



Endoscopic ultrasonography for gastric cancer

Does it influence treatment?

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Abstract

Background: This study aimed to evaluate the utility and shortcomings of endoscopic ultrasound (EUS) in tumor node metastasis (TNM) staging of gastric cancer and its influence on treatment.

Methods: The series included 126 patients (65 men and 44 women) with gastric cancer who underwent EUS from July 1997 to June 2003 at the National University Hospital, Singapore. The final analysis included 109 patients ranging in age from 29 to 97 years (mean, 63.13 years).

Results: *EUS staging for primary disease:* Specimen histology was available for 102 of the 109 patients who underwent surgery. The accuracy was 79% for T1, 73.9% for T2, 85.7% for T3, and 72.7% for T4. The overall accuracy was 80.4%. *EUS staging for nodes:* The sensitivity of EUS for detecting nodal disease was 74.2% for N0, 78% for N1, 53.8% for N2, and 50% for N3. Overall, the N staging by EUS showed a sensitivity of 82.8%, a specificity of 74.2%, a positive predictive value of 85.4%, a negative predictive value of 70.2%, and an accuracy of 77.7%. Radical gastrectomy was proposed for 95 patients on the basis of the staging with EUS and computed tomography (CT) scan, and 87 patients (91.6%) underwent the surgery. Preoperative staging accurately predicted the operative strategy for 89% of the patients. No significant predictor for accuracy was achieved by performing a logistic regression analysis for the correct staging of T stage using EUS and adjusting for tumor location (middle part/distal third/whole stomach vs proximal/cardioesophageal) ($p = 0.873$), operator ($p = 0.546$), and subject's sequence (initial 50 vs last 50 cases) ($p = 0.06$).

Conclusion: Ultrasound is the most accurate and reliable method for the preoperative staging of gastric carcinomas, and it is mandatory if a tailored therapeutic approach is planned according to stage.

Key words: Endoscopic ultrasonography — EUS — Gastric cancer — TNM staging

A tailored therapeutic approach to gastric cancers requires exact pretherapeutic staging for selection of the appropriate treatment. The possibilities vary, including endoscopic resection for mucosal lesion, the laparoscopic approach, limited resections, radical resections, palliative resections, and neoadjuvant chemotherapy.

After histologic confirmation and exact topographic location of a malignant tumor, it is essential to determine the depth of tumor infiltration into the gastric wall (T category), the lymph node status (N category), and the presence or absence of distant metastases (M category). The disparity between preoperative macroscopic staging and postoperative histologic staging must be reduced to a minimum. Endoscopic ultrasound (EUS) has the advantage of placing the transducer close to the lesion without interference of fat, bowel gas, or bone. It also has the ability to detect nodes and ascitic fluid within the range of the transducer. The search for an ideal staging method continues, but the most efficient method currently seems to be EUS.

This study aimed to evaluate the utility and shortcomings of EUS in the tumor node metastasis (TNM) staging of gastric cancer by comparing preoperative staging results with pathologic TNM staging. It also sought to evaluate the influence of EUS on the management of gastric cancer.

Patients and methods

From July 1997 to June 2003, 126 consecutive patients (72 men) with a mean age of 63.1 ± 14.1 years who had a diagnosis of gastric cancer but no computed tomography (CT) evidence of metastasis were referred to our department for EUS. All the cases were managed by one of the three experienced operators. This retrospective study evaluated the utility and shortcomings of EUS and its value in addition to CT scan for the staging of gastric cancers. The study excluded 11 patients

in whom the scope could not be adequately positioned because of the tumor location or could not be passed to the full extent of the tumor because of high-grade strictures. Three patients who declined surgery and three who underwent surgery elsewhere also were excluded. Two patients with ascites that showed positive results for malignant cells on EUS-guided fine-needle aspiration (FNA) were considered inoperable. Another five patients were explored for resection and found to be inoperable (2 underwent palliative bypass and 3 were closed after exploration).

Consequently, a total of 102 patients who had final specimen histology were included in the study for T staging sensitivity analysis. Of these 102 patients, 3 underwent endoscopic mucosal resection and were excluded from the N-staging sensitivity analysis because their pathologic N (p) stage could not be adequately determined. Endoscopic ultrasound was performed either in the same session as the initial endoscopy or within 2 weeks of endoscopy. Premedication consisted of local pharyngeal anesthesia as well as 2 to 6 mg of midazolam and 25 to 100 mg of pethidine administered intravenously. Patients were examined in the left lateral position with the rotating sector scan radial echoendoscope (7.5–12 MHz, GF-UM20; Olympus Co., Ltd, Singapore). The echoendoscope was advanced beyond the tumor mass, and serial images were obtained at pull back. An inflatable balloon surrounding the transducer was filled with deaerated water to increase the surface contact and improve the imaging window. Some 100 to 200 ml of deaerated water usually was instilled also into the gastric lumen to improve acoustic contact. Local tumor infiltration was determined according to the five-layer structure of the gastric wall [12] and classified by the TNM system.

Lymph node metastases were diagnosed in accordance with generally accepted criteria [16]. Briefly, echo-poor, roundish, well-demarcated nodes and nodes larger than 1 cm were considered to be malignant, whereas echo-rich and ellipsoid nodes with indistinct margins were considered to be benign.

Tumors classified as stages T1 to T3 were judged to be radically resectable (R0), whereas curative resectability for T4 tumors was regarded as questionable. A total of 104 patients underwent surgical exploration after adequate EUS staging. The tumor was curatively removed (R0) by standardized gastrectomy with radical lymphadenectomy from 88 of the 104 patients, and with extended excision from 4 patients. The remaining patients with advanced diseases underwent palliative resection ($n = 7$), palliative bypass ($n = 2$), or no further therapy ($n = 3$). Intraoperative findings such as tumor extension, lymph node status, and possible metastasis to the liver and peritoneum were recorded. The results of the preoperative endosonographic staging were compared with the intraoperative findings as well as definitive histopathologic results after the operation. Histopathologic assessment of the surgically resected specimens, including local lymph nodes, was performed by the Department of Pathology at our institution using the standard TNM classification system [17].

Statistical analysis

The following end points were assessed: (a) the accuracy of EUS in the staging of gastric cancer using histopathologic examination of resected specimens as the gold standard and (b) the impact of EUS on clinical decision making (i.e., indication for surgery and tumor respectability). All data were entered into a personal computer and analyzed using the Statistical Package for the Social Sciences for Windows (SPSS, Chicago, IL, USA). Categorical data were analyzed using Fisher's exact test and the chi-square test, whereas continuous data were analyzed using the Mann-Whitney U test and Kruskal-Wallis test as appropriate. Multivariate analysis was performed using logistic regression analysis. A p value less than 0.05 was considered significant.

Results

EUS staging for primary tumor

Of the 102 patients with histopathologic specimens available for T staging analysis, 19 (18.6%) were classified as pathologic stage T1. Of these, EUS correctly staged 15 but overstaged 4 patients. Three patients who showed T1m lesion on EUS underwent endoscopic

Table 1. T stage: histopathology and endoscopic ultrasound (EUS)

	Histopathologic T staging					Sensitivity (%)	PPV (%)
	1	2	3	4	Total		
EUS T staging	1	15	2	1	18	79	83.3
	2	3	17	4	24	73.9	70.8
	3	1	4	42	50	85.7	84
	4		2	8	10	72.7	80
	Total	19	23	49	11	102	

PPV, positive predictive value

Table 2. N stage: Histopathology and endoscopic ultrasound (EUS)

	Histopathologic N staging					Sensitivity (%)	PPV (%)
	0	1	2	3	Total		
EUS N staging	0	26	6	4	1	37	74.2
	1	9	25	8		42	78
	2		1	14	2	17	53.8
	3			3	3	3	50
	Total	35	32	26	6	99	100

PPV, positive predictive value

mucosal resection. Histology confirmed clear margins and correct staging. Of 23 patients (22.5%) classified as stage T2 on histopathology, 17 were correctly staged, 4 were overstaged as T3, and 2 were understaged as T1. Of 49 patients (48%) staged as T3 on histopathology, 42 were correctly staged, 2 were overstaged, and 5 were understaged. In comparison, of 11 patients (10.8%) staged as T4 on histopathology, 8 were correctly staged, and 3 were understaged. Thus, the overall accuracy for preoperative determination of T stage by EUS was 80.4%. The accuracy was highest for T3 lesions (85.7%) and lowest for T4 lesions (72.7%) (Table 1).

EUS staging for lymph nodes (Table 2)

A total of 99 patients had final histopathologic results available for nodal status. Endoscopic ultrasound correctly staged 26 (35.3%) of 35 patients classified as N0 on histopathology. The nine patients overstaged as N1 had reactive nodes on pathology. Overall, more cases were understaged than overstaged in the N1 (6 vs 1), N2 (12 vs 0) and N3 (3) pathologic states. Three patients staged as N3 on EUS also were offered surgical exploration because nodal staging on EUS is not confirmed by FNA. The sensitivity of EUS for detecting nodal disease was 74.2% for N0, 78% for N1, 53.8% for N2, and 50% for N3. Overall, N staging by EUS had a sensitivity of 82.8%, a specificity of 74.2%, a positive predictive value of 85.4%, a negative predictive value of 70.2%, and an accuracy of 77.7%.

Factors affecting EUS staging accuracy

Various factors were analyzed as potential confounding factors that might have affected the accuracy of EUS staging. These factors included the location of the tumor (proximal vs middle, distal, and whole stomach), the

Table 3. Logistic regression analysis for the correct T and N staging using endoscopic ultrasound (EUS) and adjusting for tumor location and operator and subjects' scanning sequence^a

Variable		<i>p</i> Value (T stage)	<i>p</i> Value (N stage)
Tumor location	Proximal third	0.51	0.873
Operator	A (70 cases)	0.068	0.546
	B (20 cases)	0.854	0.91
Subjects' scanning sequence	Initial 50 cases	0.483	0.06

^a The reference group included the tumor location (middle part/distal third/whole stomach), the operator (C [19 cases]), and subjects' scanning sequence (last 50 cases)

operator, and the learning curve (first 50 vs last 50 cases) (Table 3). The accuracy of EUS T staging was not related to any of these variables according to logistic regression analysis. Similarly, there was no relationship between correct staging of nodal status using EUS and any of these factors.

Decision making after EUS

A cross tabulation between the proposed treatment and the actual treatment rendered for each patient after workup with CT scan and EUS is shown in Table 4. On the basis of staging results with EUS and CT scan, resectability was deemed possible for 99 (90.8%) of the 109 patients, with radical gastrectomy, extended resection, and endoscopic mucosal resection proposed, respectively, for 95, 1, and 3 of these 99 patients. Four patients were deemed inoperable. Two had ascites detected by EUS but not by CT scan. Because the ascites was positive for malignant cell on EUS-FNA, these two patients were considered to have carcinomatosis peritonei and did not undergo surgery. As for the remaining two patients whose EUS showed T4 lesions in addition to extensive nodes, the one underwent radical gastrectomy and the other had extended surgery because operative findings showed resectable tumor and tumor involving left lobe of liver resected en bloc, respectively.

Eventually, 95 (96%) of the 99 patients underwent the following gastric cancer resection procedures with curative intent: radical gastrectomy in 88, extended resection in 4, and endoscopic mucosal resection in all 3 patients for whom this procedure was proposed. Eight of the patients for whom radical gastrectomy was proposed did not undergo this procedure because of unsuspected liver metastasis ($n = 3$), involvement of D3 nodes ($n = 2$), and insolvency of the hepatoduodenal ligament ($n = 2$) and pancreas ($n = 1$). These patients underwent open and close laparotomy ($n = 3$), bypass surgery ($n = 2$), and palliative gastrectomy ($n = 3$) instead. Thus, preoperative staging accurately predicted the operative strategy for 89% of the patients.

Discussion

The use of EUS was first described in 1980, although only in recent years of technologic advances has EUS become an established diagnostic tool for the staging of

gastric carcinoma [5]. As compared with CT scan, findings have consistently shown that EUS is better for locoregional staging of gastric carcinoma [2]. Using an MHz frequency of 7.5 to 12, the wall of the stomach can be seen as five layers of alternating hyperechoic and hypoechoic bands, which correspond from the inside out to the superficial mucosa, muscularis mucosa, submucosa, muscularis propria, and serosa. Carcinoma is identified by disruption, thickening, and irregularity of the layers involved. Our results confirmed the high accuracy of EUS for preoperative staging described by other authors [11].

The early T stages (T1 and T2) show a relatively higher rate of overstaging. This phenomenon probably is attributable to peritumoral inflammation. Endoscopic ultrasound has been regarded as the most sensitive procedure for determining the pretherapeutic staging for endoscopic mucosal resection where invasion to submucosa has to be excluded. Endoscopic resection is appropriate for patients with intramucosal gastric cancer lesions smaller than 2 cm in diameter that show neither an undifferentiated histology nor a peptic ulceration [8]. Three patients in our series were deemed suitable for endoscopic mucosal resection because they were staged as T1m after EUS. All three patients who underwent endoscopic mucosal resection had T1 cancers, with clear margins on histology. The staging of local tumor invasion can be hampered by impassable stenoses (i.e., near the cardia and pylorus). In this series, 11 patients had impassable tumor and were excluded from the analysis because T and N status could not be reliably assigned. In most cases, impassability was attributable to advanced tumor (pT3, pT4), and this feature had previously been regarded as a bad prognostic factor [9]. Other problems with EUS used to stage gastric neoplasm are distensibility of stomach as well as inadequate probe positioning and accessibility because of the tumor location [7, 10]. We excluded patients with these confounding factors to eliminate bias in the interpretation of the results. In addition, we analyzed the influence of possible confounding variables such as the location of the tumor, the learning curve, and operator dependency using logistic regression.

The endosonographic diagnosis of nodal metastases is limited by the penetration depth of EUS. The paraaortic region often is beyond the scanning range of EUS. Consequently, lymph node metastases at this location cannot be reliably detected. Lymph nodes with a round shape, a clear margin, and a hypoecho pattern similar to that of the primary tumor are more likely to be malignant [13, 18]. For detecting nodal metastasis, our study showed an accuracy of 77.7%, a sensitivity of 82.8% and a specificity of 74.2%. The sensitivity of the criteria for internal echo structure and margins is counterbalanced by a low specificity [1, 16]. The sensitivity of nodal metastasis in the current study was comparable with that in most studies. A higher specificity was attributable to meticulous assessment of nodal characteristics because specificity increases with the presence of more criteria for malignant nodes [3].

Our data confirm that EUS is the most accurate and reliable method for the preoperative staging of gastric

Table 4. Proposed decisions after endoscopic ultrasound (EUS) and actual treatment outcomes for gastric cancer

		Proposed treatment						Total
		Inoperable	Bypass	Palliative gastrectomy	Radical gastrectomy	Extended resection	EMR	
Actual treatment rendered	Inoperable	2			3			5
	Bypass				2			2
	Palliative gastrectomy			4	3			7
	Radical gastrectomy	1			87			88
	Extended resection	1	1	1		1		4
	EMR						3	3
Total		4	1	5	95	1	3	109

EMR, endoscopic mucosal resection

carcinoma. Endoscopic mucosal resection was proposed for three patients and successfully performed. Hence, EUS is most reliable for selecting such patients. Two patients showed ascites on EUS that yielded positive results for malignant cells on EUS-guided FNA, thus obviating an unnecessary surgical exploration. Others also have noted this unique advantage of EUS-FNA [4]. Overall, 89% (97/109) of the patients underwent the proposed treatment on the basis of EUS, and 92% (87/95) of the patients underwent the proposed radical gastrectomy. Only five patients explored for resection were found to have inoperable disease.

Patients with locally advanced gastric cancer in whom complete tumor resection is deemed impossible constitute the most common population for neoadjuvant treatment trials [15]. Although EUS is useful for selecting potentially eligible patients for such trials, the decision may not be based on its findings alone because the accuracy of EUS is only 72.7% for stage T4 disease. By the same token, the decision not to operate, as in current practice, should not be based on results from EUS alone unless there is cytologic evidence of carcinomatous peritonei. Under such circumstances, video-laparoscopy may enhance staging accuracy, particularly in the detection of unsuspected metastatic disease. In previous reports, findings have shown that preoperative laparoscopy is a powerful diagnostic tool for avoiding "open and close" operations [6, 14].

It may be argued that because EUS did not significantly affect the decision-making process on exploration in most instances, it might not be necessary as a part of the diagnostic workup for gastric cancer. We agree that EUS is not necessary if obvious metastasis is demonstrated on CT scan, or if an exploration is indicated on the basis of symptoms such as gastric outlet obstruction and bleeding. However, EUS may be a helpful adjunct, at least for T staging, if a stage-based therapeutic approach is adopted. Distinguishing mucosal and submucosal spread is mandatory before endoscopic mucosal resection. It may be an integral part of the workup before neoadjuvant chemotherapy should such therapy become the standard practice in the future. Endoscopic ultrasound is a valuable diagnostic tool for the preoperative staging of gastric carcinoma, predicting precisely the type of surgery for 89% of patients.

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