

Preoperative Noninvasive EUS Evaluation in Patients with Esophageal Cancer Considered for Esophagectomy

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Abstract

Background. EUS is an essential tool in the evaluation of patients with esophageal cancer allowing accurate staging and permitting stratified treatment options. **Aim.** We studied prospectively the impact of EUS in the evaluation and decision for therapy of patients with esophageal cancer. **Material and methods.** From March 2001 through March 2006, 220 patients were hospitalized at the Center of Gastroenterology and Hepatology, Fundeni Clinical Institute, with the diagnosis of esophageal cancer. Out of the 220, 41 patients, with no major comorbidities and already screened by abdominal and thoracic CT to disclose distant metastases, had EUS with the definite purpose of staging esophageal carcinoma and selecting adequate therapy. Assuming that without preoperative staging by EUS, all 41 patients in the study group would have been offered surgical treatment, we evaluated the number of patients and the modality in which EUS resulted in changes to the therapeutic plan. Statistical analysis: Fisher's exact test. **Results.** Depth of invasion was recorded for the 41 patients as follows: T1 in 2 patients (4.9%), T2 in 6 patients (14.6%), T3 in 24 patients (58.5%), and T4 in 10 patients (22%). Regional lymph node (N) status was as follows: N0 in 7 patients (17%) and N1 in 34 patients (83%). Assessment of distant metastases (M) was recorded showing 4 patients with celiac axis lymph nodes metastases (M1). Preoperative EUS staging changed the decision for surgery in 18 of 41 patients (44%) ($p < 0.0001$) and allowed primary esophagectomy in only 6 patients (15%) ($p < 0.0001$). Compared to histopathology, the overall accuracy of EUS staging for pT1 and pT2 was 80%, for staging pT3 and pT4 77% and for lymph node evaluation was approximately 75%. **Conclusion.** Esophageal EUS offers useful information to clinicians caring for patients with

esophageal cancer, impacts clinical decision making, and should be used in appropriate settings to plan patients' care.

Key words

Esophageal ultrasonography - esophageal cancer - treatment

Rezumat

Premize. Ecoendoscopia (EUS) este un instrument important în evaluarea acestor pacienți, permițând o bună stadializare ce stratifică opțiunile terapeutice. **Scop.** A fost studiat prospectiv impactul EUS în evaluarea pacienților cu cancer esofagian, urmărindu-se influența asupra deciziei terapeutice. **Pacienți și metodă.** Între martie 2001 și martie 2006, în Centrul de Gastroenterologie și Hepatologie Fundeni au fost diagnosticați 220 pacienți cu cancer esofagian. Dintre aceștia, 41 pacienți fără comorbidități asociate sau metastaze la distanță detectate prin examen CT abdominal sau toracic au fost examinați EUS pentru a stadializa preterapeutic afecțiunea. Considerând că fără evaluarea EUS toți pacienții ar fi fost tratați chirurgical, s-a studiat în ce măsură examenul EUS schimbă atitudinea terapeutică. Analiza statistică: testul exact Fisher. **Rezultate.** Profunzimea invaziei tumorale a fost înregistrată la cei 41 de pacienți precum urmează: T1 2 pacienți (4.9%), T2 6 pacienți (14.6%), T3 24 pacienți (58.5%) și T4 10 pacienți (22%). Statusul ganglionilor locoregionali a fost: N0 7 pacienți (17%) și N1 34 pacienți (83%). Evaluarea metastazelor a indicat stadiul M1 la 4 pacienți prin detectia metastazelor ganglionare în ganglionii celiaci. În urma tratamentului radiochimioterapic, stadializarea EUS preoperatorie a schimbat definitiv decizia chirurgicală pentru 18 pacienți din 41 (44%) ($p < 0.0001$) și a permis esofagectomia primară doar la 6 pacienți (15%) ($p < 0.0001$). Comparativ cu examenul histopatologic, evaluarea EUS a permis o stadializare corespunzătoare stadiilor pT1 și pT2 în 80% din cazuri, a stadiilor pT3 și pT4 în 77% din cazuri și o corectă evaluare a statusului ganglionilor locoregionali în 75% din cazuri. **Concluzii.** Ecoendoscopia esofagiană oferă informații

importante clinicienilor în stabilirea deciziei terapeutice pentru pacienții diagnosticați cu cancer esofagian, evitând un act chirurgical inutil, grevat de o mare morbiditate și mortalitate, și trebuie utilizată de rutină în cadrul protocoalelor de abordare a acestor pacienți.

Introduction

Worldwide, esophageal cancer ranks fifth in the mortality rate regarding tumor locations (1). The European weighted survival, calculated from the pool of all cancer registries, was 33% at one year and 10% at five years (2). The three year survival rate of patients with loco-regional esophageal cancer who have undergone curative resection remains low (approximately 20%), with a high postoperative mortality rate ranging from 3% to 10% (3).

Accurate staging of esophageal carcinoma is an essential step to predict prognosis, to select candidates who may be cured by surgery, to define patients requiring neoadjuvant therapy, especially when new protocols are being studied, and to detect patients with advanced disease who would be best served by palliative therapy (4). Endoscopic ultrasonography (EUS) has clearly been shown to be the most accurate non-surgical modality to stage esophageal cancer. EUS has an accuracy of 85% in determining depth of tumor invasion (T-stage) and an accuracy of 78% in the assessment of loco-regional lymphadenopathy (N-stage) (5) by using TNM staging system developed by the International Union against Cancer and the American Joint Committee on Cancer (IUC and AJCC), updated in 2002 (6). Patients in stage I and II are good candidates for surgical therapy and do not require neoadjuvant therapy before esophagectomy (4). Patients with early esophageal cancer that penetrate into the upper third of the submucosa can be treated with endoscopic mucosal resection if surgical mortality is anticipated to be more than 6%. Patients in stage IIb and III may benefit from concomitant chemotherapy and radiation therapy before surgical therapy (4). Patients with more advanced stages (stage IV) may be considered for palliative therapy.

There are limited data evaluating the clinical use of EUS and its effect on the management of patients with esophageal carcinoma. Therefore, we studied prospectively the impact of EUS in the evaluation and in the decision for therapy of patients with esophageal cancer diagnosed in our center.

Material and methods

From March 2001 through March 2006, 220 patients were hospitalized at the Center of Gastroenterology and Hepatology, Fundeni Clinical Institute, with the diagnosis of esophageal cancer. The diagnosis was based on histological or cytological examination performed by the same pathologist (GB) and was routinely followed by standard abdominal ultrasound performed by a gastroenterologist (LG) to detect patients with distant metastases.

Patients with the primary tumor located at the cardia were excluded from the study. Out of the 220 patients, 41 patients, with no major comorbidities contraindicating esophagectomy, had EUS with the definite purpose of staging esophageal carcinoma and selecting adequate therapy. The protocol for performing EUS in our center assumed that: 1) all patients had already been screened by abdominal and thoracic CT to disclose distant metastases; and 2) a high grade stenosis, which does not allow advancement with a standard echoendoscope, was not present.

EUS examinations were performed in a standard noninvasive fashion by the same investigator (CG) using Olympus radial echoendoscope UM Q130 under conscious sedation with Propofol. A noninvasive EUS procedure means that no previous dilatation of esophageal stenosis and no fine needle aspiration (FNA) for lymph nodes were performed. All patients enrolled had biopsy-proven carcinoma and the disease was EUS staged according to the TNM staging system (6). Clinical classification of depth of invasion of the primary tumor (cT) was assessed as follows: nonvisualization of tumor (cT0); invasion up to 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 assessment of lymph node involvement was as follows: no lymph node metastases (cN0); lymph node metastases (cN1). Lymph node EUS features, including size greater than or equal to 1 cm, rounded shape, well-delineated borders, and a hypoechoic internal structure (7), were used to determine whether lymph nodes were benign or malignant. The celiac axis was investigated in each patient and was defined as the celiac trunk ("whale tale" appearance) from its origin to the point where it gives rise to the splenic, gastric, and hepatic arteries. Celiac lymph nodes are defined by their location within a 2 cm area from the celiac trunk.

After the EUS staging, patients were categorized into 4 different therapeutic groups: surgery alone, surgery plus adjuvant therapy (including neoadjuvant or postadjuvant therapy), chemoradiotherapy, or palliative treatment. Esophagectomy was performed for stage I and IIA tumors by an experienced surgical team (IP, CS). For tumors in stage IIB our protocol comprised radiochemotherapy followed by curative surgery. Stage III tumors were initially treated by two experienced oncologists (AC, RA) with cisplatin and 5-fluorouracil based chemotherapy regimen and concurrent radiotherapy; these patients were reassessed by EUS for therapeutic response after two cycles of chemotherapy and radiotherapy external radiation with a dose of 3000cGy. Thus, an EUS image of the tumor was taken in the transverse plan at the location where the tumor had the greatest bulk. Tumor cross-sectional area was measured with the EUS processor and the maximal transverse cross-sectional area was obtained both before and after chemoradiotherapy. A 50% or greater reduction in maximal transverse cross-sectional area was arbitrarily defined as a positive response to chemoradiotherapy. Patients with stage IV tumors were considered for palliative chemoradiotherapy.

Esophagectomy specimens were processed in a standardized manner by a pathologist with special expertise in gastrointestinal pathology (VH). The resection specimens were staged by the TNM staging system (6). According to TNM guidelines, the number of lymph nodes removed in one resected specimen was at least six.

Assuming that without preoperative staging by EUS, all 41 patients in the study group would have been offered surgical treatment, we evaluated the number of patients and the modality in which EUS resulted in changes to the therapeutic plan. Additionally, we assessed the staging accuracy of standard noninvasive EUS compared with the histology of the resected specimens. Data acquisition was systematically performed in a database by two gastroenterologists (IB, DV).

Analysis of accuracy of EUS in resected patients was based on the histology of the resected specimens or on the surgical findings, or both. Statistical analysis was performed with the Fisher exact test. All comparisons were two-tailed and $p < 0.05$ was considered significant. Data analysis was performed by a gastroenterologist from our team (RI).

Results

Of 220 patients diagnosed with esophageal cancer over the 5-year study period, 41 patients underwent EUS assessment. Thirty-eight (92.7%) were men and 3 (7.3%) were women. The mean age was 61 years (range, 36-70). A diagnosis of squamous cell carcinoma was made in 33 patients (80.5%) and adenocarcinoma was diagnosed in the remaining 8 patients (19.5%). The primary tumor was located in the distal esophagus in 22 patients (54%), mid esophagus in 17 patients (41.5%), and proximal esophagus in 2 patients (4.5%).

All cTNM staging data are shown in Table I. Depth of invasion was recorded for the 41 patients as follows: T1 in 2 patients (4.9%), T2 in 6 patients (14.6%), T3 in 24 patients (58.5%), and T4 in 10 patients (22%). Regional lymph node (N) status as determined by EUS criteria was recorded for 41 patients as follows: N0 in 7 patients (17%) and N1 in 34 patients (83%). Assessment of distant metastases (M) was recorded showing 4 patients with celiac axis lymph nodes metastases (M1).

Table I cTNM staging for esophageal cancer in the study group

Stage	Subgroups	No. patients
I	T1N0	1
IIA	T2N0	3
	T3N0	2
IIB	T1N1	1
	T2N1	3
III	T3N1	21
	T4N0	1
IV	T4N1	5
	T4N1M1*	4

* tumors located in distal esophagus with metastases in celiac axis lymph nodes

According to our protocol, patients with cancers limited to the esophagus (stage I or IIA disease) underwent primary surgical therapy. Patients with locally advanced esophageal cancer stage IIB underwent neoadjuvant radiochemo-therapy before esophagectomy. Patients with locally advanced esophageal cancer stage III underwent primary radiochemotherapy followed by EUS reassessment; in patients with favorable response detected by EUS, resection was performed subsequently. Patients with more advanced esophageal cancer (stage IV) were treated with palliative chemotherapy and radiation therapy (Table II). Preoperative EUS staging changed the decision for surgery in 18 of 41 patients (44%) ($p < 0.0001$) and allowed primary esophagectomy in only 6 patients (15%) ($p < 0.0001$).

Table II Therapy according to EUS staging

Stage	Therapy	No. patients
I	Esophagectomy	1
IIA	Esophagectomy	5
IIB	Neoadjuvant chemoradiotherapy followed by esophagectomy	4
	Chemoradiotherapy	27
III	Favorable response: esophagectomy	13
	No response: chemoradiotherapy	14
	Chemoradiotherapy and palliation	4
IV	Chemoradiotherapy and palliation	4
Total		41

Ninety-five EUS procedures were performed, patients in stage III being reassessed after radiochemotherapy cycles. Thirteen of 27 patients in stage III (65.8%) showed an EUS response to chemoradiotherapy (a 50% or greater reduction in maximal transverse cross-sectional area) and were subsequently resected. Additionally, 10 patients EUS-allocated in stages I and II underwent esophagectomy either alone (6 patients in stages I and IIA), or following neoadjuvant radiochemotherapy (4 patients in stage IIB). The total number of patients that underwent esophagectomy was 23. Table III summarizes the results of histology and EUS in the evaluation of the depth of infiltration.

pT1 was correctly diagnosed by EUS in 2 out of 3 patients. Overstaging occurred in one patient because of apparent penetration of the hypoechoic abnormality into the muscularis propria. Histologically this extension was proved to be inflammatory. pT2 was diagnosed by EUS in 7 patients, 6 of them being correctly allocated. Overstaging occurred in one patient because of preoperative radiotherapy.

The overall accuracy of EUS staging for pT1 and pT2 was 80% (67% for pT1 and 86% for pT2). pT3 was correctly diagnosed by EUS in 9 out of 11 patients; understaging occurred in 2 patients. Correct diagnosis and understaging each by EUS in one patient in pT4 tumors. The overall accuracy of EUS staging for pT3 and pT4 was 77% (82% for pT3 and 50% for pT4).

Table III Results of histology (p) of resected specimens and EUS in assessing the depth of tumor infiltration (T)

Histology (p) Depth of tumor	No	EUS		
		No.cases cor- rect diagnosis	Overstaging	Understaging
pT1	3	2	1	-
pT2	7	6	1	-
pT3	11	9	-	2
pT4	2	1	-	1

Table IV summarizes the results of histology and EUS in the evaluation of the lymph nodes. Benign lymph nodes (pN0) were correctly diagnosed by EUS in 6 of 11 patients. Nonspecific inflammation was found histologically in the remaining 5 patients, leading to incorrect diagnosis. Lymph node metastases (pN1) were correctly diagnosed by EUS in 9 of 12 patients, 3 patients being understaged. The overall accuracy of EUS for the lymph node evaluation was 75% (55% for pN0 and 92% for pN1).

Table IV Results of histology (p) of resected specimens and EUS in the evaluation of the lymph nodes (N)

Histology (p) Regional lymph node involve- ment	No	EUS		
		No.cases correct diagnosed	False positive	False negative
pN0	11	6	5	-
pN1	12	11	-	1

Discussion

Treatment of esophageal cancer is dependent on the stage of the cancer. Pre-treatment staging is only clinically significant if the therapeutic decision could be based on these staging results. During the last decade, EUS staging has appeared to gain popularity in this regard and offers (relative to surgery) a noninvasive method of stratifying the outcome of patients before the provision of any therapy.

Despite the importance of documenting that the EUS staging changes treatment plans in patients with esophageal cancer, only a few studies have attempted to examine this aspect (8-11). Previous studies have suggested that EUS and EUS FNA influence management decisions in esophageal carcinoma in 25% to 56% of patients (8, 9). In our study, a major change such as less-complex (surgery to radiation and/or chemotherapy) or more-complex (surgery to neoadjuvant radiochemotherapy plus surgery) management strategy involved 18 (44%) of patients. Only 6 (15%) out of the 41 patients underwent primary surgery. However, interpretation of these results should be done cautiously due to various pitfalls, including design, study methodology and number of patients in these studies. For example, prior investigations examining this topic have been limited by retrospective design (8, 10) or by the small number of patients included in the study (22 patients) (9). Although it represents

the experience of a single center, evaluating therefore only a small number of patients (41), our study was designed in a prospective and practical manner, reflecting the impact of EUS results in the actual patient care decision. In numerous studies reported in the literature, the pre-EUS management plan was determined by the endosonographer and not by a team of clinicians (gastroenterologist, oncologist and surgeon) directly caring for the patient (11). Therefore, we designed our study to reflect the actual manner in which clinicians requesting EUS in our center were using these results in routine practice, thus overcoming this bias.

The accuracy for EUS-lymph node staging is usually reported to be in the range of 70% to 80% (12). Usefulness of preoperative EUS FNA in patients' assessment for esophagectomy represents an area of controversy. Usually, FNA is not routinely performed on locoregional lymph nodes and their allocation as malignant or benign is left to the endosonographer judgment. Although FNA is relatively safe, it may not be possible without traversing the primary tumor, in which case there is a risk of contamination of the sample and false positive results, leading to inaccurate nodal staging (5,10).

In our study, a significant correlation regarding T staging can be demonstrated between EUS findings and histology. According to previous series, EUS erroneously classified tumor invasion (T) in 10-20% of cases (13). The accuracy for assessing of local tumor invasion (T) was approximately 80% for T1-T2 (67% for pT1 and 86% for pT2), data consonant with the literature (82%), and 77% for T3-T4 (82% for pT3 and 50% for pT4), less than in the literature (89%) (14). In fact, only 3 patients in stages T3-T4 were understaged, 50% of them with T4 tumors; the absence of Doppler capabilities for accurate delineating of the interface between tumor and aorta and the small number of patients could have led to this figure. In our series, EUS was less sensitive in detecting T1 and T4 cancers; EUS erroneously classifies pT1 in 33% and pT4 in 50% of cases, consistent with previous series (13). Pathologically T1 cancers were more frequently overclassified, and pT4 cancers were largely underclassified.

The accuracy for noninvasive EUS staging of locoregional lymph nodes in our study was 75% compared with 77% in the literature (15). Using established descriptive criteria for assessment, EUS erroneously classified nodal involvement (N) in approximately 25% of cases, an overall figure similar to our study (16). Our series did not employ FNA for N classification. A median gain of 10% in accuracy is counteracted by the invasive character of FNA and the possibility of false positive results due to sample contamination in the tumor field. The incidence of positive lymph nodes in the advanced stages of carcinoma (T3, T4) was higher compared with the intramural stages (T1, T2), which may explain the general poor prognosis of the disease.

Disease extent is closely associated with the clinical decision; tumors confined to the esophageal wall (pT1-pT2, N0, M0) typically go directly to esophagectomy, while those advanced (pT3-pT4, N1, or M1) receive preoperative or

chemoradiotherapy alone(17). When clinical determination of disease extent establishes 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 the first line therapy in either stage. Overclassification of pT2, which fortunately occurred in only 18% of cases in our series, inappropriately labels the patients as advanced disease (regardless of N classification). This could lead to preoperative chemoradiotherapy, with its associated morbidity and mortality.

We conclude that esophageal EUS offers useful information to clinicians who treat patients with esophageal cancer, impacts clinical decision making, and should be used in appropriate settings to plan therapeutic strategy.

References

1. The World Health Report 1997. Geneva: World Health Organization, 1997.
2. Faivre J, Forman D, Esteve J et al. Survival of patients with oesophageal and gastric cancers in Europe. *Eur J Cancer* 1998; 34: 2167-2175
3. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002; 347: 1662-1669
4. Wang KK, Wongkeesong M, Buttar NS. American Gastroenterological Association technical review on the role of the gastroenterologist in the management of esophageal carcinoma. *Gastroenterology* 2005; 128: 1471-1505
5. Penman ID, Henry E. Advanced esophageal cancer. *Gastrointest Endosc Clin N Am* 2005; 15: 101-116
6. TNM classification and stage grouping of esophageal carcinoma. In: Greene FL, Page DL, Fleming ID, et al, eds. *American Joint Committee on Cancer. Cancer staging manual*. 6th edition. New York: Springer; 2002: 91-98
7. Catalano MF, Sivak MV Jr, Rice T et al. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc* 1994; 40: 442-446
8. Shumaker DA, de Garmo P, Faigel DO. Potential impact of preoperative EUS on esophageal cancer management and cost. *Gastrointest Endosc* 2002; 56: 391-396
9. Shah JN, Ahmad NA, Beilstein MC et al. Clinical impact of endoscopic ultrasonography on the management of malignancies. *Clin Gastroenterol Hepatol* 2004; 2: 1069-1073
10. Pfau PR, Ginsberg GG, Lew RJ et al. EUS predictors of long-term survival in esophageal carcinoma. *Gastrointest Endosc* 2001; 53: 463-469
11. Nickl NJ, Bhutani MS, Catalano M et al. Clinical implications of endoscopic ultrasound: the American Endosonography Club Study. *Gastrointest Endosc* 1996; 44: 371-377
12. Rösch T, Classen M. Staging esophageal cancer: the Munich experience. In: van Dam J, Sivak MV Jr, eds. *Gastrointestinal endosonography*. Philadelphia: WB Saunders; 1999: 139-145
13. Zuccaro G Jr, Rice TW, Vargo JJ et al. Endoscopic ultrasound errors in esophageal cancer. *Am J Gastroenterol* 2005; 100: 601-606
14. Tio TL, Cohen P, Coene PP et al. Endosonography and computed tomography of esophageal carcinoma. Preoperative classification compared to the new (1987) TNM system. *Gastroenterology* 1989; 96: 1478-1486
15. Rösch T. Endosonographic staging of esophageal cancer: a review of literature results. *Gastrointest Endosc Clin N Am* 1995; 5: 537-547
16. Kelly S, Harris KM, Berry E et al. A systematic review of the staging performance of endoscopic ultrasound in gastroesophageal carcinoma. *Gut* 2001; 49: 534-539
17. Rice TW, Blackstone EH, Adelstein DJ et al. N1 esophageal carcinoma: the importance of staging and downstaging. *J Thorac Cardiovasc Surg* 2001; 121: 454-464