Endoscopic Ultrasound: Doubtful Accuracy for Restaging Esophageal Cancer after Preoperative Chemotherapy

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ABSTRACT:
Background: The role of endoscopic ultrasound in evaluating the response of esophageal cancer to neoadjuvant chemotherapy is controversial.

Objectives: To evaluate the accuracy of EUS in restaging patients who underwent NAC.

Methods: The disease stage of patients with esophageal cancer was established by means of the TNM classification system. The initial staging was determined by chest and abdominal computed tomography and EUS. Patients who needed NAC underwent a preoperative regimen consisting of cisplatin and fluouracil. Upon completion of the chemotherapy, patients were restaged and then underwent esophagectomy. The results of the EUS staging were compared with the results of the surgical pathology staging. This comparison was done in two groups of patients: the study group (all patients who received NAC) and the control group (all patients who underwent primary esophagectomy without NAC).

Results: NAC was conducted in 20 patients with initial stage IIB and III carcinoma of the esophagus (study group). Post-chemotherapy EUS accurately predicted the surgical pathology stage in 6 patients (30%). Pathological down-staging was noted in 8 patients (40%). However, the EUS was able to observe it in only 2 patients (25%). The accuracy of EUS in determining the T status alone was 80%. The accuracy for N status alone was 35%. In 65% of examinations the EUS either overestimated (35%) or underestimated (30%) the N status. Thirteen patients with initial stage I-IIA underwent primary esophagectomy after the initial staging (control group). EUS accurately predicted the surgical pathology disease stage in 11 patients (85%).

Conclusions: EUS is an accurate modality for initial staging of esophageal carcinoma. However, it is not a reliable tool for restaging esophageal cancer after NAC and it cannot predict response to chemotherapy.

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KEY WORDS: endoscopic ultrasound, staging, neoadjuvant therapy, esophageal cancer

Worldwide, esophageal carcinoma is the fifth most lethal cancer. Survival rates are closely related to the stage of the disease at the time of diagnosis. The 3 year survival rate of patients with regional esophageal cancer who have undergone curative resection remains low (approximately 20%) [1]. Neoadjuvant chemotherapy has recently become the focus of interest in an effort to downstage the tumor, reduce the local recurrence rate, and prolong survival of patients with locally advanced disease. Accurate preoperative staging of esophageal cancer is essential for the selection of appropriate treatment modalities and hence the possible prolongation of survival [2].

Endoscopic ultrasound is considered the most reliable modality for preoperative staging in patients with esophageal cancer. This imaging modality can provide detailed information on the depth of invasion, the tumor site and size, and lymph node involvement. On the other hand, EUS has no role in the diagnosis and evaluation of distant metastases, except for cases of celiac lymph node involvement [3]. However, controversy remains over the role of EUS in restaging of esophageal carcinoma after NAC [4-9]. In this study, we evaluated the ability of EUS to predict the surgical pathology staging in patients with and without NAC.

PATIENTS AND METHODS

This was a retrospective cohort study. All patients who were evaluated in the Department of Surgery at Kaplan Medical Center for esophageal carcinoma between May 2003 and May 2006 were included. Patients with esophagogastric junction tumor, unresectable or metastatic disease, and those with unrecoverable EUS results were excluded.

All patients underwent endoscopy and biopsy, computed tomography of the chest and abdomen, and EUS. The study group comprised all patients with initial stage IIB-III carcinoma of the esophagus. These patients received NAC and underwent EUS restaging prior to the definitive surgery. Patients in the control group underwent primary esophagectomy without NAC. The reason for avoiding NAC was either initial stage I-IIA disease or patients at a higher stage who refused NAC.

EUS was performed by the same gastroenterologist using a radial echo-endoscope (EU-M30, Olympus, Japan).

EUS = endoscopic ultrasound
NAC = neo-adjuvant chemotherapy

The procedure was performed under conscious sedation using frequencies of 7.5–12 MHz. Four esophageal wall layers were detected: the mucosa (first hyperechoic and second hypoechoic layers), sub-mucosa (third hyperchoic layer), and muscularis propria (fourth hypoechoic layer). Malignant lymph nodes appeared as large (> 1 cm), round, hypoechoic structures with a discrete border. Although passage of the echo-endoscope was not possible because of malignant obstruction in two patients, the endoscopist could estimate the T stage of the tumor in every case.

After initial staging, all patients in the study group underwent a chemotherapy regimen consisting of cisplatin 80 mg/m^2 on day 1, followed by 5FU 1000 mg/m^2 as a 96 hour continuous infusion every 3 weeks. Every patient received two treatment cycles. After completion of their NAC, patients were restaged with EUS. No signs of tumor progression or other contraindication to surgery were observed in the study group. All patients from the two groups were referred to surgery. Surgical therapy consisted of transhiatal esophagectomy in 22 patients, transthoracic esophagectomy in 3 patients, and laparoscopic-assisted approach in 9 patients.

Pathological specimens were analyzed by an experienced pathologist. Esophagectomy surgical specimens were fixed in neutral-buffered formalin. Specimens were routinely processed according to a protocol entailing gross examination. Hematoxylin and eosin stain was performed in 3 to 4 μ thick sections of formalin-fixed paraffin-embedded tissue. Residual tumor was assessed in terms of pTNM stage, tumor regression grade, lymphovascular space invasion and resection margin involvement.

The histopathology staging of the specimens was the gold standard to which the EUS staging was compared. In the study group we evaluated the accuracy of EUS in determining T status, N status and TN staging after NAC as compared with surgical pathology. In the control group a similar comparison was made to the initial EUS.

RESULTS

During the study period 57 patients with cancer of the esophagus were investigated and treated at our center. Twenty-four patients were excluded: 5 with esophagogastric junction tumors, 14 due to unresectable or metastatic disease (8 of them received photodynamic treatment), and 5 patients in whom the post-NAC ultrasound results could not be completely recovered. The study group comprised 20 patients and the control group 13. Patients' characteristics and initial staging of carcinoma are shown in Table 1.

In the control group EUS accurately predicted the pathological T status in 12 patients (92%), while overestimating the T status in only 1 patient (8%); the N status was accurately predicted

FU = fluouracil

Table 1. Patient characteristics

All patients (n = 33)		
Age (yrs)		
Median	68	
Range	28–86	
Gender		
Male	26 (79%)	
Female	7 (21%)	
Pathology		
Adenocarcinoma	22 (67%)	
Squamous cell carcinoma	11 (33%)	
Initial EUS stage		
Stage	**Control group**	**Study group**
Stage 0 (Tis N$_0$)	1 (7%)	–
Stage I (T$_1$ N$_0$)	2 (16%)	–
Stage IIA (T$_{2-3}$ N$_0$)	8 (61%)	6 (30%)
Stage IIB (T$_{1-2}$ N$_1$)	2 (16%)	–
Stage III (T$_3$ N$_1$)	–	14 (70%)
Total	**13**	**20**

Table 2. Comparison of T and N status and TN staging of esophageal carcinoma between post-chemotherapy endoscopic ultrasound (Post-NAC EUS) and histopathological findings

Histopathologic T status					
Post-NAC EUS T status	**p T$_0$**	**p T$_1$**	**p T$_2$**	**p T$_3$**	**Total (n = pts)**
T$_2$	–	–	–	1	**1**
T$_3$	–	1	2	16 (80%)*	**19**
Histopathologic N status					
Post-NAC EUS N status	**p N$_0$**		**p N$_1$**		**Total (n = pts)**
N$_0$	3 (15%)*		7		**10**
N$_1$	6		4 (20%)*		**10**
Histopathologic staging **					
Post-NAC EUS staging	**I**	**IIA**	**IIB**	**III**	**Total (n = pts)**
IIA	–	3 (15%)*	–	6	**9**
III	1	6	1	3 (15%)*	**11**

* Accuracy of post-NAC EUS as compared to surgical pathology
** Stage I: T$_1$ N$_0$, Stage IIA: T$_{2-3}$ N$_0$, Stage IIB: T$_{1-2}$ N$_1$, Stage III: T$_{3-4}$

by EUS in 11 patients (85%). In 2 patients (15%) the N status was underestimated [Table 2]. The disease stage as determined by EUS in the control group was identical to the pathological findings in 11 of 13 patients. The overall accuracy of TN staging by EUS in patients who did not have NAC was 85%.

The accuracy of post-NAC EUS in determining T status was 80% (16 of 20 patients). Post-NAC EUS overestimated T status in 3 patients (15%) and underestimated T status in one patient (5%). The accuracy of post-NAC EUS in N status assessment fell markedly to 35% (7 of 20 patients). Post-NAC

Table 3. Comparison of T and N status of esophageal carcinoma between initial endoscopic ultrasound and histopathological findings in patients who underwent esophagectomy without preoperative chemotherapy

Histopathologic T status					
EUS T status	pT_0	pT_1	pT_2	pT_3	Total (n = pts)
T_0	1 (8%)	–	–	–	1
T_1	–	2 (15%)	–	–	2
T_2	–	1	4 (31%)	–	5
T_3	–	–	–	5 (38%)	5
Histopathologic N status					
EUS N status	pN_0		pN_1		Total (n = pts)
N_0	9 (69%)		2		11
N_1	–		2 (16%)		2

EUS overestimated N status in 7 patients (35%) and under estimated N status in 6 patients (30%). It led to a sharp decrease in accuracy of estimating TN staging [Table 2].

Post-NAC EUS was inaccurate in 70% (14 of 20 patients) as compared to surgical pathology staging [Table 3].

In addition, we compared the results of the initial EUS with the results of the post-NAC EUS in order to quantify the patients' response to chemotherapy. According to the post-NAC EUS, chemotherapy led to down-staging in 4 patients (20%): from stage III to stage IIB (1 patient) and to stage IIA (3 patients). However, in comparison with the actual pathological findings, post-NAC EUS was accurate in only one case.

DISCUSSION

The treatment strategy for cancer of the esophagus has changed in recent years, with NAC playing the prominent role [2]. The indication for NAC is not yet well defined. In most centers patients with locally advanced disease will be referred to chemotherapy or chemo-radiotherapy prior to esophagectomy. The role of EUS in evaluating the pre-treatment stage of esophageal cancer is well established. In our center the treatment strategy is based mainly on the EUS findings. Only a few studies have examined the reliability of EUS in restaging esophageal cancer and assessing the effect of NAC prior to the surgical intervention. The aim of the present study was to evaluate whether EUS can serve as a reliable modality for restaging esophageal cancer after NAC and prior to surgical resection.

We showed that EUS was an accurate modality in evaluating the initial disease stage in patients with esophageal cancer. The overall accuracy of EUS in patients who were primarily operated without NAC was 85% and this should continue to be an important modality in determining the treatment strategy. In the TN staging of post-NAC patients, EUS accurately predicted the pathological staging in only 30%. The accuracy of EUS in evaluating the pathological T status was 80%, but it failed to determine the N status after NAC.

A possible explanation for the very low accuracy of EUS in evaluating N status is that in our study we did not perform EUS-guided fine needle aspiration of malignant-appearing lymph nodes. The reason for this is our belief that it will not change our treatment algorithm.

Kalha et al. [6] evaluated the accuracy of EUS for restaging esophageal carcinoma after chemotherapy. In a retrospective analysis of 83 patients they concluded that EUS was not a useful modality after NAC for esophageal adenocarcinoma.

Recently, a large prospective study published by Mesenas and colleagues [8] assessed the value of radial EUS in 109 patients who underwent esophagectomy following NAC. The authors demonstrated that the staging accuracy of CT and non-biopsy EUS after NAC for gastroesophageal cancer was poor. They also stated that the use of radial EUS in protocols for restaging esophageal cancer is questionable.

The use of positron emission tomography (FDG-PET) has become more and more popular in the diagnosis and staging of esophageal and esophagogastric cancer. Van Vliet and team [9] recently published a meta-analysis comparing the various modalities for staging investigations for esophageal cancer. They found that EUS was the most sensitive for the detection of regional lymph node metastases, whereas CT and FDG-PET were more specific. They suggested that a combined use of the modalities could be of clinical value. However, they did not evaluate the role of FDG-PET in restaging the disease after NAC and whether it can replace the use of EUS.

In conclusion, while EUS is an accurate modality for evaluating the initial stage of esophageal carcinoma, it is not a reliable tool for restaging esophageal cancer after NAC. The role of positron emission tomography in restaging esophageal cancer seems promising but further prospective studies should be performed. For the present, we believe that endoscopic ultrasound is not a reliable modality for restaging esophageal cancer after NAC and should not be routinely used in these situations.

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FDG-PET = fluoro-2-deoxy-D-glucose positron emission tomography

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