

# Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer

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## Abstract

**AIM:** To evaluate the value of endoscopic ultrasonography (EUS) in the preoperative TNM staging of gastric cancer.

**METHODS:** Forty-one patients with gastric cancer (12 early stage and 29 advanced stage) proved by esophagogastroduodenoscopy and biopsies preoperatively evaluated with EUS according to TNM (1997) classification of International Union Contrele Cancer (UICC). Pentax EG-3630U/Hitachi EUB-525 echo endoscope with real-time ultrasound imaging linear scanning transducers (7.5 and 5.0 MHz) and Doppler information was used in the current study. EUS staging procedures for tumor depth of invasion (T stage) were performed according to the widely accepted five-layer structure of the gastric wall. All patients underwent surgery. Diagnostic accuracy of EUS for TNM staging of gastric cancer was determined by comparing preoperative EUS with subsequent postoperative histopathologic findings.

**RESULTS:** The overall diagnostic accuracy of EUS in preoperative determination of cancer depth of invasion was 68.3% (41/28) and 83.3% (12/10), 60% (20/12), 100% (5/5), 25% (4/1) for T1, T2, T3, and T4, respectively. The rates for overstaging and understaging were 24.4% (41/10), and 7.3% (41/3), respectively. EUS tended to overstage T criteria, and main reasons for overstaging were thickening of the gastric wall due to perifocal inflammatory change, and absence of serosal layer in certain areas of the stomach. The diagnostic accuracy of metastatic lymph node involvement or N staging of EUS was 100% (17/17) for N0 and 41.7% (24/10) for N+, respectively, and 66% (41/27) overall.

Misdiagnosing of the metastatic lymph nodes was related to the difficulty of distinguishing inflammatory lymph nodes from malignant lymph nodes, which imitate similar echo features. Predominant location and distribution of tumors in the stomach were in the antrum (20 patients), and the lesser curvature (17 patients), respectively. Three cases were found as surgically unresectable (T4 N+), and included as being correctly diagnosed by EUS.

**CONCLUSION:** EUS is a useful diagnostic method for preoperative staging of gastric cancer for T and N criteria. However, EUS evaluation of malignant lymph nodes is still unsatisfactory.

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**Key words:** Endoscopic ultrasonography; Preoperative staging; Gastric cancer

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## INTRODUCTION

The incidence of gastric cancer is declining worldwide. However, it still remains the second most common cause of cancer-related death in the world<sup>[1,2]</sup>. Typically, gastric cancer is asymptomatic when cancer is at early stage of disease; therefore, majority of patients present in advanced stage, and the mortality rate of this disease is still very high. The diagnosis of gastric cancer is based on esophagogastroduodenoscopy with biopsy following double-contrast x-ray examination. Presently, endoscopic ultrasonography is the most reliable nonsurgical method obtainable for assessing the primary tumor with high diagnostic rate of staging gastric cancer and lymph node involvement. EUS is also becoming a promising diagnostic modality for the evaluation of gastrointestinal submucosal tumors and large gastric folds<sup>[3-7]</sup>.

The complete treatment of gastric cancer is surgery, only tumor resection with involved lymph nodes associated with satisfactory prognosis. Survival after surgery is highly dependent on the stage of gastric cancer or anatomical extent of disease at the time of operation. Therefore, the accurate preoperative staging of gastric cancer is the most significant prognostic factor that predicts surgical outcome

**Table 1 Relationship between EUS and anatomic layers of normal gastric wall**

EUS	Histology
1 <sup>st</sup> hypoechoic layer	Water interface and superficial mucosa
2 <sup>nd</sup> hypoechoic layer	Deeper mucosa
3 <sup>rd</sup> hyperechoic layer	Submucosa
4 <sup>th</sup> hypoechoic layer	Muscularis propria
5 <sup>th</sup> hyperechoic layer	Serosa and subserosal fat

**Table 2 Correlation of UICC/AJCC classification for depth of primary esophageal or gastric cancer invasion (T) with EUS imaging for clinical staging<sup>[9]</sup>**

Stage	EUS (abnormal)
T1-mucosa/submucosa	1 <sup>st</sup> three layers
T2-muscularis propria	4 <sup>th</sup> layer
T3-through adventitia/serosa	5 <sup>th</sup> layer
T4-adjacent organ	Adjacent organ

**Table 3 Accuracy of EUS in preoperative stage determination of 41 patients with gastric cancer**

Histopathological T stage	n	EUS correct n/%	EUS over-staging n/%	EUS under-staging n/%
PT1	12	T1 10/83.3	T2 2/16.7	-
PT2	20	T2 12/60	T3 8/40	-
PT3	5	T3 5/100	-	-
PT4	4 (3)	T4 1/25	-	T2 2 (2)/50 T3 1 (1)/25
Total	41 (3)	28/68.3	10/24.4	3 (3)/7.3

Three cases of unresectable T4 N+ tumors were correctly diagnosed.

and 5 years of survival and is essential for well-informed decisions on stage depending patient management to plan appropriate treatment. Such precise stage depending management will limit the occurrence of unnecessary exploratory surgical interventions<sup>[8]</sup>.

The aim of the present study was to evaluate the usefulness of EUS in TNM staging of stomach cancer comparing with postoperative histopathological findings.

## MATERIALS AND METHODS

### Patients

Between April 2001 and April 2004, 41 patients (29 men and 12 women; age range, 28-80 years; mean age 57 years) with gastric cancer diagnosed by EGD and confirmed with biopsy specimen, underwent EUS examination prior to surgery for tumor depth of invasion and lymph node involvement at our Department of Endoscopy. Twelve of them were in early gastric cancer stage and 29 were in advanced stage. All patients underwent surgery.

### Apparatus and EUS examination procedures

The Pentax EG-3630U/Hitachi EUB-525 echo endoscope with real-time ultrasound imaging linear scanning transducers (7.5 and 5.0 MHz) and Doppler information was used in the present study. This echo endoscope also provides the instrument channel for performing fine-needle aspiration biopsy. On the tip of the endoscope, a balloon is placed which is filled by deaerated water for improved coupling of the ultrasound waves to the gastrointestinal wall by producing a fluid interface and displacing intraluminal air. Prior to each EUS, examination was performed by EGD with biopsy to confirm gastric cancer. After oropharyngeal local anesthesia, patients were examined in a left lateral position. The echo endoscope was advanced into the stomach, and the lesions were first examined endoscopically. Next the stomach was insufflated

**Table 4 Accuracy of EUS in preoperative determination of N stage in 41 patients with gastric cancer**

Histopathological N stage	n	EUS correct n/%	EUS incorrect n/%
PN0	17	N 17/100	-
PN+	24 (3)	N+ 10 (3)/41.7	N0 14/58.3 false negative
All cases	41 (3)	27 (3)/66	14/34

with 200-500 mL deaerated water and observed from the pylorus to the cardia by moving the tip of the endoscope for revealing cancer abnormalities and lymph nodes involvement. The findings were recorded at the computer database of our department and interpreted following a standard protocol with regard to tumor invasion according to the widely accepted five-layer structure of the gastric wall (Table 1).

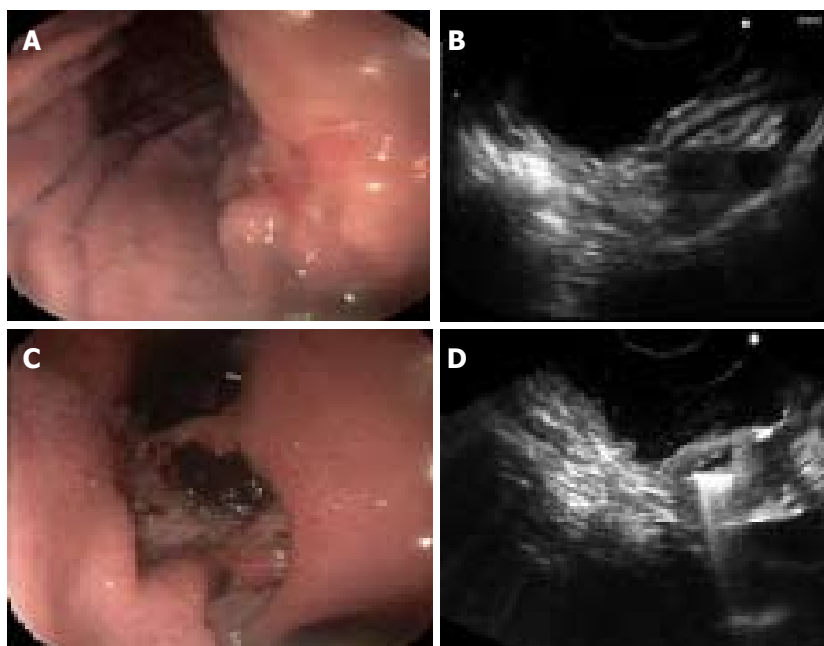
The assessment of tumor invasion depth or T stage was defined as a hypoechoic structure alternating five-layer ultrasonographic structure of gastric wall. Tumors were staged according to TNM (1997) classification criteria of International Union contrele Cancer (UICC). T1 lesion was seen as a disruption of the first three layers (tumor invades the mucosa or submucosa). T2 lesion was seen as an invasion of the fourth layer (tumor invades the muscularis propria). T3 lesion was seen as a penetration through the fifth layer (tumor invasion of the serosa). T4 lesion was seen as an invasion of the adjacent organs and structures (Table 2). T1 stage showed EUS images of early gastric cancer, T2-T4 stages showed EUS images of advanced gastric cancer. Lymph nodes had round border and hypoechoic structures were considered as malignant. Stage N0 referred to no sign of metastasis. N+ referred to metastases in perigastric lymph nodes.

## RESULTS

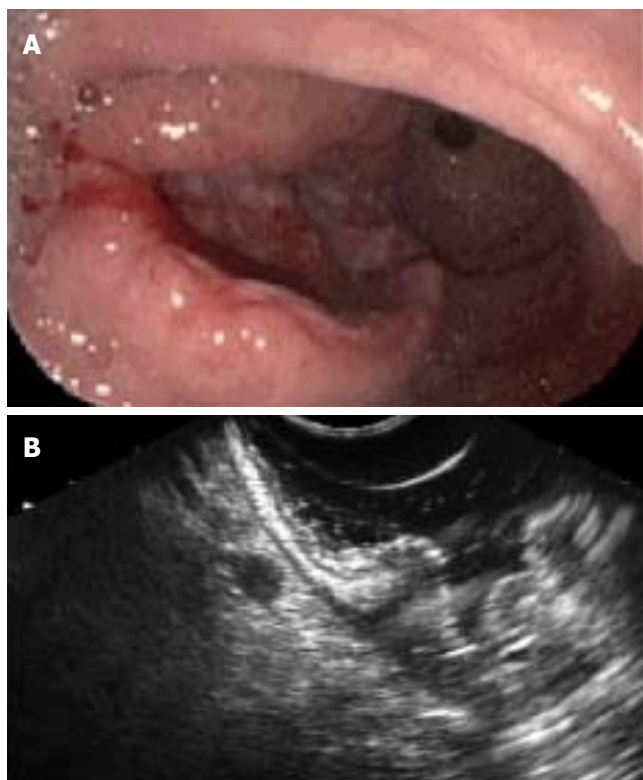
Findings of the 41 patients at preoperative EUS were postoperatively compared with histopathological findings for T and N staging.

### Surgical findings

Tumors were located in the fundus and cardia region ( $n=4$ ), in the body ( $n=11$ ), in the body and antrum ( $n=2$ ), in the antrum ( $n=20$ ) of the stomach, diffusely located ( $n=2$ ) and residual stomach ( $n=2$ ). Distribution of tumors was in the anterior wall ( $n=5$ ), posterior wall ( $n=5$ ), greater curvature ( $n=5$ ), and the lesser curvature ( $n=17$ ) of the stomach and 9 were circumferential. Three cases



**Figure 1** Early and advanced gastric cancer cases. **A:** Endoscopic view of superficial depressed type of early gastric cancer; **B:** EUS image shows cancer invasion of 1<sup>st</sup> and 2<sup>nd</sup> (mucosal) layers of gastric wall, while 3<sup>rd</sup> (submucosal) layer is clear (T1 category). Histopathological findings of the surgically resected specimen corresponded with the EUS findings; **C:** Endoscopic view of advanced Borrmann II type of gastric cancer; **D:** EUS images show disruption of 1-4 layers of the gastric wall with hypoechoic cancer tissue, but 5<sup>th</sup> (serosal) layer is not involved (T2 category).



**Figure 2** A case of advanced gastric cancer. **A:** Endoscopic view of Borrmann III type of gastric cancer; **B:** EUS image demonstrates T3 cancer with malignant lymph node. Note the hypoechoic structure and sharp margin of the lymph node (1.0 cm x 0.6 cm).

were found as surgically unresectable (T4 N+).

#### Pathohistologic findings

**T staging:** The diagnostic accuracy of EUS was 83.3% in T1 staging, 60.0% in T2 staging, 100% in T3 staging, and 25% in T4 staging, respectively. Twenty-eight of forty-one cancers were staged correctly and the overall diagnostic accuracy of T stage was 68.3%. Ten cases were overstaged

(24.4%) and 3 cases were understaged (7.3%) (Table 3). Echoendoscopic features of early and advanced gastric cancer are presented in (Figures 1A-1D).

**N staging:** EUS correctly determined 27 of 41 patients with the overall accuracy of 66.0%. The accuracy of EUS in N0 staging was high, all 17 patients without malignant lymph node metastasis were diagnosed correctly. However, EUS findings of preoperative positive metastatic lymph nodes in 10 patients were not confirmed histopathologically, and the accuracy of EUS in N+ staging was 41.7% (Table 4). The endosonographic features of advanced gastric cancer with malignant lymph nodes are shown in Figure 2.

## DISCUSSION

The accurate staging of gastric cancer is the most important prognostic factor for patient management and EUS is the most reliable method in T and N staging of gastric cancer with high diagnostic rates. Such an accurate staging will apply the stage-depending correct management of the patients (radical surgery or palliative treatment) and will provide a great benefit avoiding unnecessary laparotomy on patients with unresectable disease. EUS is considered as the most accurate modality for T staging of gastric cancer in comparison with CT and intraoperative assessment<sup>[10,11]</sup>.

The accuracy of EUS for gastric cancer from different authors ranges 64.8% - 92% in T staging and 50% - 90% in N staging (Table 5). These studies demonstrated that EUS is the most accurate staging method for gastric cancer with a few incidences of overstaging and understaging. The excellent results of accuracy of both T and N staging are shown in a study by Botet *et al.*<sup>[12]</sup> to be 92% and 78%, respectively. The high accuracy of EUS in preoperative staging of gastric cancer is proved by our results. In the current study, EUS had a diagnostic accuracy of 68.3% for tumor invasion. EUS had 24.4% overstaging in T staging, 2 of the 12 T1 tumors overstaged as T2, 3 of the 20 T2 tumors overstaged as T3. The main reason of

Table 5 Literature summary of EUS studies on gastric cancer

	Author	Period	Number of patients	Accuracy (%)	
				T stage	N stage
1	Botet <i>et al.</i> <sup>[12]</sup> (USA)	1986–1988	50	92	78
2	Akahoshi <i>et al.</i> <sup>[13]</sup> (Japan)	1986–1990	74	81.1	50
3	Ziegler <i>et al.</i> <sup>[11]</sup> (Germany)	1986–1990	108	86	74
4	Lightdale <sup>[9]</sup> (USA)	1989–1991	525	81	76
5	Dittler <i>et al.</i> <sup>[14]</sup> (Germany)	1989–1992	264	83	66
6	Francois <i>et al.</i> <sup>[15]</sup> (France)	1991–1993	35	79	79
7	Yanai <i>et al.</i> <sup>[16]</sup> (Japan)	1990–1995	104	64.8	Early stage
8	Meining <i>et al.</i> <sup>[17]</sup> (Germany)	1992–1996	33	66	Not reported
9	Yanai <i>et al.</i> <sup>[18]</sup> (Japan)	1996–1997	52	71	Early stage
10	Guo <i>et al.</i> <sup>[19]</sup> (China)	1996–1997	62	83.9	79
11	Hunerbein <i>et al.</i> <sup>[20]</sup> (Germany)	1997 <sup>1</sup>	30	82	80
12	Habermann <i>et al.</i> <sup>[21]</sup> (Germany)	1998–2000	51	86	90
13	Hizawa <i>et al.</i> <sup>[22]</sup> (Japan)	1997–2002	234	78	Early stage
14	Xi <i>et al.</i> <sup>[23]</sup> (China)	2002 <sup>1</sup>	32	80	68.6
15	Shimoyama <i>et al.</i> <sup>[24]</sup> (Japan)	1996–2003	45	71	80
16	Bhandari <i>et al.</i> <sup>[10]</sup> (Korea)	2003	63	87.5	79.1

<sup>1</sup>Year of article publication/duration of study not reported.

overstaging in T1 cancer is the thickening of gastric wall due to perifocal inflammatory reaction, which is difficult to distinguish from cancer tissue and imitates the presence of T2 cancer. Absence of serosal layer in certain regions of the stomach, the lesser curvature, the posterior wall of fundus and the anterior wall of antrum is the reason for overstaging T2 cancer. Cancers of these areas are classified histopathologically as T2 cancer, even carcinoma infiltrates through the whole gastric wall, because no serosal infiltration can be found.

EUS accuracy of metastatic lymph node involvement was 66% in the present study. Such slightly lower accuracy is related to the absence of standard differential echoendoscopic criteria for benign and malignant lymph nodes. Echoendoscopic features of metastatic lymph nodes from different authors include size > 10 mm, rounded structure, sharp demarcation of borders, and hypoechoic (dark) structure<sup>[25,26]</sup>. However, endoscopic ultrasonographic detection of metastatic lymph nodes is complicated, due to the difficulty of differentiation between malignant and inflammatory lymph nodes. Francois *et al.*<sup>[15]</sup> described that hypoechoic lymph nodes with well-defined margins and largest diameter/smallest diameter ratio less than 2 are considered to be malignant. Dittler and Siewert<sup>[14]</sup> noticed that, if EUS does not diagnose malignant lymph nodes in T1 or T2 stage, stage N0 can be assumed; if lymph nodes are visualized in stages T3 and T4, then they tend to be malignant. Results of certain studies<sup>[27]</sup> demonstrated that the EUS-guided fine-needle aspiration biopsy would be very useful to distinguish between benign and malignant lymph nodes.

Other reasons for inaccuracy of evaluation of tumor lymph nodes are related to the limited depth of transducer, and unsatisfactory visualization of distant lymph node by EUS. EUS cannot permit the assessment of tissue beyond the depth of about 5–6 cm.

The presence of ascites in gastric cancer patients is a poor prognostic sign and implies the presence of peritoneal metastasis. EUS-guided fine-needle aspiration biopsy also has been successfully used to detect malignant ascites<sup>[28–30]</sup>. EUS detection of distant metastatic lymph nodes and distant metastasis or M staging of gastric cancer

is insufficient due to limited penetration depth of this method as mentioned above. Therefore, combined use of EUS and CT, which is superior to EUS for gaining information about distant metastasis, should be effective for the management of gastric cancer patients for appropriate treatment options.

In conclusion, EUS is a useful diagnostic method for accurate preoperative staging for T and N criteria for gastric cancer. The accurate preoperative staging is extremely essential for proper stage-depending patient management, which improves the 5-year survival rate of this dismal prognostic disease. However, EUS evaluation of malignant lymph nodes is still unsatisfactory. Therefore, great effort should be taken to study differential criteria of malignant lymph nodes from benign lymph nodes.

## REFERENCES

- Mehta VK, Fisher G. Gastric cancer. Accessed 2004-11-03. Available from: URL: <http://www.emedicine.com/med/topic845.htm>
- Neugut AI, Hayek M, Howe G. Epidemiology of gastric cancer. *Semin Oncol* 1996; **23**: 281-291
- Chak A. EUS in submucosal tumors. *Gastrointest Endosc* 2002; **56**: S43-S48
- Rösch T, Kapfer B, Will U, Baronius W, Strobel M, Lorenz R, Ulm K. Accuracy of endoscopic ultrasonography in upper gastrointestinal submucosal lesions: a prospective multicenter study. *Scand J Gastroenterol* 2002; **37**: 856-862
- Chak A, Canto MI, Rosch T, Dittler HJ, Hawes RH, Tio TL, Lightdale CJ, Boyce HW, Scheiman J, Carpenter SL, Van Dam J, Kochman ML, Sivak MV Jr. Endosonographic differentiation of benign and malignant stromal cell tumors. *Gastrointest Endosc* 1997; **45**: 468-473
- Zhang QL, Nian WD. Endoscopic ultrasonography diagnosis in submucosal tumor of stomach. *Endoscopy* 1998; **30**(suppl 1): A69-A71
- Caletti G, Fusaroli P, Bocus P. Endoscopic ultrasonography in large gastric folds. *Endoscopy* 1998; **30**(suppl 1): A72-A75
- Davies J, Chalmers AG, Sue-Ling HM, May J, Miller GV, Martin IG, Johnston D. Spiral computed tomography and operative staging of gastric carcinoma: a comparison with histopathological staging. *Gut* 1997; **41**: 314-319
- Bhandari S, Shim CS, Kim JH, Jung IS, Cho JY, Lee JS, Lee MS, Kim BS. 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**: 619-626
- 10 **Ziegler K**, Sanft C, Zimmer T, Zeitz M, Felsenberg D, Stein H, Germer C, Deutschmann C, Riecken EO. Comparison of computed tomography, endosonography, and intraoperative assessment in TN staging of gastric carcinoma. *Gut* 1993; **34**: 604-610
  - 11 **Botet JF**, Lightdale CJ, Zauber AG, Gerdes H, Winawer SJ, Urmacher C, Brennan MF. Preoperative staging of gastric cancer: comparison of endoscopic US and dynamic CT. *Radiology* 1991; **181**: 426-432
  - 12 **Akahoshi K**, Misawa T, Fujishima H, Chijiwa Y, Maruoka A, Ohkubo A, Nawata H. Preoperative evaluation of gastric cancer by endoscopic ultrasound. *Gut* 1991; **32**: 479-482
  - 13 **Lightdale CJ**. Endoscopic ultrasonography in the diagnosis, staging and follow-up of esophageal and gastric cancer. *Endoscopy* 1992; **24 Suppl 1**: 297-303
  - 14 **Dittler HJ**, Siewert JR. Role of endoscopic ultrasonography in gastric carcinoma. *Endoscopy* 1993; **25**: 162-166
  - 15 **Francois E**, Peroux J, Mouroux J, Chazalle M, Hastier P, Ferrero J, Simon J, Bourry J. Preoperative endosonographic staging of cancer of the cardia. *Abdom Imaging* 1996; **21**: 483-487
  - 16 **Yanai H**, Matsumoto Y, Harada T, Nishiaki M, Tokiyama H, Shigemitsu T, Tada M, Okita K. Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest Endosc* 1997; **46**: 212-216
  - 17 **Meining A**, Dittler HJ, Wolf A, Lorenz R, Schusdziaara V, Siewert JR, Classen M, Höfler H, Rösch T. You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging. *Gut* 2002; **50**: 599-603
  - 18 **Yanai H**, Noguchi T, Mizumachi S, Tokiyama H, Nakamura H, Tada M, Okita K. A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. *Gut* 1999; **44**: 361-365
  - 19 **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**: 242-245
  - 20 **Hünerbein M**, Ghadimi BM, Haensch W, Schlag PM. Transendoscopic ultrasound of esophageal and gastric cancer using miniaturized ultrasound catheter probes. *Gastrointest Endosc* 1998; **48**: 371-375
  - 21 **Habermann CR**, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C, Dieckmann C, Schoder V, Adam G. Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. *Radiology* 2004; **230**: 465-471
  - 22 **Hizawa K**, Iwai K, Esaki M, Matsumoto T, Suekane H, Iida M. Is endoscopic ultrasonography indispensable in assessing the appropriateness of endoscopic resection for gastric cancer? *Endoscopy* 2002; **34**: 973-978
  - 23 **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**: 254-257
  - 24 **Shimoyama S**, Yasuda H, Hashimoto M, Tatsutomi Y, Aoki F, Mafune K, Kaminishi M. Accuracy of linear-array EUS for preoperative staging of gastric cardia cancer. *Gastrointest Endosc* 2004; **60**: 50-55
  - 25 **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**: 224-230
  - 26 **Catalano MF**, Sivak MV, Rice T, Gragg LA, Van Dam J. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc* 1994; **40**: 442-446
  - 27 **Vilmann P**, Hancke S, Henriksen FW, Jacobsen GK. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of lesions in the upper gastrointestinal tract. *Gastrointest Endosc* 1995; **41**: 230-235
  - 28 **Chang KJ**, Albers CG, Nguyen P. Endoscopic ultrasound-guided fine needle aspiration of pleural and ascitic fluid. *Am J Gastroenterol* 1995; **90**: 148-150
  - 29 **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**: 471-474 [PMID: 15044880 DOI: 10.1016/S0016-5107(03)02873-6]
  - 30 **Nguyen PT**, Chang KJ. EUS in the detection of ascites and EUS-guided paracentesis. *Gastrointest Endosc* 2001; **54**: 336-339

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