneously classifies T in 10–20% of cases (7). However, these values are based on series consisting primarily of advanced, but resectable tumors (primarily pT3). In our series EUS erroneously classified pT3 in 17% of cases, consistent with previous series. Importantly, in our series other EUS errors in T classification were more frequent than previously reported. EUS was insensitive in detecting pTis cancer. Pathologic T1 cancers were more frequently overclassified, and pT4 cancers largely underclassified, a manifestation in part of a "floor and ceiling effect," whereby the classification system

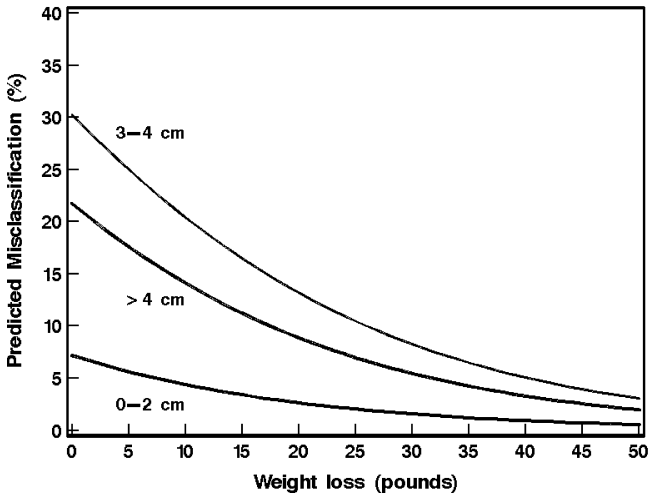

Figure 1. Model-based probability of misclassification of dichotomized T according to weight loss and tumor length.

Table 6. Characteristics Associated with Misclassification of Disease Extent

Characteristics	Odds Ratio	95% CI	*p*
Weight loss (per 5 pound increase)	0.72*	0.56–0.94	0.01
Tumor length			
0–2 cm	1.0		
3–4 cm	4.3	1.8–11	0.002
>4 cm	1.9	0.7–5.5	0.2

*More weight loss is associated with decreased odds of error.
CI: confidence interval.

only allows errors of one direction. Pathologic T2 tumors, for which errors of both under- and overclassfication are possible, were more frequently overclassified (46%) than correctly classified (29%).

Are we alone with this difficulty in classifying pT2 tumors? Catalano and colleagues compared inter- and intraobserver variability of two groups of experienced and inexperienced endosonographers in interpreting images from 50 patients with esophageal cancer (15). The inexperienced endosonographers showed poor agreement for all T stages. Although the experienced endosonographers demonstrated good agreement for pT3 tumors, and excellent agreement for pT4 tumors, their agreement for pT2 was poor. Burtin and colleagues compared interpretations by five independent observers in 46 cases of esophageal and gastric cardia cancer undergoing EUS evaluation. They found excellent agreement for pT4, good for pT3, but poor for pT2 tumors (16). We found EUS to be highly inaccurate in classification of pT4, but in this surgical series, the numbers of such tumors were small.

N CLASSIFICATION. EUS erroneously classified N in 25% of our cases, consistent with prior published series using established descriptive criteria (7). Our series did not employ FNA for N classification. In the report by Vasquez-Sequeros and colleagues, FNA of lymph nodes increased sensitivity for lymph node metastasis from 71% to 83% ($p = 0.06$) and accuracy from 74% to 87% ($p = 0.01$) (14). In their series, however, patients receiving chemoradiotherapy were included, and presumably much of the impact of FNA was appreciated in these patients. A main role for curvilinear echoendoscopy in the clinical staging of esophageal cancer, namely documentation of celiac axis lymph node metastases, was not addressed in our analysis because these patients do not go to esophagectomy.

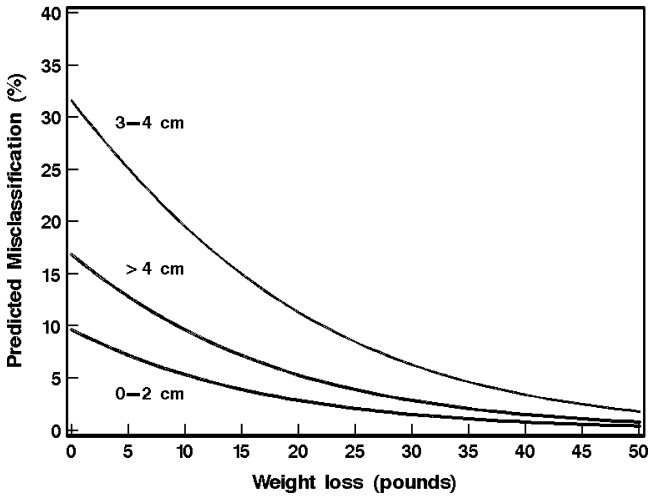

Figure 2. Model-based probability of misclassification of disease extent according to weight loss and tumor length.

DISEASE EXTENT. Errors in classification of disease extent occurred in 40 patients (15%). Disease extent is closely associated with clinical decision making; tumors confined to the wall (pTis-pT2, N0, M0) typically go directly to esophagectomy, while those advanced beyond (pT3-pT4, N1, or M1) receive preoperative chemoradiotherapy (10–12).

Clearly, when clinical determination of disease extent determines therapy, some EUS errors are more serious than others. For example, misclassification of a pT3 tumor as pT4 is an error, but chemoradiotherapy would be first line therapy in either case. However, overclassification of pT2, which occurred 46% of the time in our series, inappropriately labels the patient as advanced disease extent (regardless of N classification). This could lead to preoperative chemoradiation, with its associated morbidity and mortality. We have recently shown that survival is optimized for patients with disease limited to the esophageal wall by proceeding directly to esophagectomy; such patients suffer adverse survival consequences with induction chemotherapy due to toxicity of the regimen, particularly pulmonary toxicity, without added benefit (17).

Characteristics Associated with Misclassification

Kelly and colleagues reviewed staging performance of EUS in esophageal cancer in 27 previously published articles (7). They could identify no characteristic with a significant effect on EUS errors, but found trends suggesting that tumor traversabilitiy and anatomic location might have an influence. Our analyses indicated that weight loss and tumor length were associated with EUS errors in dichotomized T classification and disease extent; traversability and anatomic location were not. Thus, EUS errors were most increased in those circumstances where clinical and tumor characteristics were ambiguous for disease extent (intermediate tumor length, no or little weight loss). As shown in Figure 2, EUS classification of disease extent in a patient with a tumor greater than 4 cm long with associated 50 lbs. weight loss is erroneous less than 1% of the time. However, this is a judgment that can almost certainly be made without the benefit of EUS; a patient with these clinical and tumor characteristics is *almost certain* to have advanced disease. The endosonographer of course knows the patient's history and findings on endoscopy before EUS is even performed. In contrast, consider the patient with no weight loss and a 3–4 cm tumor; here, the endosonographer has no definite clues prior to EUS as to whether this

patient has limited or advanced disease (either is plausible). As seen in Figure 2, EUS in this setting was erroneous 32% of the time. Our data raise the possibility that the reported accuracy of EUS in classification of esophageal cancer may be more influenced by information known to the endosonographer prior to EUS than has been recognized. Furthermore, our data suggest an even more significant concern: in settings where EUS is most needed to classify esophageal cancer (*e.g.*, when clinical and endoscopic clues are ambiguous for disease extent), it is most likely to be in error.

LIMITATIONS

Our series suffers from biases. Due to the nature of the study design, patients who went to chemoradiation prior to surgery, those who were not operative candidates, and those who had inoperable disease were excluded. The resulting work up and spectrum biases affect our quantification of EUS errors, particularly in pT4, N1, and M1, all conditions where esophagectomy is not typically first line therapy. An improvement in N classification may be realized if FNA were utilized, but as stated above, most of this improvement would be in patients offered chemoradiation rather than those going immediately to esophagectomy. This is a single institution study, and our conclusions may not apply to others of different experience.

SUMMARY AND CLINICAL IMPLICATIONS

Multiple biases influence the results of clinical series on EUS classification of esophageal cancer, so much so that we believe its true efficiency remains unknown. Our series, with its own limitations, indicates that errors in T classification may be more common than previously reported. Errors are not associated with tumor characteristics such as location or nontraversability, as suggested by previous authors. Rather, our analyses indicate that weight loss and tumor length were the only factors associated with EUS errors in dichotomized T classification and disease extent. Our data raise the possibility that in settings where EUS is most needed to classify esophageal cancer (*e.g.*, when clinical and endoscopic clues are ambiguous for disease extent), it is most likely to be in error. Further analysis of the relationship between clinical and tumor characteristics and EUS may identify the subset of patients with esophageal cancer that will most benefit from EUS classification.

Reprint requests and correspondence: Gregory Zuccaro Jr., M.D., Department of Gastroenterology and Hepatology, Desk A 30, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195.

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