ORIGINAL ARTICLE

Routine vs. selective EUS-guided FNA approach for preoperative nodal staging of esophageal carcinoma

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Background: EUS-guided FNA (EUS-FNA) is the most accurate method for lymph-node staging of esophageal carcinoma; however, it may not be necessary when EUS features are present that strongly suggest a benign or a malignant origin.

Aims: (1) To identify a combination of EUS criteria that have a sufficient sensitivity and specificity to preclude the need for EUS-FNA and (2) to assess the cost savings derived from a selective EUS-FNA approach.

Methods: A total of 144 patients with esophageal carcinoma were prospectively evaluated with EUS. Accuracy of standard (hypoechoic, smooth border, round, or width > 5 mm) and modified (4 standard plus EUS identified celiac lymph nodes, >5 lymph nodes, or EUS T3/4 tumor) criteria were compared (receiver operating characteristic curves). Resource utilization of two diagnostic strategies, routine (all patients with lymph nodes) and selective EUS-FNA (FNA only in those patients in whom the number of EUS malignant criteria provides a sensitivity and a specificity <100%), were compared.

Results: Modified EUS criteria for lymph-node staging were more accurate than standard criteria (area under the curve 0.88 vs. 0.78, respectively). No criterion alone was predictive of malignancy; sensitivity and specificity reached 100% when a cutoff value of >1 and >6 modified criteria were used, respectively. The EUS-FNA selective approach may avoid performing FNA in 61 patients (42%).

Conclusions: Modified EUS lymph-node criteria are more accurate than standard criteria. A selective EUS-FNA approach reduced the cost by avoiding EUS-FNA in 42% of patients with esophageal carcinoma. These results require confirmation in future studies. (Gastrointest Endosc 2006;63:204-11.)

The incidence of esophageal adenocarcinoma is rising.[1,2] Although intense efforts have been undertaken, the prognosis of esophageal carcinoma remains poor.[3-11] Survival of patients with esophageal carcinoma (10% survival at 5 years) correlates with tumor infiltration into the esophageal wall (T stage) and lymphatic spread of the disease (N stage).[3-11] Optimal therapy for esophageal carcinoma is debated. Some reports demonstrate that preoperative chemotherapy (5-fluorouracil and cisplatin) and radiation therapy, followed by surgery, significantly increases the likelihood of cure in patients with locally advanced tumors.[11,12] On the basis of these data, many will recommend that patients with early-stage disease (stage IIA or lower) should undergo surgical resection, patients with locally advanced tumors (stage IIB-III) should receive preoperative adjuvant chemoradiation therapy, and patients with metastatic disease (stage IV) should be considered for palliative measures.[3-14]

Preoperative tumor staging of patients with esophageal carcinoma is obtained by means of chest and abdomen CTs to exclude distant metastasis and EUS with EUS-guided FNA (EUS-FNA) of lymph nodes for locoregional staging.[15-28] The role of positron emission tomography in esophageal carcinoma is evolving but may be helpful for detecting distant metastasis.[29] EUS has been shown to be the most accurate technique to determine tumor depth of infiltration (T stage accuracy: EUS, 85% vs. CT, 55%) and lymph-node involvement (N stage accuracy: EUS, 81% vs. CT, 56%).[15-28] EUS assessment of lymph nodes (benign vs. malignant) is based on EUS features (lymph-node size, roundness, smooth border, echogenicity).[30-32] Recent publications by our group[28] and by others have demonstrated EUS-FNA is even more accurate than CT or EUS for preoperative lymph-node staging of esophageal carcinoma (N stage accuracy: CT, 51% vs. EUS, 74% vs. EUS-FNA, 87%; $p < 0.05$).[28,33-36] Unfortunately,

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EUS-FNA of lymph nodes has limitations. EUS-FNA is not always technically possible (e.g., peritumoral nodes or tumoral stenosis), prolongs the length of the procedure, may increase the likelihood of complications, and, finally, raises the cost of the examination (needle cost, extra complexity of the EUS examination, pathology costs for the specimen).[28,33-39] Although EUS-FNA is the most accurate method for lymph-node staging, some experts have suggested that EUS-FNA may not be necessary when EUS features that strongly suggest a benign or malignant origin are present.[39]

The aims of the present study, involving patients with esophageal carcinoma, are the following: (1) to identify whether a newly defined combination of EUS lymph-node criteria has sufficient sensitivity and specificity to preclude the need for EUS-FNA and (2) to assess the cost savings derived from a selective EUS-FNA approach compared with routine sampling of lymph nodes.

Capsule Summary

What is already known on this topic

- Treatment of esophageal adenocarcinoma depends on preoperative tumor-stage assessment with
  - chest and abdominal CT to exclude distant metastasis
  - EUS-FNA of lymph nodes for locoregional staging
- EUS-FNA is not always technically possible, prolongs the procedure, may have complications, and increases cost.

What this study adds to our knowledge

- Lymph-node status is more accurately predicted on EUS if 3 criteria (lymph node in the celiac region, >5 lymph nodes identified, and tumor staged T3/4) are added to the standard criteria (hypoechoic, round, smooth border, width >5 mm) and FNA can be avoided.

PATIENTS AND METHODS

Patients

From December 1999 to August 2001, all patients seen at the Mayo Clinic Rochester (Gastroenterology and Hepatology, Oncology and Thoracic Surgery Division) for preoperative evaluation of an esophageal carcinoma were considered for the study.

Criteria for the study

Inclusion criteria included the following: (1) patients with adenocarcinoma or squamous-cell carcinoma of the esophagus and no distant metastatic disease on helical CT (patients with known/confirmed distant lymphadenopathy or solid organ metastasis, stages M1a and/or M1b, were not considered for the study) and (2) patients who were candidates for surgical resection on the basis of overall health status as assessed by the primary physician.

Exclusion criteria included the following: (1) tumors that were not a primary esophageal neoplasia, (2) patients who had received prior chemoradiation therapy, (3) uncorrectable coagulopathy, (4) the absence of nonperitumoral lymph nodes precluding EUS-FNA performance, and (5) patient refusal or inability to provide informed consent for the research protocol.

Institutional review board approval was obtained for the study, with all patients providing written informed consent for the study and the procedures described in this report. Patient information was collected at baseline.

Methods

All patients underwent preoperative tumor staging (as per the American Joint Committee on Cancer classification) (Table 1)[3] with helical CT, EUS, and EUS-FNA in a prospective blinded fashion. EUS tumor-stage assessment (TN stage) was obtained without knowledge of CT findings. The endosonographer committed to a lymph-node stage and defined EUS lymph-node characteristics (lymph nodes identified on EUS examinations were classified as benign or malignant, based on EUS diagnostic criteria) before performing EUS-FNA, as per our previously described lymph-node selection algorithm.[28]

EUS. The EUS examination was preceded by an upper EGD and tumor dilation if necessary to allow echoendoscope passage into the stomach. EUS examination (7.5-12 MHz frequencies, mechanical radial echoendoscope, Olympus GF-UM130; Olympus America Corp, Melville, NY) was performed by an experienced endosonographer with the patient under conscious sedation (midazolam and meperidine).

Lymph nodes identified by EUS were evaluated and assessed for malignancy by using standard and modified EUS criteria (Table 2): (1) standard EUS malignant lymph-node criteria[30-32]: (1-a) lymph node > 5 mm in width, (1-b) round shape, (1-c) hypoechoic pattern, (1-d) smooth border (the endosonographer considered a lymph node to be malignant if 3 or more of the standard EUS criteria were present); (2) modified EUS malignant lymph-node criteria: (2-a) lymph node > 5 mm in width, (2-b) round shape, (2-c) hypoechoic pattern, (2-d) smooth border, (2-e) lymph node in the celiac region, (2-f) >5 lymph nodes identified on EUS examination, (2-g) tumor was T3/4 on the basis of EUS examination. The additional features involved in the modified EUS criteria arose from prior investigations that we and others had performed in lymph-node staging of esophageal carcinoma.[36,40,41] Although other aspects, such as tumor length or a smaller number of lymph nodes identified on EUS examination, may also help differentiate benign and malignant lymph nodes, we a priori elected to investigate these listed criteria (2e-2g). We hypothesized that adding 2e to 2g to the original EUS criteria of 2a to 2d would

TABLE 1. TNM and stage grouping for esophageal carcinoma*

Primary tumor (T)

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: Tumor invades lamina propria or submucosa

T2: Tumor invades muscularis propria

T3: Tumor invades adventitia

T4: Tumor invades adjacent structures

Regional lymph nodes (N)

Nx: Regional lymph nodes cannot be assessed

N0: No regional lymph-node metastases

N1: Regional lymph-node metastases

Distant metastases (M)

Mx: Distant metastases cannot be assessed

M0: No distant metastases

M1: Distant metastases

Tumors of the lower thoracic esophagus

M1a: Metastases in celiac lymph nodes

M1b: Other distant metastases

Tumors of the mid-thoracic esophagus

M1a: Not applicable

M1b: Nonregional lymph nodes and/or other distant metastases

Tumors of the upper thoracic esophagus

M1a: Metastases in cervical nodes

M1b: Other distant metastases

Stage group	T stage	N stage	M stage
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2/T3	N0	M0
Stage IIB	T1/T2	N1	M0
Stage III	T3	N1	M0
Stage IV	Any T	Any N	M1
Stage IVA:	Any T	Any N	M1a
Stage IVB:	Any T	Any N	M1b

*From Ref. 3.

TABLE 2. N staging accuracy: standard vs. modified EUS lymph-node criteria

Standard EUS lymph-node criteria

≥5 mm in short diameter

Hypoechoic

Smooth/sharp bordered

Round shape

Modified EUS lymph-node criteria

≥5 mm in short diameter

Hypoechoic

Smooth/sharp bordered

Round shape

Lymph node in celiac region

≥5 Lymph nodes identified on EUS

EUS diagnosed T3/4 tumor

help define, with greater accuracy, patients most likely to have lymph-node metastases. Collection of data required for the modified EUS criteria was done in a prospective and blinded fashion, and analysis of its diagnostic accuracy compared with the standard criteria was performed post hoc. Diagnostic accuracy of standard and modified EUS lymph-node criteria were evaluated by means of receiver operating characteristic (ROC) curves (described in the statistical analysis section).

EUS-FNA. EUS-FNA of nonperitumoral lymph nodes was performed with the electronic multi-element curved linear array echoendoscope (GF-UC30P or GF-UC30PX; Olympus) and a 22-gauge needle with stylet (Cook Endoscopy, Winston-Salem, NC), with our previously described technique.[42] The smear obtained was stained (Diff-Quick [Dade Behring, Inc., Newark, Del) and Papanicolaou's stain) by an on-site cytotechnologist. Malignant cytology demonstrated at least 3 groups of cell clusters with malignant cytologic morphology present in a background population of lymphocytes.

Lymph-node stage criterion standard. Studies evaluating esophageal carcinoma patients are difficult to conduct and analyze because most patients will not undergo direct surgical resection. For this reason ''hybrid/combined'' criteria standards need to be adopted to evaluate lymph-node staging accuracy of different imaging techniques or diagnostic criteria. In the present study, the criterion standard adopted for comparisons of accuracy of standard vs. modified EUS lymph-node criteria, consisted of the surgical pathology result (those patients receiving direct surgical resection) or a malignant cytology result (EUS-FNA of lymph node) in patients who did not undergo direct surgical resection (received preoperative chemoradiation therapy or palliative therapy). Although this type of combined criterion standard may provide different results (N0 vs. N1 stage disease) than a criterion standard consisting of surgical pathology, one may reasonably assume that standard and modified criteria accuracy

should be equally influenced by the criterion standard adopted in the study. Furthermore, this is the type of criterion standard adopted in most studies published in the literature.[34-36,42]

Statistical analysis. Commercially available statistical software packages (SPSS, Chicago, Ill, and JMP, SAS Institute Inc, Cary, NC) were used for statistical analysis. Descriptive analysis of data is presented in the manuscript as follows: (a) discrete variables (percentage and 95% confidence interval [CI]) and (b) continuous variables (mean ± standard deviation and range).

Performance characteristics (sensitivity, specificity, and overall accuracy) of standard and modified EUS malignant lymph-node criteria were assessed and compared by using the ROC curves,[43] with the area under the curve (AUC) representing the overall diagnostic accuracy of EUS lymph-node criteria (standard and modified). ROC curves, by estimating sensitivity and specificity of diagnostic criteria (standard and modified), allow one to (1) measure the sensitivity and the specificity of each set of criteria at different cutoff points, (2) determine the most accurate cutoff point, and (3) calculate the overall diagnostic accuracy of each set of diagnostic criteria (AUC) to differentiate between benign and malignant lymph nodes. The AUC were compared, recognizing that:

AUC = 0.90-1.0 is excellent
AUC = 0.80-0.90 is good
AUC = 0.70-0.80 is fair
AUC = 0.60-0.70 is poor
AUC = 0.50-0.60 implies the test fails

Because the 3 added criteria of the modified set (lymph node in the celiac region, >5 lymph nodes identified on EUS examination, T3/4 tumor based on EUS examination) may be measuring the same information that already provided the standard ones (e.g., an interaction could exist between depth of tumor invasion and the size of the lymph nodes identified), the specific value of each of these 7 criteria was tested by performing the Fisher exact test (univariate analysis) and multiple logistic regression (multivariate analysis).

Economic analysis. The second aim of the present study was to assess the costs derived from routine sampling (as performed in this prospective protocol and in clinical practice) of lymph nodes in esophageal carcinoma and to compare it with a selective EUS-FNA approach. ''Routine EUS-FNA'' was defined as performing EUS-FNA of nonperitumoral lymph nodes in all patients included in the study (as performed in routine clinical practice), while ''selective EUS-FNA'' consisted of a hypothetical approach in which EUS-FNA would have only been performed in those patients in whom the lymph-node stage (benign vs. malignant), based on the modified criteria, had a sensitivity/specificity <100%. At those cutoff points where sensitivity or specificity is 100%, our predictive value for malignancy or benign lymph nodes would also be 100% in this cohort of patients. Modified EUS lymph-node criteria were adopted for comparisons in this study (routine vs. selective EUS-FNA).

Direct costs associated with EUS/EUS-FNA staging were estimated for both staging strategies: routine EUS-FNA and selective EUS-FNA. Costs were analyzed from a payer's perspective by using the Medicare fee schedule for the year 2004. Current procedural terminology codes[44] used were the following: 43259 (EUS), 43242 (EUS-FNA), 88172 (on-site cytology), and 88171 (final cytology) (Appendix 1, online at www.giejournal.org). The total EUS cost without EUS-FNA/cytology interpretation ($706.73/patient) and the total EUS/EUS-FNA/cytology interpretation combined cost ($984.90/patient) were compared for both strategies.

RESULTS

During the aforementioned period of time, 144 unselected patients who met the inclusion criteria for the study were prospectively enrolled. All patients included in the study had nonperitumoral lymph nodes, and EUS-FNA was performed in all 144 patients. Four additional patients were excluded because no nonperitumoral lymph node could be identified on EUS examination; therefore, EUS-FNA could not be performed. The criterion standard for lymph-node stage, as described in the Methods section, was available in all 144 patients (direct surgical resection, 47 patients [33%]; EUS-FNA malignant cytology, 97 patients [67%]). Patient baseline characteristics are shown in Table 3. Most patients presented with an adenocarcinoma of the distal esophagus. Eighty-four percent of patients evaluated presented with malignant lymph nodes at the time of diagnosis (N1 stage), whereas the remaining 16% showed no lymphatic spread of the disease and were classified as N0 stage as per the criterion standard.

According to the criterion standard adopted in this study, modified EUS criteria for lymph-node staging were found to be more accurate than standard criteria (ROC curve/AUC 0.88 vs. 0.78, respectively (Figs. 1 and 2). Although subgroup analysis was not initially considered, a posterior analysis in the subgroup of 38 patients with an EUS T1/2 tumor showed that modified EUS criteria (excluding the T-stage criteria) were also more accurate to differentiate benign from malignant lymph nodes than the standard criteria (AUC modified vs. standard, 0.84 vs. 0.76). The maximum accuracy of modified EUS criteria (86%) was observed when the presence of 3 or more of the 7 modified EUS criteria were required to diagnose lymph-node malignancy (Fig. 2). Although no single criterion was predictive of malignancy, the cutoff number of 6 or more of the modified criteria (cutoff at that point) provided a specificity of 100% and, in this cohort of patients (prevalence of malignant lymph nodes, 84%), had a positive predictive value (PPV) of 100% (40/40): 95% CI [90%, 100%] (Fig. 2). Thus, all patients with one or more lymph nodes with >6 modified EUS criteria had

TABLE 3. Patient demographics at baseline and tumor characteristics in the study group

Characteristics (n = 144 patients)		N (%)
Age, y*		65.4 + 10.3 (35, 85)
Gender f/m		16/128 (11/89)
Tumor location	Upper third esophagus	2 (1)
	Mid third esophagus	28 (20)
	Lower third esophagus	114 (79)
Barrett's esophagus		83 (58)
Histologic type	Adenocarcinoma	126 (88)
	Squamous-cell carcinoma	18 (12)
Smoker		45 (31)
T stage†	T1/T2/T3/T4	8/6/17/1 (25/19/53/3)
T stage‡	T1/T2/T3/T4	17/21/97/9 (12/15/67/6)
N stage (N0/N1)§		23/121 (16/84)

*Mean ± standard deviation; (minimum, maximum).
†Pathology T stage for patients who underwent direct surgical resection (n = 32).
‡T stage as assessed by EUS examination with radial echoendoscope.
§N stage as per criterion standard.

N1 stage disease in this cohort of patients. Additionally, the cutoff of one or more of the modified EUS criteria (cutoff at that point) provided a sensitivity of 100%, and, in this cohort of patients (prevalence of benign lymph nodes, 16%), the negative predictive value (NPV) was 100% (21/21): 95% CI [82%, 100%] if zero criterion was present (Fig. 2). That is, none of the patients included in this study who had lymph nodes with <1 positive modified EUS criteria presented with N1 stage disease. A detailed analysis of single criteria used for lymph-node diagnosis (multiple logistic regression analysis) disclosed that lymph-node width >5 mm, round shape, >5 lymph nodes identified on EUS examination, and T3/4 tumor as per EUS assessment were the criteria that best predicted malignancy in this cohort of patients (Table 4). However, as previously mentioned, no single criterion of the 7 modified ones was 100% predictive of malignancy.

The routine EUS-FNA approach for preoperative lymph-node staging of esophageal carcinoma resulted in a direct cost of $141,825 for evaluating all 144 patients, whereas a hypothetical selective EUS-FNA approach would have avoided performing FNA in 61 of 144 patients (42%: 95% CI [35%, 51%]) with the same accuracy as routine

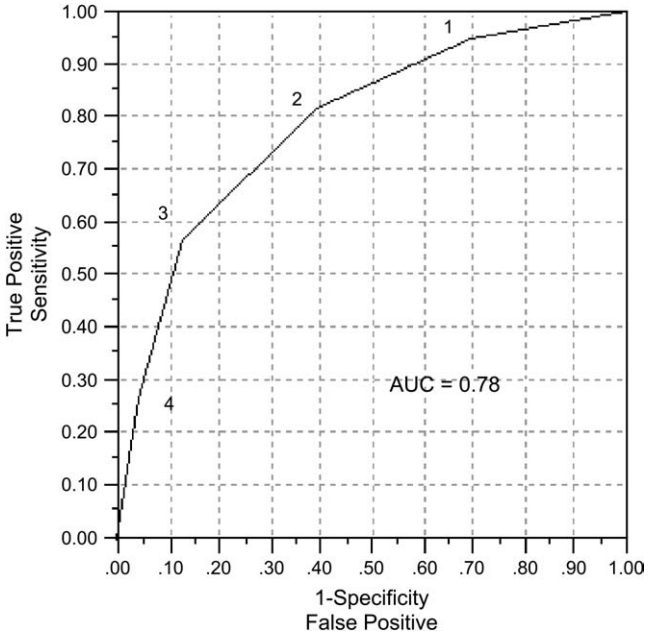

Figure 1. N staging accuracy comparisons. Standard vs. modified EUS lymph node criteria: ROC (receiver operating characteristic) curves. (*AUC*, Area under the curve.) ROC curve shows that 2 positive standard criteria is the cutoff point with the highest accuracy (78%).

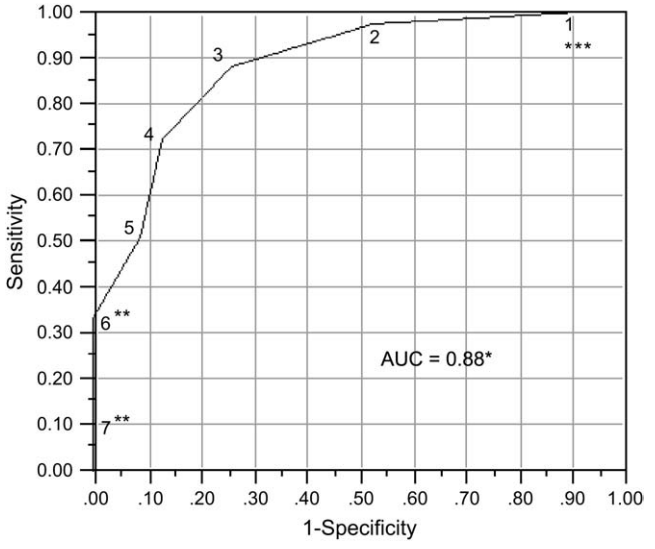

Figure 2. N staging accuracy comparisons. Standard vs. modified EUS lymph node criteria: ROC curves. (*AUC*, Area under the curve.) ROC curve shows that 3 positive modified criteria is the cutoff point with the highest accuracy (86%).

EUS-FNA at a total cost of $124,857.23 for preoperative lymph-node staging in this group of patients (Table 5).

DISCUSSION

Accurate esophageal carcinoma stage assessment is not only important to provide the patient with an estimation

TABLE 4. N staging accuracy: modified EUS LN criteria; univariate and multivariate (multiple logistic regression) analysis of diagnostic criteria used to differentiate between benign and malignant LN

EUS LN criteria	Benign LN (n = 23), n (%)	Malignant LN (n = 121), n (%)
Width > 5 mm	10 (43)	102 (84)
Roundness	5 (22)	67 (55)
Hypoechoic	5 (22)	64 (53)
Sharp border	9 (39)	83 (69)
Celiac lymph nodes on EUS	0 (0)	17 (14)
Number of LN on EUS > 5	1 (4)	65 (54)
EUS T3/4	6 (26)	100 (83)

EUS LN criteria	Univariate analysis, *p* value	Multivariate analysis, *p* value, OR (95% CI OR)
Width > 5 mm	<0.0001	0.008; 5.90 (1.65, 24.20)
Roundness	0.005	0.047; 4.29 (1.07, 20.21)
Hypoechoic	0.011	0.283; 0.38 (0.05, 2.08)
Sharp border	0.009	0.239; 2.25 (0.58, 9.18)
Celiac LNs on EUS	0.074	0.89; 79,966.58 (1.43, >100,000)
No. LNs on EUS >5	<0.0001	0.014; 29.32 (3.24, 947.854)
EUS T3/4	<0.0001	0.0005; 12.29 (3.30, 60.30)

LN, Lymph node; *OR*, odds ratio.

TABLE 5. Cost comparison of routine EUS-FNA vs. selective EUS-FNA for preoperative lymph-node staging

Cost comparison routine vs. selective EUS-FNA; 2004 Medicare fees: EUS = $706.73; EUS/EUS FNA/cytology interpretation (on-site/final) = $984.90

	Routine EUS-FNA	Selective EUS-FNA
N	144 patients (EUS-FNA)	144 – 61 = 83 patients (EUS-FNA)
Cost		
Total group	144 × $984.9 = $141,825.6	(83 × $984.90) + (61 × $706.73) = $124,857.23
Per patient	$141,825.6/144 = $984.90	$124,857.23/144 = $867.06
Differences in cost	(routine: selective EUS FNA)	
Total group	$141,825.60 – $124,857.23 = $16,968.37	
Per patient	$984.90 – $867.06 = $117.84	

of prognosis but also to decide what is the best therapeutic option.[3-14] Therapy options differ among early, locally advanced, and metastatic tumors.[3-14] Patients with locally advanced disease (T3 and/or N1) are typically advised to receive preoperative neoadjuvant therapy (chemoradiation).[11-13] Because this type of therapy may be associated with significant side effects, tissue confirmation of the N1 stage allows for greater certainty when recommending therapy with an associated morbidity and mortality. EUS-FNA is a technique that provides a tissue confirmation of lymph-node status (N0 vs. N1) with a high level of accuracy[28,34-36] and also has been shown to have a significant impact on final treatment decisions in these patients.[28] This has been described by our group when comparing the preoperative staging accuracy of EUS, EUS-FNA, and CT for esophageal carcinoma patients.[28] Encouraging results obtained in that study led our group to conduct the present study.

We have tested, in a large cohort of patients (n = 144), a new set of EUS lymph-node criteria (modified-EUS criteria) and compared them with standard EUS criteria in an attempt to better select those patients who may obtain benefit from EUS-FNA for assessing lymph-node tumor stage (N0 vs. N1). These modified criteria include the same 4 standard EUS lymph-node criteria (size, roundness, echogenicity, border) and also incorporate 3 morphologic and clinical features that may help to better predict which lymph nodes are benign and which are malignant. These 3 morphologic and clinical features are (a) number of lymph nodes identified on EUS (>5), (b) location of lymph nodes in specific areas (celiac axis in this case), and (c) presence of an advanced tumor on EUS examination (T3/4). Inclusion of these new criteria is based on (a) prevalence of lymph-node metastasis increases with advancing T stage (T1, 0%; T2, 56%; T3, 78%; T4, 100%); (b) contrary to the mediastinum and gastrohepatic ligament, the celiac axis region is not a frequent area for lymph-node detection; and (c) the greater the number of lymph nodes visualized on EUS examination in a patient with an esophageal tumor, the more likely any will be involved by tumor.[35,36,40,41,45] The results of the present study have clearly shown that, by adding these 3 features (modified-EUS lymph-node criteria), one may better predict the lymph-node status of the patient (AUC measuring overall diagnostic accuracy [modified vs. standard EUS criteria]: 0.88 vs. 0.78 [good vs. fair]). The modified-EUS lymph-node criteria are more accurate than the 4 standard EUS criteria; therefore, adoption of these modified EUS criteria should be encouraged. Furthermore, in this cohort of patients, the modified, but not the standard EUS criteria, had certain cutoff points that provided us with a sensitivity and a specificity of 100% (as well as a positive or NPV of 100% in this cohort of patients; PPV, 95%

CI [90%, 100%]; NPV, 95% CI [82%, 100%]). In those cases with either >6 or <1 criteria, EUS-FNA may be avoided, because we may predict if the lymph node is malignant or benign in nature, respectively. EUS-FNA results are unlikely to change the lymph-node stage in these patients. Although previous studies have shown that 4 positive standard criteria provide a PPV of 100% (only present in 25% of patients evaluated), in our cohort of patients, 4 standard criteria were present in 23% of patients (95% CI [17%, 31%]) and had a PPV of 94% (95% CI [79%, 99%]).[30,31] We hypothesize that this may be because of the mixed populations of patients affected by esophageal, gastric, and rectal tumors described in previous reports vs. the present study with a cohort of patients, all affected by esophageal carcinoma.[30,31] Additionally, the larger number of patients evaluated in this study further supports our study results and conclusions.

The major limitation of our analysis resides in retrospectively assessing the performance characteristics of new criteria for N staging accuracy. We did not a priori identify the threshold number of criteria (i.e., <1 or >6) necessary to exclude or include lymph-node metastases when using the modified criteria. Whether this approach would result in a similar outcome when applied prospectively is uncertain. However, the relatively narrow 95% CIs for sensitivity, specificity, PPV, and NPV at these thresholds support that it would. Additionally, although the modified criteria were applied to a data set, their development was done before any analysis and was based on observed trends in esophageal carcinoma staging. Specifically, larger numbers of lymph nodes, celiac lymph nodes, and deeper mural invasion all portend a greater likelihood of N1 disease based on previously published studies from our center and others.[35,36,40,41] Nonetheless, verification of this selective EUS-FNA approach is needed in a prospective study. Furthermore, as with any imaging technique (e.g., EUS and EUS-FNA), performance characteristics of the test are operator dependent, and it would be desirable to test how well these criteria would perform in centers with a lower degree of experience in EUS and EUS-FNA. It should also be mentioned that, as per the staging protocol for all patients with esophageal carcinoma evaluated at our institution, EUS-FNA of lymph nodes is performed in every patient if at least one lymph node located in a nonperitumoral location is identified (regardless of size and degree of suspicion for malignancy). This explains why EUS-FNA of at least one nonperitumoral lymph node was performed in all but 4 patients during the study period (majority of patients with esophageal carcinoma evaluated).

EUS lymph-node criteria that are able to accurately detect malignancy in patients with esophageal carcinoma will diminish the need for EUS-FNA. If one compares only the direct costs derived from both approaches (routine vs. selective EUS-FNA), selective EUS-FNA practice is associated with a cost saving of $117.84 per patient ($16,968.37 in the total cohort of patients evaluated). Although these numbers may differ, depending on the payer, procedure reimbursement, clinical setting and country, avoiding EUS-FNA in 42% of patients with esophageal carcinoma (95% CI [35%, 51%]) will reduce costs without diminishing test accuracy. Therefore, patient therapy and, potentially, survival should not be adversely affected by adopting this selective EUS-FNA approach.

In summary, results from the present study support the inclusion of lymph-node location, tumor T stage, and number of nodes identified on EUS as diagnostic criteria for esophageal carcinoma lymph-node staging (N stage). The addition of these new criteria may enhance our ability to differentiate benign from malignant lymph nodes. In those patients who have <1 or >6 EUS modified lymph-node criteria, EUS-FNA may be avoided without affecting the staging accuracy of EUS. This selective EUS-FNA approach could reduce the cost of preoperative staging of esophageal carcinoma. Prospective validation of these criteria is warranted before they are adopted into routine practice.

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