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Accuracy of endoscopic ultrasound staging of gastric cancer in routine clinical practice in Singapore

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OBJECTIVE: Endoscopic ultrasound has emerged as the leading modality to assess the T and N stage in gastric cancer. This study aimed to assess the accuracy of TN staging by endoscopic ultrasound in routine clinical practice in Singapore.

METHODS: Over a period of 7 years, 77 patients (male: 70%; median age 62.8 years) with gastric cancer underwent preoperative staging with endoscopic ultrasound. Fifty-seven patients eventually underwent surgery with tissues available for histopathological staging and comparison.

RESULTS: The tumor locations were: cardia: 13; corpus: 20; incisura: 19; antrum: 25. The majority was poorly differentiated (57.1%); 26% were moderately differentiated and 16.9% were well differentiated adenocarcinoma. Compared to pathological staging, the overall accuracy of T staging by endoscopic ultrasound was 77.2% (17.5% under-staged: 5.3% over-staged). The staging accuracy of T1 (92.9%) and T3 (81.8%) was higher than T2 (57.1%) and T4. For N staging, the accuracy of endoscopic ultrasound was 59.6% (26.3% under-staged; 14% over-staged); this was significantly superior to computer tomography (43.9%).

CONCLUSION: Endoscopic ultrasound is useful for the T staging of gastric cancer, with an overall accuracy rate of 77%, and up to 93% for T1 lesions. Under-staging may occur due to microscopic tumor infiltration, while over-staging may arise due to inflammatory reactions. The accuracy of N staging is lower at 60%, but could be further improved with the use of fine needle aspiration.

KEY WORDS: endoscopic ultrasound, gastric cancer staging.

INTRODUCTION

Endoscopic ultrasound (EUS) was introduced into clinical practice in the early 1980s. EUS has become the investigation of choice for loco-regional staging of gastrointestinal cancer.[1] In the context of gastric cancer, it is considered the most important diagnostic test after esophagogastroduodenoscopy (OGD).[2] Its ability to identify the individual layers of the gastric wall, as well as the presence of enlarged regional lymph nodes, provides the basis for cancer staging according to the TNM classification.[3] In addition, the presence of ascites detected by EUS is an important predictor for peritoneal metastases.[4,5] EUS is thus vital for planning the appropriate treatment strategy, such as neoadjuvant chemotherapy for advanced gastric cancer or mucosal resection for early gastric cancer.

There have been several western and Japanese series on the accuracy of EUS in the loco-regional staging of gastric cancer. A recent systematic review of published western and Japanese data confirmed that EUS was highly effective for discrimination of stages T1 and T2 from stages T3 and T4 in the context of gastric cancer.[6] Similar results were obtained from recent Chinese

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studies as well.[7,8] However, there are limited published data from other parts of Asia.[9,10]

In this study, we evaluated the T and N staging of gastric cancer using EUS when compared to the gold standard of histopathological staging. As a secondary endpoint, we compared the performance of N staging between EUS and computer tomography (CT). This study adds to the current literature on the loco-regional staging of gastric cancer using EUS by providing additional Asian, non-Japanese data and also provides a perspective on its applicability and accuracy in the context of routine clinical practice.

PATIENTS AND METHODS

Patients

The data of patients who were referred to the Gastroenterology Division, Changi General Hospital, Singapore, for preoperative staging of gastric cancer using EUS were collected prospectively over a 7-year period (1995–2001). All patients had undergone prior OGD with histological evidence of primary gastric cancer based on biopsy specimens.

Endoscopic ultrasound

Patients were sedated using intravenous midazolam and fentanyl. A radial echoendoscope (GF UM20, Olympus Optical Co Ltd, Tokyo, Japan) with frequencies of 7.5 and 12 MHz was used. The mucosal layers were visualized using a 12 MHz frequency, while perigastric lymph nodes were visualized using a 7.5 MHz frequency. The echoendoscope was advanced into the stomach, and the lesion was located. Next, the balloon at the tip of the echoendoscope was filled with deaerated water. About 200 mL of deaerated water was also instilled through the accessory channel into the stomach. The depth of mucosal involvement of the tumor was then assessed, and this was followed by a further inspection of the gastric mucosa, as well as a search for perigastric lymph nodes, by withdrawing the tip of the echoendoscope from the pylorus to the cardia. The entire procedure took about 10–20 min and there were no procedural complications. Staging was based on the 5th edition of the TNM classification.[11] For the purpose of N staging, a lymph node size of greater than 1 cm was taken to be significant.[12]

Computed tomography

Computed tomography of the abdomen was performed by contrast enhanced single slice CT using 7-mm cuts. Lymph node metastases were defined as enlarged lymph nodes of more than 8 mm in diameter.[13]

Statistical evaluation and ethical considerations

Statistical analysis of the patients' data and clinical parameters were expressed as mean and median values and ranges. The findings of the T and N staging by EUS, and the N staging by CT, were compared with the results of postoperative histopathological staging. A P value of < 0.05 was taken as statistically significant. All patients provided their informed consent for the procedure. Formal Institutional Review Board approval was not required for the study because it was an observational study of an established procedure.

RESULTS

Demographic and clinical data (Table 1)

During the study period, 88 patients underwent EUS staging of gastric cancer. Eleven patients had gastric lymphoma rather than gastric adenocarcinoma and were hence excluded from further analysis. The median age was 62.8 years (range 23–85) with males comprising 70%. In terms of tumor location, the majority was located at the antrum (32.5%), followed by the corpus (26%), incisura (24.7%) and cardia (16.9%). In terms of histological subtype, the majority was poorly differentiated (57.1%), followed by moderately differentiated (26%) and well differentiated (16.9%) adenocarcinoma. Twenty patients did not undergo surgical resection, leaving 57 patients with histopathological staging for comparison with EUS.

T staging of gastric cancer (Table 2)

EUS revealed 21 cases (27.3%) of T1 (Fig. 1), eight cases (10.4%) of T2 (Fig. 2), 46 cases (59.7%) of T3 (Fig. 3), and two cases of T4 lesions (2.6%). Histopathology showed 14 cases of T1 (24.6%), seven cases of T2 (12.3%), 33 cases of T3 (57.9%) and three cases of

Table 1. Demographic and clinical data

Clinical characteristics	Number
Age	62.8 years (23–85[†])
Gender (male:female)	54:23
Tumor location:	
Cardia	13
Corpus	20
Incisura	19
Antrum	25
Histological grade:	
Well differentiated	13
Moderately differentiated	20
Poorly differentiated	44

[†]Median age and age range in brackets.

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Table 2. Correlation of endoscopic ultrasound and histopathological T staging of gastric cancer

Endoscopic ultrasound T staging	T staging based on histopathology (n = 57) T1	T2	T3	T4
T1	13	1	4	0
T2	1	4	2	1
T3	0	2	27	2

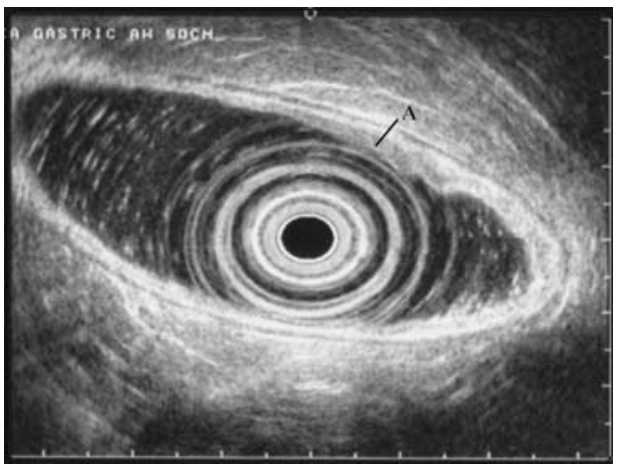

Figure 1. Endoscopic ultrasound appearance of T1 gastric cancer. There was thickening of the mucosal layer (A), with the submucosal layer (B) and the muscularis propria (C) remaining intact.

T4 (5.3%) lesions. Using histopathology as the gold standard, EUS correctly staged 92.9% of T1 lesions, 57.1% of T2 lesions and 81.8% of T3 lesions. The two cases of T4 lesions staged by EUS could not be compared against histopathology because they did not undergo surgery. Among the three cases of T4 lesions staged by histopathology, one case was under-staged by EUS as T2 and two cases as T3. Among the T1 lesions, 7.1% were over-staged as T2 by EUS. Among T2 lesions, 28.6% were over-staged by EUS as T3, while 14.3% were under-staged as T1. Among T3 lesions, 6.1% were under staged as T2 and 12.1% as T1. EUS correctly assessed the T staging in 77.2% overall.

N staging of gastric cancer (Table 3)

EUS revealed 39 cases of N0 (50.6%), 31 cases of N1 (40.3%) and seven cases of N2 (9.1%). CT showed 45 cases of N0 (69.2%), 16 cases of N1 (24.6%) and four cases of N2 (6.2%). Histopathology showed 26 cases of N0 (45.6%), 23 cases of N1 (40.4%) and eight cases

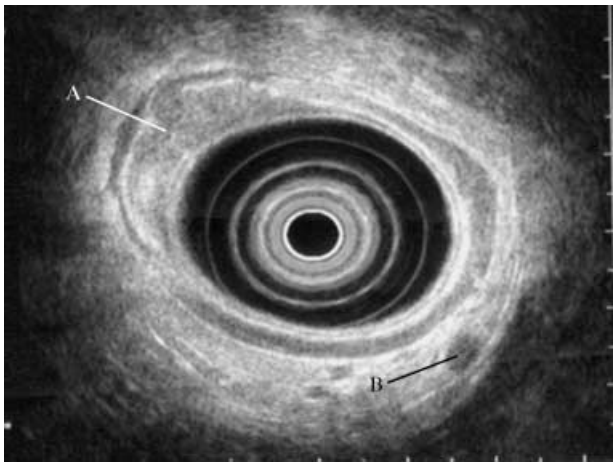

Figure 2. Endoscopic ultrasound appearance of T2 gastric cancer. Involvement of the muscularis propria was present (A) and there was a round hypoechoic lymph node suspicious for malignancy (B).

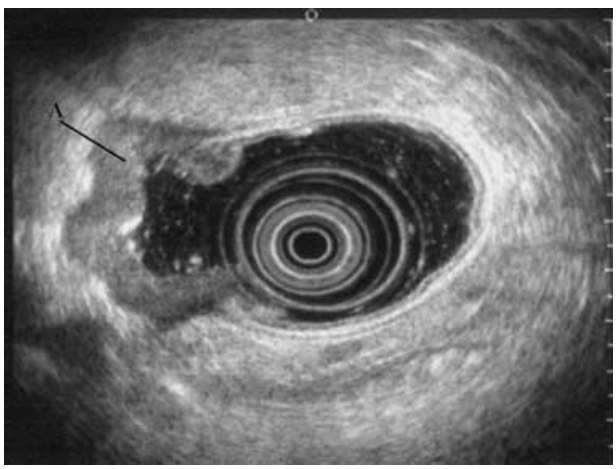

Figure 3. Endoscopic ultrasound appearance of T3 gastric cancer, in which the tumor had gone beyond the muscularis propria (A).

Table 3. Correlation of Endoscopic ultrasound and histopathological N staging of gastric cancer

Endoscopic ultrasound N staging	N staging based on histopathology (n = 57) N0	N1	N2
N0	20	10	2
N1	6	11	3
N2	0	2	3

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Table 4. Endoscopic ultrasound staging of gastric cancer based on selected published data

Author and year	N	Accuracy T staging (%)	Accuracy N staging (%)
Asian studies			
Guo (1997)[15]	62	83.9	79
Xi (2003)[7]	32	80	68.6
Tsendsuren (2006)[8]	41	68.3	66
Akahoshi (1991)[16]	74	81.1	50
Yanai (1997)[17]	104	64.8 (early gastric cancer)	NA
Yanai (1999)[18]	52	71 (early gastric cancer)	NA
Hizawa (2002)[19]	234	78 (early gastric cancer)	NA
Shimoyama (2004)[20]	45	71	80
Bhandari (2004)[10]	63	87.5	79.1
Western studies			
Tio (1989)[21]	72	84.7	50–81
Botet (1991)[22]	50	92	78
Lightdale (1992)[23]	525	81	76
Ziegler (1993)[24]	108	86	74
Dittler (1993)[2]	264	83	66
Francois (1996)[25]	35	79	79
Hunerbein (1998)[26]	30	82	80
Meining (2002)[27]	33	66	NA
Habermann (2004)[28]	51	86	90

of N2 (14.0%). Using histopathology as the gold standard, EUS correctly staged 76.9% of N0 lesions, 47.8% of N1 lesions and 37.5% of N2 lesions, while for CT the results were 82.6% for N0, 15% for N1 and 37.5% for N2. Among the N0 lesions, EUS over-staged 23.1% as N1; among N1 cases, EUS under-staged 43.5% as N0 and over-staged 8.7% as N2; among N2 cases, EUS under-staged 25% as N0 and 37.5% as N1. Overall, the accuracy of EUS for N staging was 59.6%, while the accuracy of CT for N staging was 43.9%; EUS was significantly better than CT in N staging ($P = 0.032$).

DISCUSSION

Gastric cancer is an important cancer in Singapore. It is the third most common malignancy, comprising 10.1 percent of all cancers. Among the three ethnic groups in Singapore, the highest incidence occurs in the Chinese, the predominant ethnic group, with the relative risks for Indians and female Malays being about half, and that of Malay males 25 percent compared to their Chinese counterparts.[14] Recognizing that the accurate staging of gastric cancer is the cornerstone for informed decision making on stage dependent management and prognosis assessment, we evaluated the utility of preoperative gastric cancer staging using EUS in the context of routine clinical practice in Singapore.

In this study, we evaluated a series of 77 patients with gastric cancer referred to our department over a 7-year period for EUS staging. Overall, the accuracy of T staging was 77.2% while that of N staging was 59.6%. These results are comparable to the results of other published series[7,8,10,15–28] (Table 4). It is recognized that the accuracy of EUS in T staging is superior to that in N staging. The poorer result with N staging may be due to a larger area in the stomach to scan for lymph nodes and the fact that lymph nodes lying beyond 3 cm are not well visualized. Consistent with other published studies,[22,24] the nodal staging by EUS was significantly superior to CT (59.6% vs. 43.9%, $P < 0.05$).

When we sub-analyzed the performance of EUS in gastric cancer staging on the basis of specific T and N stages, the accuracy of EUS was higher for T1 and T3 lesions (92.9% and 81.8%, respectively) when compared to T2 and T4 lesions. This could have been due to the small number of patients with T2 and T4 lesions in our series. With regards to N staging, the accuracy was higher for N0 when compared to N1 and N2 lesions (76.9% compared to 47.8% and 37.5%, respectively). The outcome of EUS staging reported by other authors when the T and N staging were sub-analyzed was as follow: T1: 71.4–100%; T2: 62.6–88.9%; T3: 62.2–83.3%; T4: 63.6–94.1%; N0: 46.7–88%; N1: 50–85.7%; N2: 57–87.5%.[21,22,24,29,30] In our series, the accuracy in staging T1 and T3 lesions, as well as N0 lesions, were similar to published data.

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Underestimation of depth of invasion may occur in the presence of microscopic or focal invasion of deeper layers not detected by EUS or when the serosal ultrasound layer is not well visualized. Other factors affecting T staging include difficulty in assessing the involvement of adjacent air-containing hollow organs such as the colon, which contains air that interferes with the ultrasound transmission of local organ invasion for T4 lesion. The depth of invasion may be overestimated if there is an ulcer scar or inflammatory reaction below the cancer. With regards to nodal staging, over-staging may occur in the context of hyperplastic benign lymph nodes, while false negative results may occur in the context of microscopic metastases in normal-sized nodes. EUS-guided fine needle aspiration may have a role in distinguishing benign from malignant lymph nodes.

In conclusion, this study confirms the efficacy of EUS in routine clinical practice in a regional general hospital, with results that are comparable to other published series. We used the older generation radial scanner (GF UM20, Olympus Optical Co Ltd, Japan) in our study. With the availability of newer models of echoendoscopes, such as the GF UM160 with 4 frequencies, and the electronic radial echoendoscope GF-UE160-AL5 (Olympus Optical Co Ltd, Japan), the accuracy rate should improve. Nonetheless, there are limitations of the EUS. Its use complements that of the CT scan, and the addition of fine needle aspiration of lymph nodes will improve the accuracy of N staging.

REFERENCES

1 Byrne MF, Jowell PS. Gastrointestinal imaging: endoscopic ultrasound. *Gastroenterology* 2002; **122**: 1631–48.
2 Dittler HJ, Siewert JR. Role of endoscopic ultrasonography in gastric cancer. *Endoscopy* 1993; **25**: 162–6.
3 Takemoto T, Yanai H, Tada M *et al.* Application of ultrasonic probes prior to endoscopic resection of early gastric cancer. *Endoscopy* 1992; **24** (Suppl. 1): 329–33.
4 Lee YT, Ng EK, Hung LC *et al.* Accuracy of endoscopic ultrasonography in diagnosing ascites and predicting peritoneal metastases in gastric cancer patients. *Gut* 2005; **54**: 1541–5.
5 Chu KM, Kwok KF, Law S, Wong KH. A prospective evaluation of catheter probe EUS for the detection of ascites in patients with gastric carcinoma. *Gastrointest Endosc* 2004; **59**: 471–4.
6 Kelly S, Harris KM, Berry E *et al.* A systemic review of the staging performance of endoscopic ultrasound in gastroesophageal carcinoma. *Gut* 2001; **49**: 534–9.
7 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**: 254–7.
8 Tsendsuren T, Jun SM, Mian XH. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. *World J Gastroenterol* 2006; **12**: 43–7.
9 Ganpathi IS, So JB, Ho KY. Endoscopic ultrasonography for gastric cancer: does it influence treatment? *Surg Endosc* 2006; **20**: 559–62.
10 Bhandari S, Shim CS, Kim JH *et al.* Usefulness of three-dimensional, multidetector row CT (virtual gastroscopy and multiplanar reconstruction) in the evaluation of gastric cancer: a comparison with conventional endoscopy, EUS, and histopathology. *Gastrointest Endosc* 2004; **59**: 619–26.
11 Gress FG, Bhattacharya I, eds. *Endoscopic Ultrasonography*. Boston: Blackwell Science, 2001.
12 Catalano MF, Sivak MV Jr, Rice T. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc* 1994; **40**: 442–6.
13 Dehn TCB, Reznek RH, Nockler IB, White FE. The preoperative assessment of advanced gastric cancer by computed tomography. *Br J Surg* 1984; **71**: 413–7.
14 Ang TL, Fock KM, Dhamodaran S, Teo EK, Tan J. Racial differences in *Helicobacter pylori*, serum pepsinogen and gastric cancer incidence in an urban Asian population. *J Gastroenterol Hepatol* 2005; **20**: 1603–9.
15 Guo W, Zhang YL, Li GX, Zhou DY, Zhang WD. Comparison of preoperative staging of gastric carcinoma by endoscopic ultrasonography with CT examination. *China Natl J New Gastroenterol* 1997; **3**: 242–5.
16 Akahoshi K, Misawa T, Fujishima H *et al.* Pre-operative evaluation of gastric cancer by endoscopic ultrasound. *Gut* 1991; **32**: 479–82.
17 Yanai H, Matsumoto Y, Harada T *et al.* Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest Endosc* 1997; **46**: 212–6.
18 Yanai H, Noguchi T, Mizumachi S *et al.* A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. *Gut* 1999; **44**: 361–5.
19 Hizawa K, Iwai K, Esaki M, Matsumoto T, Suekane H, Iida M. Is endoscopic ultrasonography indispensable on assessing in the appropriateness of endoscopic resection of gastric cancer? *Endoscopy* 2002; **34**: 973–9.
20 Shimoyama S, Yasuda H, Hashimoto M *et al.* Accuracy of linear-array EUS for preoperative staging of gastric cardia cancer. *Gastrointest Endosc* 2004; **60**: 50–5.
21 Tio TL, Coene PPLO, Schouwink MH, Tytgat GNJ. Esophagogastric carcinoma: preoperative TNM classification with endosonography. *Radiology* 1989; **173**: 411–7.
22 Botet JF, Lightdale CJ, Zauber AG *et al.* Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. *Radiology* 1991; **181**: 419–25.
23 Lightdale CJ. Endoscopic ultrasonography in the diagnosis, staging and follow-up of esophageal and gastric cancer. *Endoscopy* 1992; **24** (Suppl. 1): 297–303.
24 Ziegler K, Sanft C, Zimmer T *et al.* Comparison of computed tomography, endosonography and intraoperative assessment in TN staging of gastric cancer. *Gut* 1993; **34**: 604–10.
25 Francois E, Peroux J, Mouroux J *et al.* Preoperative endosonographic staging of cancer of the cardia. *Abdom Imaging* 1996; **21**: 483–7.
26 Hunerbein M, Ghadimi BM, Haensch W, Schlag PM. Transendoscopic ultrasound of esophageal and gastric cancer using miniaturized ultrasound catheter probes. *Gastrointest Endosc* 1998; **48**: 371–5.
27 Meining A, Dittler HJ, Wolf A *et al.* You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging. *Gut* 2002; **50**: 599–603.

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28 Habermann CR, Weiss F, Riecken R *et al.* Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. *Radiology* 2004; **230**: 465–71.
29 Rosch T, Lorenz R, Zenker K *et al.* Local staging and assessment of resectability in carcinoma of esophagus, stomach and duodenum by endoscopic ultrasonography. *Gastrointest Endosc* 1992; **38**: 460–7.
30 Grimm H, Binmoeller KF, Hamper K, Koch J, Henne-Bruns D, Soehendra N. Endosonography for preoperative locoregional staging of esophageal and gastric cancer. *Endoscopy* 1993; **25**: 224–30.

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