Efficacy of endoscopic ultrasound in patients with esophageal cancer predicted to have N0 disease

Mohamad A. Eloubeidi a,*, Robert James Cerfoliob, Ayesha S. Bryant b, Shyam Varadarajulu a

a Division of Gastroenterology, University of Alabama at Birmingham (UAB), Birmingham, AL, USA
b Division of Cardiothoracic Surgery, UAB, Birmingham, AL, USA

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Abstract

Objective: Esophageal endoscopic ultrasound with fine needle aspiration (EUS-FNA) is a critical staging tool for patients with esophageal cancer. Previous reports suggest that it is frequently incorrect when it predicts a patient to be N0. The purpose of this study is to assess the efficacy of EUS-FNA in patients clinically staged N0.

Methods: A retrospective cohort study of patients who had a computed tomography scan, EUS-FNA and a positron emission tomography scan prior to undergoing Ivor Lewis esophagogastrectomy with abdominal and thoracic lymphadenectomy. Results: From January 2002 to June 2009, 207 patients underwent Ivor Lewis esophagogastrectomy by one general thoracic surgeon. Ninety-five patients did not undergo neo-adjuvant therapy. Ninety-nine patients had an EUS-FNA preoperatively and 82 were staged as N0. Seventy-seven (94%) were confirmed as N0 on final pathology (sensitivity 94%, accuracy 95%). Their overall 3-year Kaplan—Meier survival was 68%. Neo-adjuvant chemo-radiotherapy was given to the remaining 112 patients and 107 had a restaging EUS-FNA. Ninety of these patients were staged by EUS as N0. Seventy-seven (94%) were confirmed as N0 on final pathology (sensitivity 94%, accuracy 95%). Their overall 3-year Kaplan—Meier survival was 68%. Neo-adjuvant chemo-radiotherapy was given to the remaining 112 patients and 107 had a restaging EUS-FNA. Ninety of these patients were staged by EUS as N0. Seventy-seven (94%) were confirmed as N0 on final pathology (sensitivity 94%, accuracy 95%).

Conclusion: EUS-FNA is very accurate and sensitive when it clinically stages patients with esophageal cancer as N0. In addition, it is even accurate and sensitive when restaging patients as N0 after neo-adjuvant chemo-radiotherapy. These results, which differ from previous reports, are critical for guiding treatment decisions.

Keywords: Esophageal cancer; Staging; Endoscopic ultrasound; PET scan; Adenocarcinoma of the esophagus

1. Introduction

Esophageal cancer (ECA) is a leading health problem worldwide. In 2009, about 16 470 cases were diagnosed in the United States of which 14 530 will die of the disease [1]. Survival has slightly improved in patients with esophageal adenocarcinoma in the United States but overall 5-year survival remains dismal [2]. Treatment and outcomes of patients with ECA are stage dependent [3—5]. EUS may help in staging (and thus in the management and treatment planning) of patients with ECA by providing accurate T (tumor stage) and N (nodal stage) staging that are vital to triage patients for therapy [6]. Perhaps, the most important role for EUS is to initially triage patients to receive neo-adjuvant therapy or undergo immediate surgical resection. Patients with T3 lesions or those with nodal involvement would typically receive neoadjuvant therapy, while patients with T1 lesions or those without nodal involvement would typically undergo surgery. The second important role for EUS is to restaging patients after they receive chemotherapy and radiation therapy. While EUS is less accurate in determining the true stage in these patients, it helps choose the group of patients who are less likely to benefit from surgical resection or the group who could potentially benefit from additional second-line chemotherapy prior to surgical resection, such as those with recalcitrant lymph nodes in residual cancer in the celiac axis area or persistent T4 disease. However, several studies have shown that EUS had a 21—25% false negative rate in detecting nodal metastatic disease in patients with ECA [7—10]. In addition, T-stage errors were common with staging EUS [11]. This false negative rate, if true, has serious clinical ramifications, as it changes therapy. While these studies were performed in high-volume ECA centers, the frequency of

Abbreviations: CR, complete response (responder); CT, computerized tomography; EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound with fine needle aspiration; AJCC, American Joint Committee on Cancer; PET, positron emission tomography; PDT, photodynamic therapy; RFA, radio frequency ablation; TNM, tumor stage, nodal stage, metastasis; ECA, esophageal cancer; CLA, curvilinear array echoendoscope; HFCP, high-frequency catheter probe; HGD, high-grade dysplasia.

* Corresponding author. Address: Endoscopic Ultrasound Program, Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, 1530 3rd Ave. S. — ZRB 636, Birmingham, AL 35294-0007, USA.
Tel.: +44 205 934 7955; fax: +44 205 975 6381.
E-mail addresses: eloubeidi@uab.edu, me75@aub.edu.lb (M.A. Eloubeidi).
unsuspected nodal involvement appeared unacceptably high in these two experiences and higher than ours. The purpose of this study was to assess the true negative rate of EUS-FNA in our practice in patients predicted to be N0 by EUS-FNA.

2. Patients and methods

This was a retrospective cohort study of patients with biopsy-proven ECA. All patients were evaluated by one general thoracic surgeon, who applied a consistent preoperative algorithm as shown in Fig. 1. The entry criteria for this study mandated that all patients: underwent preoperative staging with chest computed tomography (CT) and integrated positron emission tomography with computed tomography (PET/CT), have biopsy-proven ECA, and have an EUS-FNA by one of two experienced endosonographers at our institution (with more than 5000 EUS examinations both). Patients with obstructive tumors were dilated to allow the passage of the echoendoscope and full evaluation of the celiac axis. If no peritumoral lymph nodes were imaged, EUS-guided FNA was performed to confirm nodal disease as previously described [4,12]. Patient T stage was classified by EUS as follows: At frequencies raging from 5 to 10 MHz, the esophageal wall is imaged as a five-layer structure (first hyperechoic layer: superficial mucosa, second hypoechoic layer: deep mucosa, third hyperechoic layer: submucosa, fourth hypoechoic layer: muscularis propria, and fifth hyperechoic layer: adventitia). The EUS features of malignant lymph nodes were as follows: greater than 1 cm, round, sharply demarcated, and hypoechoic.

Patients with T1 or T2 but without nodal disease underwent an open Ivor Lewis esophagogastrectomy with complete abdominal lymph node removal and complete thoracic lymphadenectomy as previously described [13]. Patients staged as T2N0M0 were referred for resection only if they could not obtain neo-adjuvant therapy, were considered too old for therapy (usually 75 years or older), or refused therapy and desired resection first. Most patients with T3 and higher or any N1 underwent preoperative combination therapy first followed by surgery if there was lack of evidence of progression of metastatic disease.

Efficacy was defined as follows: a true negative (TN) was defined when EUS or EUS-FNA staged the patient as node negative and if, after resection, all of the lymph nodes were pathologically negative (N0); a false negative (FN) was defined as the previous biopsy of a lymph node that was called benign, but after another biopsy or removal was found

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Fig. 1. Our treatment algorithm for patients with esophageal cancer. Note: Selected patients with T2N0 lesions who are older than 75 years of age and/or who are too weak or frail to undergo neo-adjuvant chemo-radiotherapy and surgical resection were selected for surgical resection alone.
to have metastatic cancer; a true positive (TP) was considered if the EUS-FNA biopsied a lymph node and on cytology it was called positive or if a lymph node was peritumoral and could not be sampled, but its echogenicity was highly suggestive of cancer. Standard definitions for efficacy were used: Sensitivity — TP/(TP + FN), Specificity — TN/(TN + FP), Positive predictive value (PPV) — TP/(TP + FP), Negative predictive value (NPV) — TN/(TN + FN), and accuracy — (TP + TN)/(TP + TN + FN + FP).

The University of Alabama at Birmingham’s Institutional Review Board approved this study; as all procedures performed were standard of care, individual patient consent was waived for this study; however, consent was received for entry into our prospective database.

Data were imported from Excel (Microsoft Corp, Seattle, WA, USA) into SAS v. 9.01 (SAS Inc., Cary, NC, USA). Continuous variables are expressed as means and categorical data are expressed as counts and proportions. The efficacy of these tests and the definitions of accuracy, positive predictive value, and negative predictive value are the same as those previously published [14]. Comparisons were done with paired, two-tailed t-tests for means of normally distributed continuous variables and Wilcoxon rank sum tests for skewed data. Either the χ² or the Fisher exact test was used to compare categorical data. Kaplan–Meier analysis was used to estimate survival. The log-rank test was used to compare survival between groups. Operative mortalities were included in computation of the survival. Follow-up was censored for end of study or date of last follow-up contact or clinic visit.

3. Results

From January 2002 until June 2009, 207 patients underwent Ivor Lewis esophagectomy by one general thoracic surgeon. A total of 196 patients were staged by EUS-FNA (89 of these patients did not receive neo-adjuvant therapy, whereas 107 patients did receive it). Their patient characteristics for this cohort are shown in Table 1. As shown in Fig. 2, 89 patients had an EUS-FNA preoperatively and 82 were staged as N0. In general, patients with T2N0M0 lesions underwent neo-adjuvant chemo-radiotherapy except those who were older than 75 years of age and/or were too weak or too fragile after cancer conference discussion to go directly to surgical resection. These patients also went directly for surgical resection alone. In addition, as shown in Fig. 2, seven patients with suspected N1 disease on EUS did not undergo neo-adjuvant therapy either because they were too weak or because they refused triple therapy. These patients also went directly for surgical resection. The median number of lymph nodes removed at the time of Ivor Lewis esophagectomy was 29 (range 14–41). A total of 77 nodes were N0 on final pathology (sensitivity of EUS for determining N0 was 94%, accuracy 95%). Thus, EUS was falsely negative concerning the presence of nodal disease in only 5 of the 82 patients. Table 2 shows these patient characteristics for these five patients. Interestingly, the number of lymph nodes that were positive was only one in all five patients. The mean maximum standardized uptake value (maxSUV) of these five patients’ esophageal tumors was 10.3 compared with the mean maxSUV of the other 75 patients, which was 6.7 (p = 0.02). The overall 3-year Kaplan–Meier survival for the 82 patients, who did not receive neo-adjuvant therapy and were staged by EUS-FNA as node negative, was 68% is shown in Fig. 3. The 3-year survival for those with N0 disease was 76% compared with 20% for those with N1 disease (p = 0.003) as shown in Fig. 4.

A total of 112 patients received preoperative radiation and chemotherapy and 107 of them underwent a restaging EUS-FNA. Of these 107 patients, 90 were staged as N0. As many as 77 patients were N0 on final pathology (sensitivity of EUS for determining N0 was 82%, accuracy 68% for restaging by EUS as N0). Therefore, 13 patients had an FN test. The

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**Table 1. Patient characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>No neo-adjuvant therapy (N = 82)</th>
<th>Neo-adjuvant therapy (N = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>62.8 (25–88) ± 9.4</td>
<td>61.2 (30–88) ± 7.3</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>73 (89%)</td>
<td>75 (83%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
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<tr>
<td>High grade dysplasia (HGD)</td>
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<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>49 (60%)</td>
<td>82 (91%)</td>
</tr>
<tr>
<td>Squamous</td>
<td>9 (10%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Associated Barrett’s</td>
<td>29 (35%)</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>Location of tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid</td>
<td>3 (3.6%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Mid-lower</td>
<td>5 (6.0%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Lower</td>
<td>74 (90.4%)</td>
<td>84 (94%)</td>
</tr>
<tr>
<td>Pathologic T-stage a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0 (HGD or CR)</td>
<td>21 (26%)</td>
<td>39 (43%)</td>
</tr>
<tr>
<td>T1</td>
<td>39 (48%)</td>
<td>14 (16%)</td>
</tr>
<tr>
<td>T2</td>
<td>16 (20%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>T3</td>
<td>6 (7%)</td>
<td>21 (23%)</td>
</tr>
<tr>
<td>T4</td>
<td>1 (1%)</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Neo-adjuvant therapy</td>
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</tr>
<tr>
<td>Chemotherapy</td>
<td>Not applicable</td>
<td>107 (100%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>96 (90%)</td>
<td></td>
</tr>
<tr>
<td>Mean dose radiation</td>
<td>5040 cGy (range) 4500-6480</td>
<td></td>
</tr>
</tbody>
</table>

*One patient had two foci of tumor (T1 and T2), CR: complete responder, HGD: high grade dysplasia.

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**Fig. 2. Patient flow of this study.** Some patients with suspected N1 disease on EUS who either had integrated PET/CT data that suggested no nodia disease and/or refused or were denied neoadjuvant chemoradiotherapy were selected after cancer conference discussion to go directly to surgical resection.
Kaplan–Meier 3-year survival for the 90 patients, who had resection after neo-adjuvant chemo-radiotherapy, was 57%.

### Discussion

Preoperative accurate staging is mandatory in patients with ECA, as it directs the choice of therapy [15]. Several studies that relied on pathologic determination or preoperative EUS or CT-PET confirm that nodal disease status is extremely important to dictate the initial course of treatment and is highly predictive of survival of these patients [3,4,16]. A large study that analyzed the outcomes of patients with ECA from the Surveillance Epidemiology and End Results (SEER) registry suggests even the number of lymph nodes is an important predictor of survival. With the use of EUS, we can now determine with a high degree of accuracy the presence of these lymph nodes, and, more importantly, we can sample them by means of EUS-FNA to confirm their status [12,17].

EUS has two important roles in the management of patients with ECA. The first one is the initial staging and the second is in restaging after chemotherapy and radiation. EUS plays a key role in the management and treatment planning of patients with ECA by providing accurate T and N staging that are essential to triage patients for therapy. Perhaps, the most important role for EUS is to initially triage patients to receive neo-adjuvant therapy or undergo immediate surgical resection. Patients with any nodal involvement would typically receive preoperative therapy, whereas patients with either T1 and selected patients with T2 tumors (those fit and younger than 75 years of age without nodal involvement) would go directly for surgical resection. Based on our data presented in this article, we have shown that following this rationale in most patients, EUS and EUS-FNA had a high degree of accuracy in determining the initial treatment plan for this subgroup of patients who went to the operating room. This study featured the best gold standard, which is surgical resection with complete removal of the regional lymph nodes. This practice also reflected very favorably on survival of these patients. Our patient cohort survival was 78% at 3 years and 67% for 5 years and that included patients who were N1 positive.

This study’s finding differs from other reports. We found that EUS provided an excellent performance profile as N0 on final pathology with a sensitivity of 94% and overall accuracy of 95%. These results are in complete opposition with those from another high-volume ECA surgery center that showed that nearly 25% of patients with T1 ECA had N1 disease at the
time of surgery [7]. This could be reflected by careful patient selection, the use of state-of-the-art technology, such as EUS and integrated PET-CT, in addition to perhaps the local expertise in EUS as well as surgical technique. Moreover, the results from the literature are varied. A systematic review of the literature that included 13 studies that met inclusion criteria found that EUS has a sensitivity range of 59.5—100% and a specificity range of 40—100% for N staging. The true positive rate was 79% (95% confidence interval (CI) 0.75—0.83) [18]. To eliminate or reduce uncertainty, EUS-FNA provides a means of documenting nodal involvement prior to neo-adjuvant therapy. A major limitation to EUS-FNA is the fact that intervening tumor does not allow sampling of these lymph nodes without the risk of contamination [17].

Interestingly, the number of lymph nodes that were positive in our study was only one in all five patients, and all patients had T2 and higher T stage. None of the errors occurred in T1 staging, and N1 disease was not found in patients who were staged as T1N0 patients. Thus, our results suggest that EUS is highly accurate in staging patients for T1N0 disease, and we still believe that the appropriate therapy is surgical resection for this group. Based on our results, one could argue whether patients with T2 disease should uniformly undergo preoperative therapy as some patients harbor undetected N1 disease despite performing all imaging, including integrated PET-CT and EUS. This has been our practice except for patients with co-morbidities or those older than 75 years of age, or those patients who opt for surgery without preoperative therapy.

The second important role for EUS is restaging after chemotherapy and radiation. While we agree that EUS has a difficult time separating T stages from scarring due to radiation, this is a moot point as, with the exception of T4 persistence that precludes surgery, the only available treatment for these patients is surgical resection. Repeat EUS is mostly performed at our institution to determine whether there is a compelling reason not to offer a definitive surgical cure for these patients such as liver metastases or persistent celiac or non-peritumoral lymph nodes. This investigation supports a reasonable and acceptable degree of accuracy in these patients. The sensitivity of EUS and accuracy for nodal staging was 82%, and 68%, respectively.

This study has several strengths and limitations. First, our experience allowed us to study a group of patients that underwent an operation, and we have a gold standard in all patients which is pathologic evaluation. That is particularly true in patients, who underwent surgery without any intervention, such as chemotherapy and radiation therapy. This cohort is very difficult to identify in an era where treatment with preoperative neo-adjuvant therapy is so popular. We still believe, however, based on our excellent results and survival of early disease that these patients can be offered surgery without preoperative therapy. We believe, however, that patients with T2 and higher disease should be considered for preoperative chemotherapy to potentially eradicate undetected nodal disease that remains elusive despite advances in PET and EUS imaging. Second, we follow a rigorous preoperative staging approach before making a decision regarding an operation, although there were some individual exceptions for some patients. Third, the team assembled to care for these patients is highly skilled in endoscopic staging by EUS and surgical evaluation and resection. This emphasizes the importance of a multi-disciplinary approach in caring for patients with gastrointestinal (GI) malignancy in general and thoracic surgery in specific. The limitations of this study are inherent in its retrospective design and the fact that a few patients with T2N0M0 and seven patients with EUS suspicious nodal disease did not undergo neo-adjuvant therapy for patient specific clinical reasons. However, with the presence of a surgical gold standard, this bias is limited. Moreover, these results might not be translated to low-volume centers where EUS is not routinely or sparingly performed for staging ECA.

In conclusion, EUS-FNA is very accurate and sensitive when it clinically stages patients with ECA as N0. In addition, it is even accurate and sensitive when restaging patients as N0 after neo-adjuvant chemo-radiotherapy. These results, which differ from previous reports, are critical for guiding treatment decisions.

References


