

Original Article

Distant Lymph Node Metastases in Gastroesophageal Junction Adenocarcinoma: Impact of Endoscopic Ultrasound-Guided Fine-Needle Aspiration

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Abstract

Objective: Endoscopic ultrasound (EUS) is established as the most accurate technique for pre-operative locoregional staging of gastroesophageal junction (GEJ) adenocarcinoma, the purpose of the present study was to evaluate the distant lymph nodes (LNs) EUS-fine-needle aspiration (FNA) impact in therapeutic decision for patients with GEJ adenocarcinoma.

Materials and Methods: Retrospective study was made, with cross-sectional, non-probabilistic analysis from prospectively collected database for all GEJ adenocarcinoma staging patients referred between January 2009 and August 2012 in Paoli-Calmette Institute in Marseille-France.

Results: A total of 154 patients with GEJ adenocarcinoma were managed in our institution, of whom 113 (73.3%) had non-distant metastatic disease at computed tomography (CT) scan and underwent EUS for initial tumor staging prior to a treatment decision. On A total of 113 patients undergoing EUS, 8 (7%) patients underwent endoscopic resection and 6 (5.3%) underwent direct surgical resection. Of the remaining 99 patients (87.6%), 24 (21.2%) distant LN EUS-FNA were made. Seventeen LN had EUS malignant features, including 9 (52.9%) that were confirmed as malignant and underwent palliative treatment with chemotherapy. Ninety (79.6%) patients were treated with pre-operative neoadjuvant therapy and were reevaluated after. 4 (4.4%) had metastatic disease at CT scan (underwent palliative treatment) and 65 (72.2%) underwent EUS restaging to treatment decision reevaluation. Of these, twelve (18.4%) distant LN EUS-FNA were performed. Seven had LN EUS malignancy features, including 4 (57.1%) that were confirmed as malignant and underwent palliative treatment. The remaining 61 patients underwent surgery. As stated above, 21 patients (23.3%) did not undergo EUS restaging, including 10 (47.6%) that did not go to surgery because patient's age, poor general status and comorbidities, 6 (28.5%) had a loss of follow-up, 1 (4.7%) underwent to surgery due to chemotherapy collateral effects, 3 (14.2%) were still on pre-operative chemotherapy and 1 (4.7%) died for sepsis after mediastinal EUS-FNA, this was the only complication event evidenced. EUS-FNA changed clinical management in 54.2% of patients who met the criteria inclusion (distant LN with malignancies EUS features), which corresponds to 11.5% of patients with GEJ adenocarcinoma.

Conclusion: EUS-FNA was able to provide a different tumor staging and these differences were associated with treatment received. EUS-FNA had a significant impact on treatment decision.

Keywords: endoscopic ultrasound; gastroesophageal junction adenocarcinoma; lymph node metastases

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INTRODUCTION

Although the overall incidence of the gastroesophageal

junction (GEJ) adenocarcinoma is rare, the impact of this disease is considerable throughout the world because of its increasing incidence and significant mortality (5-year mortality 80%). Staging is extremely important since it helps differentiate treatment options based upon patient survival. Surgery is still de main treatment, but it is not recommended when there are distant metastases, including those in distant lymph nodes (LN) (considering as stage M+).^{1,2}

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Endoscopic ultrasound (EUS) is established as the most accurate technique for pre-operative locoregional staging of GEJ adenocarcinoma, clearly superior to computed tomography (CT) and magnetic resonance imaging. EUS accuracy for tumor depth (T stage) determination ranges between 85% and 90%, while nodal (N) staging accuracy ranges 70%-90%.^{3,4} EUS-guided fine needle aspiration (FNA) has enhanced N staging accuracy to 86%-95%.⁵⁻⁸ Patients with advanced disease are unlikely to benefit from surgery and a conservative palliative treatment is indicated.

The purpose of the present study was to evaluate the distant LN EUS-FNA impact in therapeutic decision for patients with GEJ adenocarcinoma.

MATERIALS AND METHODS

Retrospective study was made, with cross-sectional, non-probabilistic analysis from prospectively collected database for all GEJ adenocarcinoma staging patients referred between January 2009 and August 2012 in Paoli-Calmette Institute in Marseille-France.

Institutional review board approval was obtained for the study. Patients were included in the study if they had GEJ adenocarcinoma. Adenocarcinoma diagnosis was made by upper gastrointestinal endosc with biopsy and histopathology. GEJ adenocarcinoma was defined as a tumor with the epicenter within 5 cm proximal and distal of the esophagogastric junction.

All patients underwent abdominal ultrasonography (USG) and thoracoabdominal CT for diagnosing distant organs metastases. Cases that did not metastasized to distant organs were referred for EUS with guided FNA if necessary. Data collected from the electronic medical records included general patient characteristics, EUS staging results and treatment modalities. Exclusion criteria were as follows: Metastases in distant organs and cases that were not possible to evaluate the data.

EUS protocol

All EUS examinations were performed by one of four experienced endosonographers and carried out under anesthesiology sedation. All EUS examinations were performed with Pentax Hitachi EG38UT or EG38UTK linear electronic probes (Pentax Precision Instruments, Orangeburg, New York) connected to a Hitachi scanner (8500 or Prerius system). Dilatation was not performed to facilitate passage of the echoendoscope. EUS reports for lesions that could not be traversed provided information only on the proximal extent of the tumor.

LNs malignant features were recorded if three or more of the following criteria were present: Width > 10 mm, round shape, echo poor pattern and/or smooth border.^{9,10} It were also evaluated the EUS elastography features to distinguish benign from malignant LNs.¹¹⁻¹⁴

However, when the LN was considered to be distant (cervical, supraclavicular, mediastinal and aortico-caval), a

EUS-FNA was performed even if the LN did not fulfill EUS criteria for malignancy. If multiple suspicious lesions were present, the most suspicious lesion EUS-FNA was performed.

EUS-FNA was performed with a 22-gauge needle (Wilson-Cook Medical Inc., Winston-Salem) passed through the echoendoscope channel under ultrasound guidance. Aspiration was done with a 20 ml syringe, with movement of the needle back and forth the lesion. In general, 1-3 passes were necessary to obtain a microbiopsy. The micro specimen was then placed in the cytolyte (monolayer technique). Diagnoses were categorized as follows: Positive for malignancy, benign, or non-diagnostic. There was not a cytopathologist in site.

The endosonographers were not blinded to the other tests results and used these to interpret their own tests as they would in standard practice. After the procedure, the patient was monitored until recovery from anesthesia. Prophylactic antibiotics were not administered. Limitations and contraindications included: Lesions smaller than 5 mm; distance to the probe of more than 6-7 cm; interposed vessels; and clotting abnormalities (TP <60%, platelets <80,000/mm³).

According to EUS and EUS-FNA results, patients were staged on tumor depth, nodal involvement, metastases (TNM) classification¹⁵ and therapeutic approach was decided. Patients were divided in four groups: (1) Endoscopic treatment alone, (2) Surgical treatment without neoadjuvant therapy, (3) Neoadjuvant therapy followed by surgery and (4) Palliative treatment, patients considered as M+.

Exclusive endoscopic treatment with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection was indicated for patients with T1aN0.

Surgical treatment without neoadjuvant therapy was given to patients with T1bN0 or T2N0.

Neoadjuvant therapy follow by surgery was indicated to patients with T2N+, T3N0 or T3N+.

Palliative treatment, including palliative chemotherapy according to clinical conditions by Karnofsky performance score, was indicated for patients with distant LN metastases or tumor invading adjacent structures (T4Nx or TxNxM1).

In patients that underwent neoadjuvant therapy it was performed a restaging with USG, CT and EUS for treatment decision reevaluation.

EUS-FNA impact

If distant LN metastases were confirmed, that prohibits potentially curative resection, this was considered a change in therapeutic approach due to EUS-FNA and considered as impacting.

Statistical analysis

The study primary end point was the EUS-FNA clinical impact, avoiding surgical interventions.

Distant LN final diagnosis was based on EUS-FNA revealing malignancy. True EUS-FNA diagnostic values in the

LN metastases diagnosis could not be established, because no surgical or necropsy biopsies were performed.

RESULTS

During the study period, 154 patients with GEJ adenocarcinoma were managed in our institution, of whom 113 (73.3%) had non-distant metastatic disease at CT scan and underwent EUS for initial tumor staging prior to a treatment decision (Tab. 1). The average age of the patients was 65.9 years (range 30-88) and 71 (46%) were men. 77% of the lesions were traversed successfully by the echoendoscope.

One hundred and thirteen patients undergoing EUS, 8 (7%) patients underwent endoscopic resection and 6 (5.3%) underwent direct surgical resection.

Of the remaining 99 patients (87.6%), 24 (21.2%) distant LN EUS-FNA were made (Tab. 2). LN locations were: Supraclavicular,³ cervical,⁷ superior mediastinum,¹³ aortocaval.¹ Seventeen LN had EUS malignant features, including 9 (52.9%) that were confirmed as malignant and underwent palliative treatment with chemotherapy.

Ninety (79.6%) patients were treated with pre-operative neoadjuvant therapy and were re-evaluated later. Four (4.4%) had metastatic disease at CT scan (underwent palliative treatment) and 65 (72.2%) underwent EUS restaging to treatment decision reevaluation.

Of these, 12 (18.4%) distant LN EUS-FNA were performed. LN EUS-FNA locations were: Supraclavicular,¹ cervical,² superior mediastinum,⁷ aortico-caval.² Seven had LN EUS malignancy features, including 4 (57.1%) that were confirmed as malignant and underwent palliative treatment (Tab. 3).

The remaining 61 patients underwent surgery. As stated above, 21 patients (23.3%) did not undergo EUS restaging, including 10 (47.6%) that did not go to surgery because patient's age, poor general status and comorbidities, 6 (28.5%) had a loss of follow-up, 1 (4.7%) underwent to surgery due to chemotherapy collateral effects, 3 (14.2%) were still on pre-operative chemotherapy and 1 (4.7%) died for sepsis after mediastinal EUS-FNA, this was the only complication event evidenced.

EUS-FNA changed clinical management in 54.2% of patients who met the criteria inclusion (distant LN with malignancies EUS features), which corresponds to 11.5% of patients with GEJ adenocarcinoma.

DISCUSSION

Pre-operative accurate staging is mandatory in GEJ adenocarcinoma management at diagnosis time to direct the treatment modality.¹⁶

Long-term survival predictors are T stage, N stage, and M stage. An important EUS benefit for staging is avoiding unnecessary surgery in patients with advanced disease. In these patients, EUS may lead to avoidance of surgical morbidity and mortality and improvements in quality of life.¹⁷

Table 1. TNM classification of the study population

TNM classification	n (%)
T1aN0	8 (5.2)
T1bN0	1 (0.6)
T2N0	5 (3.2)
T2N+	2 (1.3)
T3N0	21 (13.6)
T3N+	70 (45.4)
T4Nx	6 (3.9)
TxNxM1	41 (26.6)

TNM: tumor depth; nodal involvement; metastases.

Table 2. Correlation of the first pre-operative TN staging with EUS and EUS-FNA in the diagnosis of distant LNs metastasis

EUS staging	Distant LNs EUS-FNA positive
T3N1	Cervical
T3N1	Superior mediastinum
T3N1	Cervical
T4N1	Superior mediastinum
T3N1	Superior mediastinum
T3N1	Superior mediastinum
T3N1	Superior mediastinum
T3N1	Supraclavicular
T4N1	Cervical

TN: tumor depth, nodal involvement; EUS: endoscopic ultrasound; FNA: fine-needle aspiration; LNs: lymph nodes.

Table 3. Correlation of TN staging after neoadjuvant therapy with EUS and EUS-FNA in the diagnosis of distant LNs metastasis

EUS staging	Distant LNs EUS-FNA positive
T3N1	Superior mediastinum
T3N1	Cervical
T3N1	Celiac
T3N1	Superior mediastinum

TN: tumor depth, nodal involvement; EUS: endoscopic ultrasound; FNA: fine-needle aspiration; LNs: lymph nodes.

EUS is also essential in staging patients with early cancers in the work-up for local endoscopic treatment, selecting those patients who are amenable to EMR, thereby obviating the need for unnecessary esophagectomy with its consequent risks and expense.¹⁸

Finally, EUS can be used to evaluate the response to neoadjuvant treatment with radiotherapy and/or chemotherapy. While EUS is less accurate in determining the true stage in these patients, it helps choose the patient group who are less likely to benefit from surgical resection.

The major advantage of EUS is the ability to perform FNA during the procedure for tissue diagnosis. In comparison with alternative options, the procedure is safe, less invasive and does not require general anesthesia or hospitalization. The complication rate is extremely low (0.5%-2.3%) with several studies reporting no complications.^{19,20}

In our study, despite the fact that EUS-FNA was performed in all distant LN found during EUS staging,

there are well-established malignancy criteria for LN staging.^{9,10,13,14,21,22} Decisions concerning treatment were modified in 9/17 patients (52.9%) by distant LN EUS-FNA results at the first pre-operative EUS staging when taken into account those with malignancies EUS features. At EUS restaging after the neoadjuvant therapy, decisions concerning treatment were modified in 4/7 patients (57.1%) due to distant LN EUS-FNA results.

There are a few studies reported concerning distant LN EUS-FNA in pre-operative staging of esophageal carcinoma and no one after neoadjuvant therapy for treatment decision reevaluation.

Giovannini *et al.*¹⁹ retrospectively evaluated the EUS-FNA impact in patients with esophageal cancer, in which a positive cytology result of distant LNs changed therapeutic approach. In this study, EUS-FNA changed the clinical management in 60% of patients who met the criteria inclusion (lymphadenopathy distance of initial tumor could represent as stage M1a), which corresponds to 12% of patients with esophagus cancer.

Mortensen *et al.*²³ reported 13% of change in therapeutic approach in a study with the same type of patients.

Ginès *et al.*,²⁴ in a prospective study published in abstract form and with a similar design, EUS management changed treatment in 24% of the patients and EUS-FNA addition changed therapy in more 8%. The low EUS-FNA impact is, according to the authors, because most patients with metastatic nodes were previously detected and treatment modified.

Vazquez-Sequeiros *et al.*⁷ contraindicated surgical resection based on advanced or metastatic disease detection in 77% of patients undergoing pre-operative nodal staging of esophageal carcinoma. This includes all patients with esophageal carcinoma, including those in whom unresectable disease was detected with other prior imaging (CT). Patients in whom surgery was not planned due to other factors, for example, health status or patient age, are also likely to be included in this study.

Stahl *et al.*¹⁸ reported that EUS-FNA directed management in all patients biopsied. However, the pretest management plan for these patients was not reported and there may have been no change in the management plan.

Harewood *et al.*³ showed that EUS increased patient's selection for pre-operative neoadjuvant chemotherapy, increased survival and reduced the recurrence rate.

EUS management studies varied widely in study design and the reporting quality discrepancy between the different studies results in proportion terms of patients in whom EUS-FNA changed the therapeutic management. These differences should be attributed to the heterogeneity of the methodology used.

A limitation of this study is the absence of direct histopathology correlation in patients evaluated. Current trends in therapy for GEJ adenocarcinoma include the adjuvant therapy addition before surgical resection in those patients with locally advanced disease. Standard EUS staging criteria are not accurate after neoadjuvant chemoradiation

because the inflammatory changes and fibrosis induced by chemoradiation lead to wall thickening and decreased visibility of the five layers.²⁵⁻²⁷

There are few studies evaluating EUS in esophageal cancer restaging after neoadjuvant chemoradiotherapy and none can be compared with the current study. Isenberg *et al.*²⁶ made an estimate of tumor size to evaluate the response of pre-operative chemoradiotherapy in 31 patients, Kalha *et al.*²⁵ did not assess lymph-node-distant metastasis and Machlenkin *et al.*²⁷ utilized as exclusion criteria tumors of esophagogastric junction.

Although, EUS did not retain its usefulness as a restaging modality after neoadjuvant chemoradiation for GEJ adenocarcinoma when the standard TNM classification system was used, it can be able to evaluation distant LNs metastases and changing the treatment approach.

EUS-FNA was able to provide a different tumor staging and these differences were associated with treatment received. EUS-FNA had a significant impact on treatment decision.

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