

# Endoscopic ultrasonography in preoperative staging of gastric cancer: determination of tumor invasion depth, nodal involvement and surgical resectability

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**Received:** 2002-04-18 **Accepted:** 2002-08-23

## Abstract

**AIM:** Current study was aimed to evaluate the usefulness of EUS in TNM staging of gastric cancer by comparing EUS preoperative staging with pathological findings, and the preliminary exploration of possible reasons for overstaging and understaging phenomenon was especially intended.

**METHODS:** A total of 35 patients with histologically confirmed gastric adenocarcinoma were referred to EUS and staged preoperatively by using the TNM system. The preoperative endosonographic results were compared with the histopathological staging.

**RESULTS:** The overall accuracy of EUS for determination of the T stage was 80.0 %, and for T1, T2, T3, and T4 was 100 %, 71.4 %, 87.5 % and 72.7 %, respectively. For N stage, EUS had the accuracy of 68.6 %, with sensitivity and specificity of 66.7 % and 73.7 %, respectively. Resectability was predicted with sensitivity and specificity of 87.5 % and 100 %, respectively.

**CONCLUSION:** EUS is an accurate staging modality in most cases, with a few exceptions of overstaging and understaging. Patients with gastric cancers can benefit from preoperative EUS staging for establishing individualized therapy. However, EUS criteria to differentiate benign from malignant nodes still need to be further defined by future studies.

Xi WD, Zhao C, Ren GS. Endoscopic ultrasonography in preoperative staging of gastric cancer: determination of tumor invasion depth, nodal involvement and surgical resectability. *World J Gastroenterol* 2003; 9(2): 254-257  
<http://www.wjgnet.com/1007-9327/9/254.htm>

## INTRODUCTION

Gastric cancer is one of the most encountered gastrointestinal malignancies. The overall 5-year survival rates are still not encouraging, although many advances in diagnostic modalities and therapeutic regimens have been achieved during last a few decades. The improvement of survival rates depends primarily on early detection and treatment of the tumor. Many large-scale clinical trials indicate that the majority of patients are in

advanced stage at time of diagnosis and the outcome is dismal. It has been well accepted that accurate preoperative staging is not only important for prediction of the prognosis, but also essential to establishment of individualized cancer therapy<sup>[1]</sup>. The staging was previously made by analysis on the bases of clinical presentations, laboratory test results, and various imaging findings such as trans-abdominal B-mode Ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI). However, precise conclusion was often difficult to obtain due largely to limitations on or local unavailability of these techniques themselves<sup>[2,3]</sup>.

Endoscopic ultrasonography (EUS) was first introduced by a German doctor in the early 1980s and is now used worldwide. Without interference by abdominal fat, bones and gut gases, the probe can be placed in where is nearest to the target organ or tissue of interest and the more accurate imaging can be obtained. Because of the use of transducers of high frequency, it facilitates the early detection of minute lesions and the TNM staging of tumors<sup>[4,5]</sup>. The ability of EUS to accurately visualize and differentiate the different layers of the gut wall makes it possible to determine the penetration depth of a gastrointestinal cancer more precisely. Simultaneously, the observation of the involvement of lymph nodes and other organs adjacent to the cancer within the range of EUS scanning can provide more detailed additional information to the disease. Currently, EUS is becoming one of the routine methods in staging of gastrointestinal cancers, including gastric carcinoma<sup>[6-8]</sup>. Published data showed that the accuracy of T and N staging for gastric cancer is 78-92 % and 63-78 %, respectively<sup>[9,10]</sup>, being imperative in prognostic prediction and especially in decision-making regarding to individualized therapeutic regimens<sup>[11,12]</sup>.

It has been noticed that overstaging and understaging are the common problems encountered in current EUS practice, and accuracy for lymph node staging exhibits discrepancy between observers<sup>[9,13]</sup>. Current study was aimed to evaluate the usefulness of EUS in TNM staging of gastric cancer by comparing EUS preoperative staging results with pathological findings, and the preliminary exploration of possible reasons for above-mentioned phenomenon was especially intended.

## MATERIALS AND METHODS

### Patients

Thirty-five patients with gastric cancer proven pathologically underwent EUS preoperative T and N staging, including 25 male, 10 female, aged 28-78 years with average of 61.7. Of them, 32 were treated surgically (two were found unresectable due to adjacent organ involvement). The diagnosis was reconfirmed and pathological TN staging made. Three cases were diagnosed T4N1M1 based on EUS, B ultrasound, and CT scanning findings and treated unsurgically. Therefore, 32 patients were finally enrolled in this study.

### EUS examination procedures

A Pentax 3840T double-channeled video-gastroscope was

employed and Fujinon SP-701 radial scanning probes (with frequency of 7.5MHz, 12MHz, and 20MHz) introduced via one of the working channels. EUS preoperative staging for gastric cancer followed the TNM staging as of the Union Internationale Contre le Cancer (UICC)<sup>[10]</sup>. Early cancer is clinically defined as the tumor confined to mucosa or submucosa regardless of lymph node metastasis<sup>[14]</sup>. The extension of the cancer into muscularis propria is classified as the advanced. The judgment of local tumor invasion depth by EUS is according to the determination of the outmost involved layer of the gastric wall<sup>[15]</sup>. Regional lymph node staging is classified as N0 (no lymph node involvement found) and N+ (perigastric lymph node metastasis confirmed). M refers to distant metastasis, defined as M0 and M1 (with or without distant metastasis).

## RESULTS

### EUS staging

EUS preoperative staging results were listed in Table 1.

**Table 1** Accuracy of EUS preoperative T staging in 35 patients with gastric carcinoma

EUS stage	n	Pathologicstage				Accuracy of EUS (%)
		T1	T2	T3	T4	
T1	1	1	0	0	0	100
T2	7	1	5	1	0	71.4
T3	16	0	2	14	0	87.5
T4	8(3)	0	0	3	5(3)	72.7
Total	32(3)	2	7	18	5(3)	80.0

### Surgical findings

Among 32 cases of the current study, cancer located in gastric atrium was found in 18 patients, gastric corpus in 9 and fundus in 5. Radical gastrectomy was performed in 15, total gastrectomy in 13, and palliative surgery in 2. Unresectable tumors were found in 2 patients. The sensitivity and specificity of EUS for predicting resectability were 87.5 % and 100 % respectively.

### The comparison between EUS and pathologic T staging

By compared to the postoperative pathology, the overall accuracy of EUS T staging was 80.0 % (Table 1). Much attention should be paid to overstaging and understaging found in T2, T3, and T4. The assessment of tumor invasion in postoperative pathology was mostly consistent with preoperative EUS findings, except seven cases including 4 ulcerated type, 2 protruded type, and 1 flat type. Pathologically, the understaged one was due to micro-tumor invasion undetectable by EUS. The overstaged six cases were owing to local inflammatory reaction, edema, and fibrosis undifferentiable by EUS.

### The comparison between EUS and pathologic N staging

The accuracy, sensitivity and specificity of EUS for N staging (Table 2) were 68.6 %, 66.7 %, and 73.3 %, respectively. However, 11 patients had inconsistent pathologic findings compared with EUS. Although four of them were diagnosed N+ by EUS during operation, the pathology confirmed inflammatory lymphadenopathy with no evidence of tumor metastasis. Lymph nodes susceptible of metastasis were not detected in 2 cases both by EUS during operation but confirmed

later pathologically. EUS-undetected lymph nodes in 3 cases were also diagnosed during operation and by postoperative pathology.

**Table 2** Accuracy of EUS preoperative N staging in 35 patients with gastric carcinoma

EUS stage	n	Pathologic stage		Accuracy of EUS(%)
		N0	N+	
N0	20	14	6	70.0
N+	12(3)	5	7(3)	66.7
Total	32(3)	19	13(3)	68.6

(NOTES: three cases of T4N+ not surgically treated were included as being the correctly diagnosed).

## DISCUSSION

Clinical experience with EUS used as an important preoperative staging tool for gastric cancer has been widely reported. On EUS imaging, early gastric cancer is visualized as hypo-echo masses invading the first, second, and third layers of the stomach, resulting in disruption, thickening, and irregularity of the layers involved. The fourth and fifth layers are often intact. Gastric cancer in advanced stage is usually accompanied by disruption of submucosa and muscularis propria, disappearance and replacement of the normal structures by hypo-echo mass as result of tumor invasion<sup>[16-18]</sup>. Willis *et al*<sup>[19]</sup> reported that overall accuracy of EUS for T, T1, T2, T3, and T4 staging was 78 %, 80 %, 63 %, 95 %, and 83 %, respectively. Regional lymph node staging was correctly conducted in 77 % of all 116 patients. Our results were similar to Willis' s, with 80.0 % and 68.6 % for T and N staging, respectively. Together with reports elsewhere, it is accepted that EUS is an accurate staging modality in most cases, with a few exceptions of overstaging and understaging. In our study, seven incorrectly staged patients consisted of ulcerated type in 4 cases, protruded type in 2, and flat type in 1. By careful examination and analysis, we found pathologically that reasons contributing to overstaging can be misinterpretation of necrotic tissue overlaying the ulcer surface, scars and fibrosis, inflammatory reaction in the peripheral structure of cancer, thickened gastric wall or ball-balloon alteration. Microscopic cancer invasion or focal destruction of a certain layer undetectable with lower-frequency ultrasound often results in understaging. In general, staging for elevated type may be more readily than that for ulcerated one, being with higher accuracy. To achieve the best visualization of the cancer and improve the diagnostic accuracy, high frequency probes (20MHz) may be more suitable for early cancer, while low frequency transducers (7.5 or 12MHz) for advanced ones<sup>[20,21]</sup>.

Lightdale<sup>[22]</sup> and Zuccaro *et al*<sup>[10]</sup> pointed out those lymph nodes of round shape, clear margin, and hypo-echo pattern similar to that of the primary tumor were more likely to be malignant. Heintz *et al*<sup>[23]</sup> reported that the sensitivity and specificity could be 85 % and 45-85 % respectively if the followings were taken as the diagnostic criteria for malignant nodes: larger than 10 mm in diameter, heterogeneous echo pattern, and sharp border. EUS accuracy for N staging in this study was 68.6 %. Inaccuracy may be as the result of lack of reliable differential standard for benign and malignant nodes. The diameter, location, and the distance of lymph node to the primary lesion, and the endoscopists' expertise are important as well. Other factors affecting the accuracy may also include the frequency and penetration depth of the transducers used,

and intra-gastric substance. We recommend that based on our experience, visualization of lymph nodes by EUS should start with the site of primary tumor followed by gradual detection of each perigastric lymph node group. The differentiation of lymph nodes from other perigastric structures such as vessels on EUS imaging can be made by moving the probe forward and backward or using linear EUS equipped with color Doppler. Since many factors may influence the detection of nodes, negative EUS does not reliably indicate the absolute absence of nodal involvement and further assessment should be carried out to obtain definite diagnosis. EUS-guided fine needle aspiration (EUS-FNA) is now clinically available and has been accepted as the most reliable cytology for differentiation in this situation<sup>[24,25]</sup>.

The accurate preoperative staging for gastric cancer is very important in predicting prognosis and in determining individualized therapeutic regimens<sup>[26-28]</sup>. Since EUS has its own limitations on accuracy of M staging, it must be emphasized here that precise staging results and proper management decision-making should rely on clinical presentations, laboratory tests and various imaging technologies. Nevertheless, EUS is undoubtedly superior to B ultrasound, CT, and conventional endoscopy in the assessment of primary tumor invasion depth and regional lymph node status<sup>[4]</sup>. The therapeutic goals for gastric cancer should be set to maximally prolong the survival time, significantly improve the patient's quality of life, avoid any unnecessary procedure and any operation with no proven benefit, and also, reduce the economic burden on the patient. To achieve those, optimal therapy must be carefully individualized to meet the need of each patient based on precise TNM staging. Because early cancers confined to mucosa can be effectively managed by endoscopic resection and thus laparotomic surgery and its related complications can be avoided<sup>[29-32]</sup>, these lesions must be recognized clinically prior to the treatment decision-making. The very limited penetration depth of early tumors can be clearly displayed and reliably determined on EUS scanning especially when high-frequency probes are used, as reported by our team<sup>[17]</sup>. Although surgery is still recommended as the first line therapy for T1-T3N1M0 cancer<sup>[33]</sup>, Rohde *et al*<sup>[10]</sup> found that 30 % of 1 420 gastric cancer patients undergoing surgery eventually had no curative results because of tumor invasion. For patients with T4 cancers, further investigation should be performed to determine whether there is any hope of surgical cure<sup>[34,35]</sup>. Patients with cancer invading into adjacent organs such as the pancreas proven by EUS should not undergo radical management. For them, palliative surgery can be a treatment choice if digestive tract obstruction is present, and radiotherapy or chemotherapy may be instituted when indicated. Treatment plans for three patients initially considered as surgical candidates in this study were eventually amended because of the preoperative staging of T4N1M1. In these patients, the pancreas invasion, large vessel involvement and liver metastases were the major indicators against curative surgery, which were demonstrated clearly by EUS imaging (for pancreas and vessel involvement) and CT scanning (for liver metastases).

In summary, EUS is a useful study for accurate staging of gastric carcinoma. Its unique advantages make EUS become one of the reliable methods in guiding prediction of the prognosis and establishment of cancer therapy regimens, although not likely to replace other imaging modalities used to stage these patients. Further large-scale clinical trails and carefully planned investigations should be conducted to clarify those questions about the ability of EUS to differentiate tumor infiltration from fibrosis or inflammatory tissues, to detect microscopic invasions, and to discriminate the benign from malignant nodes.

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Edited by Zhang JZ