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Staging esophageal cancer: low EUS accuracy in t2n0 patients

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Authors

Germana de Nucci[1], Maria Chiara Petrone[2], Nicola Imperatore[3], Emanuele Asti[4], Gemma Rossi[2], Giampiero Manes[1], Maurizio Vecchi[5], Luca Pastorelli[6], Luigi Bonavina[4], Paolo Giorgio Arcidiacono[2]

Institutions

1 Gastroenterology and Endoscopy Unit, ASST Rhodense, Garbagnate Milanese-Milan, Italy
2 Bilio-pancreatic Endoscopy and Endoscopic Ultrasound Unit, San Raffaele Hospital, Milan, Italy
3 Gastroenterology and Endoscopy Unit, AORN Cardarelli, Naples, Italy
4 Division of General and Foregut Surgery, IRCCS Policlinico San Donato, University of Milano, Milan, Italy
5 Gastroenterology and Endoscopy Unit, Ca Granda Policlinic Major Hospital, Milan, Italy
6 Gastroenterology Unit, IRCCS Policlinico San Donato and Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author
Germana de Nucci, MD, Gastroenterology and Digestive Endoscopy Unit, ASST Rhodense, Viale Forlanini 98, Garbagnate Milanese, Milan, Italy
Fax: +39 02994302905
germanadenucci1@gmail.com

ABSTRACT

Background and study aims Esophageal cancer (EC) is one of the most lethal malignancies worldwide. Staging of EC is performed with computed tomography (CT), positron-emission tomography (PET), and endoscopic ultrasonography (EUS). Patient management mostly depends on lymph node status. Compared to histopathology, the accuracy of EUS for T and N parameters is about 85 % and 75 %, respectively. Errors in staging may change prognosis. The aim of this study was to assess the role of EUS in T2-N0 EC considering the experience of two high-volume digestive endoscopic centers.

Methods Two prospectively collected databases were queried to identify all patients with EC, staged as cT2N0 by EUS, with no distant metastases at CT/PET scan and who underwent transthoracic esophagectomy. Preoperative EUS staging (cTNM) was compared to histopathology of the surgical specimen (pTNM) to evaluate accuracy.

Results Of 729 consecutive patients with EC between January 2011 and September 2018, 72 (49 men) had cT2N0 disease. CT and PET scans confirmed the absence of distant metastasis. In 43 of 72 patients (60 %), the evaluation was correct, 23 of 72 (31,7 %) were understaged, and six of 72 patients (8,3 %) were overstaged. Among the understaged patients, eight were understaged by tumor depth (35 %), seven by nodal involvement (30 %), and eight by both (35 %). All six patients who were overstaged had T1b-N0 disease. EUS accuracy was 77 % in staging for tumor depth and 82 % in staging for nodal metastases. The positive predictive value (PPV) for cT2N0 EC was 60 % (43 pT2N0/72 cT2N).

Conclusions The accuracy of EUS staging of T2N0 EC is low, with only 60 % of patients undergoing appropriate therapy based on histopathology.

Introduction

Esophageal cancer (EC) is the seventh most common malignancy and the sixth most common cause of cancer-related death worldwide [1]. More than half of the patients are first diagnosed with unresectable or metastatic disease [2]. Early-stage disease has a better prognosis, with 80 % to 90 % 5-year survival after surgical resection [3], whereas locally advanced tumors (T3-T4, any N +) carry a worse prognosis with 5-year survival of 20 % to 40 % [4]. Neoadjuvant therapy has been demonstrated to improve survival and quality of life in locally advanced disease, and has become the current standard of care worldwide [5, 6]. Staging of EC is generally performed by combining computed tomography (CT), 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET), and endoscopic ultrasonography (EUS). [7]. Treatment strategies for patients with EC are usually discussed by a multidisciplinary team based on the results of clinical staging and patient comorbidities. Patients with disease that potentially can be cured can be managed in different ways according to the N-stage of the disease [8]. Different strategies include surgery alone, neoadjuvant chemotherapy and definitive chemoradiotherapy (dCRT), but evidences in choice of treatment are still lacking [9].

After distant metastases have been ruled out with CT or PET-CT, the next critical step in staging is to use EUS to evaluate the involvement of the five layers of the esophageal wall and the involvement of other structures up to 5 cm from the esophagus [10]. EUS is very reliable in defining tumor depth and offers the additional benefit of visualizing and sampling locoregional nodes suspicious for presence of cancer metastasis, if possible [11, 12].

The sensitivity and specificity of EUS in establishing tumor depth (T) is 80 % to 90 % and more than 90 %, respectively, with increased accuracy for advanced T stages. In contrast [13, 14], the pooled sensitivity of EUS for nodal staging is 84.7 % and the specificity is 84.6 % and with use of fine needle aspiration (FNA) of suspicious nodes, the sensitivity and specificity for N stage increase to 96.7 % and 95.5 %, respectively [15]. EUS staging of tumor depth, however, is reported to be less accurate in early disease with about only 60 % concordance with surgical pathology [16]. It is especially challenging to differentiate between T2 tumors that invade the muscularis propria and T3 tumors invading the adventitia. The distinction is critically important, as it determines which patients should undergo upfront surgery and which, instead, could benefit from induction therapy prior to curative resection with potential consequences even on patients' survival [17, 18].

The aim of our study was to assess the accuracy of EUS in staging an uncommon subset of patients with cT2N0 cancers, comparing its results with postsurgical pathology; we also aimed to identify factors that can hamper this diagnostic ability.

Methods

We conducted a retrospective analysis from the prospectively collected databases of the Endoscopy Units of San Raffaele Hospital and San Donato Milanese Hospital, and from the database of the Division of General and Foregut Surgery of Policlinico San Donato Hospital. Overall, 729 patients underwent EUS for clinical staging of EC between January 2011 and September 2018. Among these patients, we selected only those staged as cT2N0 at EUS. All patients had been evaluated previously with total body CT and PET-CT that confirmed the absence of distant parenchymal or nodal metastasis.

Data on patient demographics, tumor characteristics, radiological staging, operative treatment, perioperative outcomes, surgical pathology, and long-term outcomes were collected. Patients who received neoadjuvant therapy or palliative surgery, who received their diagnosis or had clinical staging done elsewhere or had neoplasia arising from the gastric cardia were excluded from the analysis.

After obtaining informed consent, a diagnostic esophagogastroduodenoscopy with a standard 9-mm gastroscope was performed on each patient, lying on the left side, prior to EUS to assess the length of the tumor, the distance from the dental arcade and from the cardia, its epicenter and the presence and degree of a stricture. Multiple biopsies were performed if needed. All subjects received sedation with various combinations of intravenous midazolam, meperidine, fentanyl or propofol under appropriate cardiorespiratory monitoring. The equipment used to perform EUS included in both the centers a linear echoendoscope (Pentax EG 3870 UTK, frequency between 7.5 and 10 Mhz). EUS was performed by four experienced gastroenterologists (MC.P, G.R, G.D.N, P.G.A) who had advanced training in EUS with several years of practical experience (> 10 years of experience and about 1000 diagnostic and therapeutic procedures for each endosonographer/year). Fine needle aspiration (FNA) and fine needle biopsy (FNB) were performed, if the node position was favorable, to asses suspicious nodes metastasis and assessed for consistency with rapid onsite evaluation (ROSE). Staging was performed using the TNM classification system according to the American Joint Committee on Cancer (AJCC) guidelines in force at the time [19] as well as: T1, invasion up to the third layer (submucosal layer); T2, invasion into but not through the fourth wall layer (muscularis propria); T3, invasion beyond the fourth wall layer into the adventitia; T4, invasion of adjacent structures, (pleura, aorta, lung). The EUS criteria to assess nodes malignancy were the presence of a hypoechoic pattern, a round shape, the evidence of a distinct border, and a short axis diameter of ≥ 5 mm [20].

All patients underwent upfront standard esophagectomy and two-field lymph node dissection via a laparoscopic and transthoracic approach (Ivor-Lewis procedure). Alimentary continuity was reconstructed using a a gastric conduit. None of the patients had previous neoadjuvant chemo/radiotherapy. All operations were performed by experienced surgeons using the same surgical technique during all the study period. The inclusion criteria for surgery were the absence of local nodes suspicious for metastatic disease at EUS/CT/PET evaluation, the

absence of distant metastasis of the primary tumor and an ASA physical status score ≤ o 3, because of the huge complexity of this type of surgery and the chance of severe comorbidities and its mortality.

Preoperative EUS staging (cTNM) was then compared to surgical pathology (pTNM) results.

The sensitivity and specificity of EUS for T and N staging were calculated using standard formulas for sensitivity (true positivity/true positive + false negative) and specificity (true negative/true negative + false positive). Furthermore, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated. Cohen's k was also calculated in order to establish the agreement between EUS staging and surgical staging. Statistical analysis was carried out with SPSS software version 23 (Chicago, Illinois, United States). Continuous variables were described with means and standard deviations and dichotomous variables were expressed as simple proportions with or without 95 % confidence limits. Student's *t* test and Fisher's exact test or chi-square test was used to compare variables. Two-sided *P* was used with $P<0.05$ considered statistically significant. Logistic regression analysis was used to determine if clinical variables such as age, gender, tumor location, length and histology, lag time between EUS and surgery were associated with EUS accuracy. Multivariate analysis was performed using the stepwise backward method (Wald) and it included all the variables with $P<0.1$ at univariate analysis. Coefficients obtained from the logistic regression analysis were also expressed in terms of odds of event occurrence (odd ratio–OR). $P<0.05$ was considered statistically significant. Institutional review board approval was obtained prior to initiation of the study.

▶ **Table 1** Baseline clinical, endoscopic, and pathologic characteristics of the study population.

		N	%
Male gender		49	68
Caucasian ethnicity		69	96
Hispanic ethnicity		3	4
Mean age (years)		76.7	
Endoscopy tumor location	Proximal esophagus	7	10
	Mid esophagus	17	27
	Distal esophagus	39	50.5
	GE junction	9	12.5
Endoscopy tumor length	< 30 mm	14	19.5
	> 30 mm	58	80.5
Histopathology type	Adenocarcinoma	64	89
	Squamous	8	11
Histologic grade	G1	34	47
	G2	28	39
	G3	10	14
ASA pre-surgery	1	13	18
	2	29	40
	3	30	42

GE, gastroesophageal; G1, well differentiated tumor; G2, moderately differentiated tumor; G3, poorly differentiated tumor.

Results

A total of 72 patients were identified to have cT2N0 tumors by EUS and were enrolled in the study. Demographics and tumor-related characteristics are summarized in ▶ **Table 1**. No complications from endoscopic procedures were registered. In eight patients (11 %), six EUS-FNA cytology (22 G needle, Cook, United States; mean passes, 2.8; range, 2–4) and two FNB histology (19 G needle Expect slim line Boston Scientific USA; mean passes, 1.8; range 1–3) were performed of celiac (n = 5) or periesophageal (n = 3) lymph nodes. All the sampled nodes were found to be benign.

The mean time between EUS and surgery was 21 days (range 8–47). Median follow-up post-surgery was 69 months (range 1–98 months), and the median overall survival was 39 months (range 7–69).

Prediction of T and N stage

▶ **Table 2** compares the results of preoperative EUS staging of cT2N0 patients with final surgical pathology. Oof the 72 patients, 43 (59.7 %) were evaluated correctly for T and N stage. Twenty-three patients of the 72 (31.9 %) were understaged and six of 72 (8.3 %) were overstaged. In the understaged group, eight of 23 patients were understaged only for tumor depth (34.8 %), seven only for nodal involvement (30.4 %) and eight for both (34.8 %). In the overstaged group, all the patients had a T1b stage without nodal involvement. The sensitivity and PPV of EUS-staged T2 were 76.9 % (95 %CI 64.8 %–86.5 %) and 89.3 % (95 %CI 87.9 %–90.5 %), respectively, with an overall accuracy in staging T2 EC of 70.4 % (95 %CI 58.4 %–80.7 %) (specificity was 0 % because no true negative was found due to study design). Concordance between EUS staging and surgical staging for T was good (Cohen's k = 0.7). On the other hand, 15 of 72 patients were found to be N + at surgery; therefore, the diagnostic accuracy of EUS in determining N0 was 79.2 % (95 %CI 67.9 %–87.8 %), with a good agreement between the two staging systems (Cohen's k = 0.79). Finally, the overall positive predictive value (PPV) of a cT2N0 EC was 59.7 % (95 %CI 47.5 %–71.1 %) (43 pT2N0/72 cT2N0). It wasw interesting to observe as the average survival time of all the patients was 39 months, but among the understaged group (23/72), we observed a huge reduction in this time to an average of 21.1 months with the worst prognosis for those who were understaged for nodes alone and for tumor depth and nodes. The understaged group has faster disease progression and also more frequent complications and comorbidities after upfront unnecessary surgery, considering their final pathological staging.

▶ **Table 2** Diagnostic accuracy of EUS and surgery in staging T2N0 esophageal cancer.

	Sensitivity (95 %CI)	Specificity (95 %CI)	PPV (95 %CI)	NPV (95 %CI)	Accuracy (95 %CI)
T2	76.92 % (64.81 %–86.47 %)	0 % (0 %–45.93 %)	89.29 % (87.94 %–90.49 %)	0 %	70.42 % (58.41 %–80.67 %)
N0	0 % (0 %–21.8 %)	100 % (93.73 %–100 %)	0 %	79.17 % (79.17 %–79.17 %)	79.17 % (67.98 %–87.84 %)
T2N0	65.15 % (52.42 %–76.47 %)	0 % (0 %–45.93 %)	87.76 % (85.73 %–89.53 %)	0 %	59.72 % (47.5 %–71.12 %)

EUS, endoscopic ultrasound; T, tumor depth; N, lymph nodes; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

▶ **Table 3** Binary logistic regression for predicting wrong T2N0 EUS staging.

		Univariable analysis			Multivariable analysis		
Variables		**OR**	**95 %CI**	***P***	**OR**	**95 %CI**	***P***
Age		1.23	0.78–1.87	0.7			
Male gender (vs female)		0.82	0.67–0.95	0.02	0.91	0.72–1.12	0.2
Location	Upper	0.76	0.57–1.12	0.7			
	Middle	1.06	0.75–1.34	0.6			
	Lower	1.54	0.95–3.12	0.07	1.35	0.87–2.23	0.3
	GEJ	1.82	1.19–2.68	0.004	1.71	1.15–2.73	0.02
Tumor length > 3 cm (vs < 3 cm)		2.56	1.86–3.25	< 0.01	2.21	1.58–3.15	< 0.01
Tumor grade (G3 vs G1/G2)		2.15	1.43–3.12	< 0.01	2.02	1.36–2.78	< 0.01
Histology (adenocarcinoma vs squamous cell)		0.95	0.67–1.43	0.8			
Lag time between EUS and surgery > 20 days (vs < 20 days)		1.21	0.79–1.73	0.5			

EUS, endoscopic ultrasound; GEJ, gastroesophageal junction.
Significant results have been highlighted in bold.

Other factors influencing EUS staging

Logistic regression was performed to evaluate whether patient-related features (age, gender), tumor location (upper, middle/lower esophagus or GE junction), lesion length, histology (adenocarcinoma/ squamous cellular carcinoma), or timing between EUS and surgery significantly affected EUS accuracy. The only independent predictors for EUS understaging were tumor location at the gastroesophageal junction (OR 1.71, 95 %CI 1.15–2.73, p = 0.02), tumor length > 3 cm (OR 2.21, 95 %CI 1.58–3.15, $P < 0.01$) and G3 tumor grade (OR 2.02, 95 %CI 1.36–2.78, $P < 0.01$) as reported in ▶ **Table 3**.

Discussion

This study confirms that the accuracy of EUS in staging cT2N0 EC is very low, with a PPV of only 60 %. Only 68 % of our patients, considering both properly and overstaged patients, underwent surgical treatment that was appropriate for their pathological stage; the remaining 32 %, understaged for tumor depth or nodal involvement or both, would have been better treated with neoadiuvant radio-chemotherapy instead of being candidates for surgery.

EUS has been demonstrated to be superior to conventional CT for locoregional staging and assessment of T and N status [20, 21]. However, cT2N0 cancers remain a crucial point in decision-making for management of EC.

Understaging of EC is related to the inability of EUS to identify with certainty transmural tumor extension because of its similarity to peritumoral inflammation. Moreover, EUS has difficulty to identify local nodal involvement when there are no clear morphological criteria suggestive of neoplastic involvement and FNA/FNB is not feasible [21]. Failed diagnosis of nodal involvement represents a true problem in practice because it leads to unreliable prognostication and inappropriate treatment selection. The importance of this issue is demonstrated by the poor 5-year survival rate for patients with node metastasis [22]. Several studies have demonstrated a survival advantage for patients with lymph node involvement treated with neoadjuvant therapy plus surgery [23, 24]. In our series, 15 of

72 patients (21 %) had unrecognized nodal disease preoperatively. Had their clinical staging been accurately assessed, neoadjuvant chemoradiation would have been recommended prior to proceeding with surgical resection, and this group of patients had worse prognosis, more complications after surgery, and faster disease progression, probably because they were treated with unnecessary surgery at that time. The role of adjuvant therapy in these patients is controversial and the delivery of chemotherapy and/or radiation therapy following surgical resection could be less effective and poorly tolerated compared to neoadjuvant therapy [25–27].

EUS overstaging also may be due to the presence of peritumoral inflammation that is indistinguishable from the tumor itself [28]. Overstaging may lead, in some cases, to unnecessary surgery with associated risks. Esophagectomy is major surgery with mortality and morbidity rates of 2 % to 6 % and 50 % to 64 %, respectively, in several clinical series [29]. In our study, six patients were overstaged (pT1b N0 vs uT2N0), but that did not change the planned surgical approach.

Besides lymphovascular invasion, tumor size > 3 cm, higher grade (G3), and tumor location at the GEJ were independently and significantly associated with worse EUS performance as described previously by Hardacker et al [30, 31] probably because all these factors affect the capacity of the endosonographer to properly evaluate the lesion and its extension and all the peritumoral nodes and catch minimal tissue changes in the subverted layers. It's important to observe that EUS is a precise tool but it's always a bidimensional exam.

In the present series, EC subjects labeled as T2Nx were excluded from analysis. The Nx stage was indicated when there was only suspicion of nodal involvement (one ultrasound criteria out of four) but no FNA/FNB was performed because the location of the nodes was not safely accessible (passage through the neoplasia with risk of intra mediastinal dissemination). Although this is a critical group of patients, we opted to discard this subset of data because there was no chance to definitively compare with postsurgical pathology and these patients were treated with neoadjuvant chemotherapy after multidisciplinary discussion

Our study has some limitations, which deserve consideration. The first one is its retrospective, non-randomized design, which makes it subject to selection bias. Actually, we analyzed two different databases that had been collected prospectively in two high-volume EUS centers. Both surgical and pathological examination of resected specimens were centralized during the study period. However, there is a spectrum bias, as only operable patients were referred for surgery and included in the analysis. In addition, the participating endosonographers were aware of the clinical data and endoscopic findings, and this might have influenced the interpretation of EUS (clinical review bias). A third limitation could be related to the number of physicians performing EUS and possible interobserver variability (four endoscopists); however, all of them were experts and there were no trends toward improvement or worsening of EUS performance over the years (data not shown). It is clear that the methods used to stage EC need further improvement because T, and especially N status, are significantly and independently associated with survival. We need further improvement in EUS instruments to reach this goal, because the principal difficulty for endosonographers is distinguishing what is normal peritumoral inflammation from real neoplastic infiltration [32]. Both these situations appear in EUS mode as hypoechoic microdigitations, so it is really hard to assess with the available technology what is pathologic and what is not. It is also difficult to identify all the peritumoral pathologic nodes because it is often not feasible to reach and sample all the suspicious ones, with the result that EUS evaluation in this setting often has a degree of uncertainty. In the future, perhaps use of artificial intelligence can overcome challenges in misidentification of lesions at standard endoscopy and play a role in improving software imaging to reduce artifacts and help endosonographers to study lesions more effectively and faster.

Conclusions

Proper treatment for patients with T2N0 EC remains a challenge considering the available actual diagnostic tools. EUS staging clearly has limits in this rare subset of patients. In the absence of applicable technology improvement, it may be safer to consider neoadjuvant treatment, after a detailed discussion regarding the risks and benefits, for all patients with T1b plus EC to minimize above all understaging and improve the overall post-surgical performance and survival of these patients.

Competing interests

The authors declare that they have no conflict of interest.

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