Abdominal Imaging

Published online: 29 January 2005

Abdom Imaging (2005) 30:518–523
DOI: 10.1007/s00261-004-0287-z

Diagnostic ability of high-frequency ultrasound probe sonography in staging early gastric cancer, especially for submucosal invasion

S. Yoshida,[1] S. Tanaka,[1] K. Kunihiro,[1] Y. Mitsuoka,[2] M. Hara,[2] Y. Kitadai,[2] J. Hata,[3] M. Yoshihara,[2] K. Haruma,[3] N. Hayakawa,[4] K. Chayama[2]

[1]Department of Endoscopy, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
[2]Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
[3]Division of Gastroenterology, Department of Internal Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan
[4]Department of Epidemiology, Division of Bio-Medical Informatics, Research Institute for Radiation Biology and Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8553, Japan

Abstract

Background: Advances in gastrointestinal endoscopy have resulted in endoscopic mucosal resection becoming the main therapy for many early gastric cancers confined to the mucosa and, in some cases, of minimal submucosal invasion. Thus, preoperative determination of the depth of the cancer is important. We compared the results of high-frequency ultrasound probe sonography with those of histologic study to clarify the usefulness of identifying of submucosal invasion and determining the depth of early gastric cancer.
Methods: Subjects were 295 patients diagnosed with early gastric cancer who had undergone endoscopic mucosal or surgical resection. High-frequency ultrasound probe sonographic findings were compared with histologic findings.
Results: The muscularis mucosae was visualized in 63% of cases of early gastric cancer. By construction on receiver operator characteristics curve, we determined that submucosal invasive cancer could be diagnosed by high-frequency ultrasound probe sonography to a depth of about 600 μm. There was no case in which invasion deeper than 1000 μm was diagnosed as a hypoechoic area limited to the mucosal layer or a fan-shaped hypoechoic area in the submucosal layer. The depth of early gastric cancer was accurately determined in 90% of cases.
Conclusions: High-frequency ultrasound probe is a useful tool for accurately determining the depth of invasion of early gastric cancer when its limitations are understood.

Key words: Early gastric cancer—Endoscopic ultrasonography—High-frequency ultrasound probe sonography—Submucosal invasion—Endoscopic mucosal resection

Advances in gastrointestinal endoscopy have resulted in endoscopic mucosal resection (EMR) becoming the main therapy for many early gastric cancers (EGCs) confined to the mucosa [1]. Because of the association between differentiated gastric adenocarcinoma and lymph node metastasis, the indications for endoscopic resection are being expanded to such adenocarcinomas if submucosal invasion is minimal [2, 3]. Thus, preoperative determination of the depth of cancer invasion is important.

Endoscopic ultrasonography (EUS) was developed in 1979 [4, 5]. Rapid advances ensued, and the miniprobe, which can be passed through the instrument channel of the conventional diagnostic endoscope, was reported in 1989 [6]. Accurate determination of the depth of invasion of gastric cancer was made much easier. We compared the results of high-frequency ultrasound probe sonography (HFUPS) with those of histology to clarify the usefulness of HFUPS in identifying submucosal invasion and accurately determining the depth of invasion in cases of EGC.

Correspondence to: S. Tanaka; *email:* colon@hiroshima-u.ac.jp

Materials and methods

Subjects were recruited from a series of 302 consecutive patients with EGC who were examined by HFUPS before therapy at Hiroshima University Hospital between November 1998 and September 2002. The diagnosis of EGC was confirmed in all cases by histologic study of resected specimens. Seven of the 302 patients were excluded because the ultrasonographic image was not sufficient for determining cancer depth. Of the remaining 295 patients, 213 underwent endoscopic mucosal resection, and 82 underwent surgical resection. These were 222 men and 73 women whose ages ranged from 38 to 91 years (mean 66.6 years). Informed consent was obtained from patients and/or family members for participation in the study.

We examined the depth of tumor infiltration ultrasonographically by intraluminal scanning of the stomach before treatment. To improve transmission of the ultrasound beam, aspiration of sufficient intragastric duodenal air and instillation of de-aerated water (300 to 500 mL) were performed. SP-701 series miniprobes (7.5, 12, 15, and 20 MHz; Fuji Photo Optical Co., Ltd., Saitama, Japan) and UM series miniprobes (12, 20, and 30 MHz; Olympus Co., Ltd., Tokyo, Japan) were used. We used the highest frequency possible. If accurate diagnosis could not be achieved because of attenuation of the ultrasound beam, we lowered the frequency.

Our interpretation of the layered structure of the gastrointestinal wall depicted by EUS was in accordance with the guidelines of the Japan Gastroenterological Endoscopy Society [7]. Under the best scanning conditions, tumors were identified as a thickening or a disruption of the layers of the wall by a hypoechoic mass. Cancer depth was determined simply by HFUPS as a hypoechoic area limited to the mucosal layer or a fan-shaped hypoechoic area in the submucosal layer (EUS-M·SM1), as an arch-shaped hypoechoic area in the submucosal layer (EUS-SM2; Figs. 1, 2, 3), or as an arch-shaped hypoechoic area spreading to the muscularis propria (EUS-AD).

Histologic examination of the entire resected cancerous lesion was carried out in parallel sections graduating in thickness from 2 to 4 mm, each of which was stained with hematoxylin and eosin. Depth of cancer invasion and histologic type of gastric cancer were determined histologically in resected specimens according to the Japanese Classification of Gastric Carcinoma of the Japanese Gastric Cancer Association [8, 9]. Gastric cancers were classified as differentiated or undifferentiated. Papillary and tubular adenocarcinomas were considered differentiated, whereas poorly differentiated adenocarcinoma and signet ring cell carcinoma were considered undifferentiated. Mucinous carcinoma was considered differentiated or undifferentiated depending on other predominant characteristics (papillary, tubular, poorly differentiated, or signet ring cell elements). Depth of submucosal invasion was subclassified histologically into two grades: penetration into the submucosal layer no farther than 500 μm from the muscularis mucosae (SM1) or penetration of at least 500 μm (SM2).

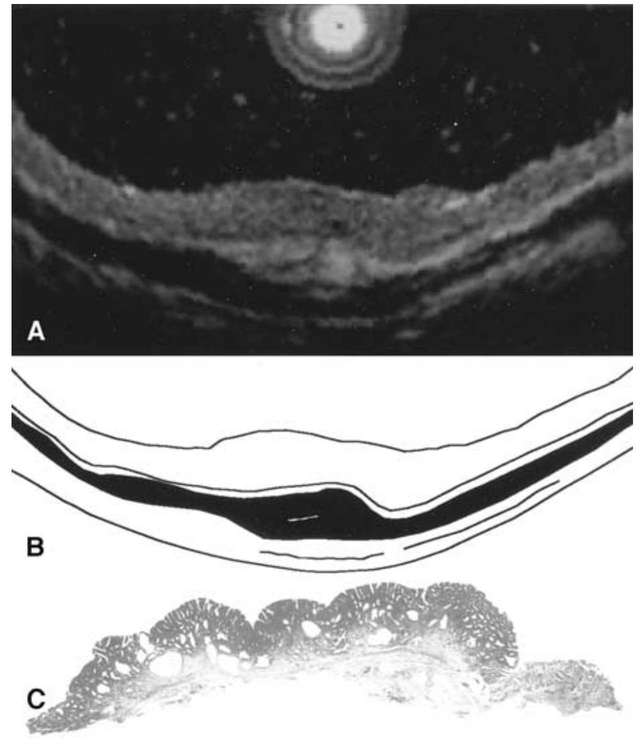

Fig. 1. **A** The HFUPS hypoechoic area is limited to the mucosal layer. The border between the mucosal and submucosal layers is smooth, and the muscularis mucosae is visible. There is no change in the submucosal layer. Cancer depth is EUS-M·SM1. **B** Schema of HFUPS image. **C** Histologic examination demonstrates mucosal cancer. Hematoxylin and eosin stain, original magnification 4×.

In each case, the EUS image was compared with the histopathologic features of the resected specimen, and the actual measurement of submucosal invasion was measured in every specimen with a microscopic scale. We compared the HFUPS diagnosis with the actual measurement of submucosal invasion in 52 submucosally invasive cancers.

We evaluated the diagnostic usefulness of HFUPS for minimal submucosal cancer by means of receiver operator characteristics (ROC) curve analysis. Using the histologic findings of the resected specimens as the gold standard for determination of depth of cancer invasion, an ROC curve was constructed for each parameter by plotting sensitivity (true-positive rate) against 1-specificity (false-positive rate) over all possible threshold levels at which EUS recognizes minimal submucosal invasion. A description of the derivation and use of this method of analysis has been provided by Metz [10, 11]. To determine the accuracy of HFUPS, we compared histologic

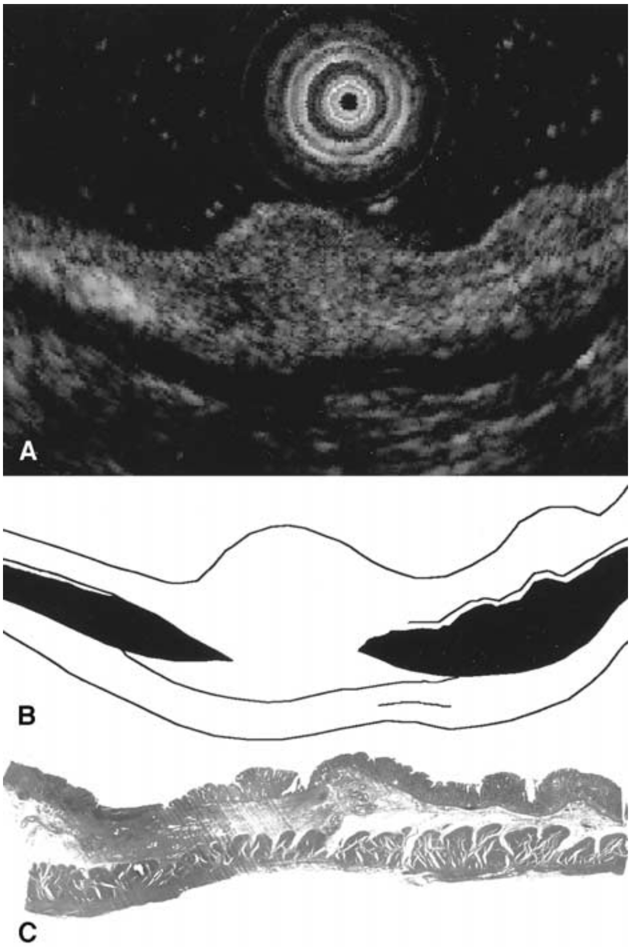

Fig. 2. **A** The fan-shaped hypoechoic area is in the submucosal layer. Cancer depth is EUS-M·SM1. **B** Schema of HFUPS image. **C** Histologic examination shows mucosal cancer with ulcer fibrosis. Hematoxylin and eosin stain, original magnification 4×.

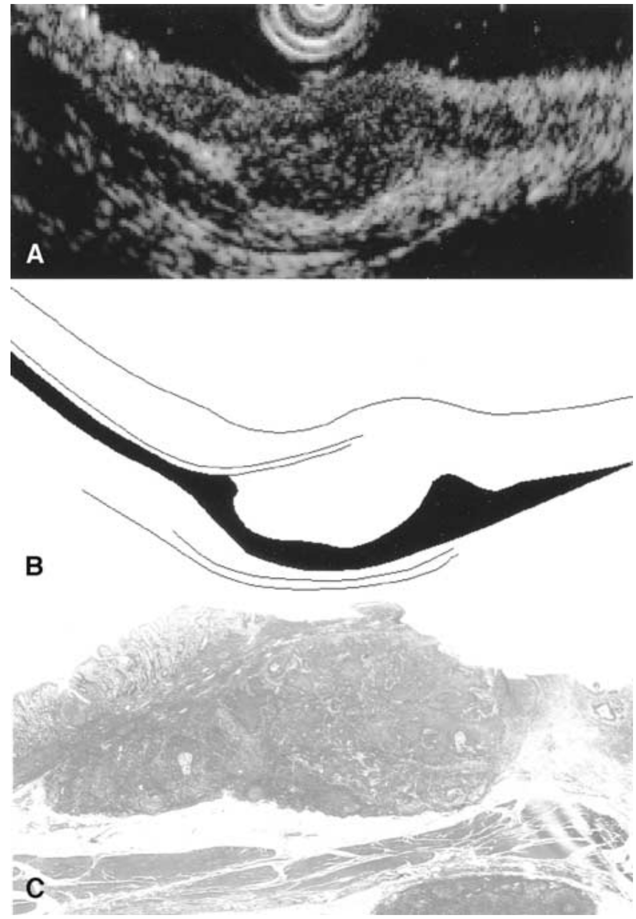

Fig. 3. **A** The arch-shaped hypoechoic area is in the submucosal layer. Cancer depth is EUS-SM2. **B** Schema of HFUPS image. **C** Histologic examination shows submucosal cancer. Hematoxylin and eosin stain, original magnification 5×.

findings with HFUPS findings by considering M and SM1 tumors together as EUS-M·SM1 tumors and by considering SM2 tumors as EUS-SM2 tumors. The presence or absence of ulcerative lesions or scarring from previous ulceration (converging folds, deformity of the muscularis propria, or fibrosis in the submucosa or deeper layer) was considered, and thus tumors were described as UL^+ or UL^-.

Bonferroni correction was applied to compare the actual measurements of submucosal invasion across three groups of lesions (EUS-M·SM1, EUS-SM2, and EUS-AD). Accuracy rates for diagnosis by HFUPS are reported as percentages and 95% confidence intervals, and differences were analyzed by chi-square test. A p value less than 0.05 was considered statistically significant.

Results

The gastrointestinal wall was visualized ultrasonographically as a five-layered, seven-layered, or nine-layered structure that included the muscularis mucosae in 72, 37, and 186 cases, respectively. Actual measurements of submucosal invasion showed that the EUS-SM2 lesions were significantly deeper than the EUS-M·SM1 lesions. Of the EUS- M·SM1 lesions, 62% (18 of 29) were within 500 μm of the lamina muscularis mucosae. Of the EUS-SM2 and EUS-AD lesions, 86% (19 of 22) and 100% (1 of 1), respectively, were farther than 500 μm from the lamina muscularis mucosae. In all cases of EUS-M·SM1, the actual measurement of submucosal invasion was shorter than 1000 μm (Fig. 4). Sensitivity (true-positive rate) and 1-specificity (false-positive rate) of HFUPS were plotted in relation to actual measurements of submucosal invasion at 125-μm increments. The curve was closest to the upper left corner of the graph at 625-μm depth of invasion (Fig. 5).

For EGC identified histologically as M and SM1, depth was accurately measured by HFUPS in 93% (246 of 264) of cases. For SM2 cancers, accurate depth measurements were obtained by HFUPS in 61% (19 of 31) of

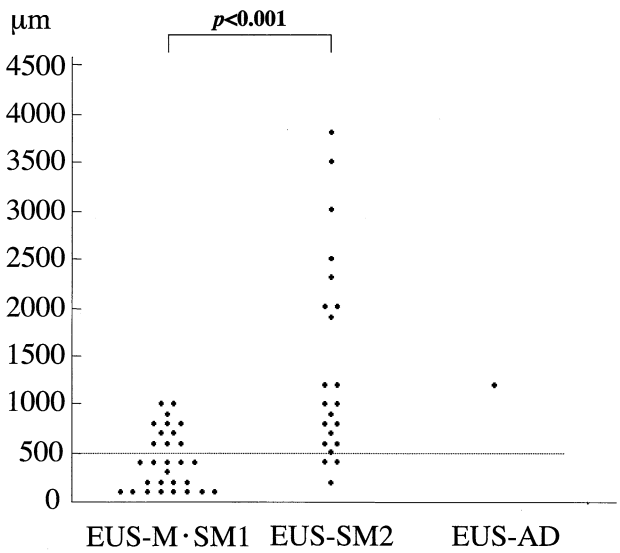

Fig. 4. Submucosal gastric cancer depth in relation to the actual measurement under the muscularis mucosae and HFUPS diagnosis.

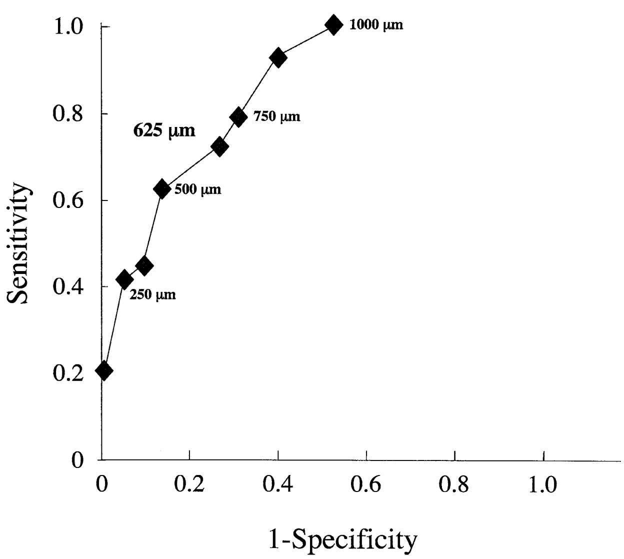

Fig. 5. ROC curve of accuracy of HFUPS for diagnosing submucosal gastric cancer depth in relation to the actual measurement under the muscularis mucosae in 125-μm increments. The ROC curve is used to graphically assess the tradeoff between sensitivity and specificity over all cutoff points of a test. The sensitivity and 1-specificity at 625 μm were 0.72 and 0.26, respectively.

cases. The overall accuracy rate for EGC was 90% (265 of 295; Table 1). The accuracy of HFUPS for determining gastric cancer depth according to histologic type and ulcerative status are presented in Table 2. Overall accuracy rates were 90% for differentiated EGCs (230 of 255) and 88% for undifferentiated EGCs (35 of 40). Overall accuracy rates were 94% for UL^- EGCs (204 of 217) and 78% for UL^+ EGCs (61 of 78).

Table 1. Accuracy of high-frequency ultrasound probe sonography lor determining depth of EGC

	Histologic diagnosis		
	M	SM1	SM2
EUS diagnosis[a]			
EUS-M·SMI	227	19	11
EUS-SM2	15	2	19
EUS-AD	1	0	1
Accuracy (95% CI)	93% (90–96)	90% (70–99)	61% (42–78)[b]
Cases/patients	227/243	19/21	19/31
Total (M and SMI)	93% (89–96), 246/264		
Total accuracy for detection of EGC	90% (86–93), 265/295		

[a]Numbers of tumors unless otherwise indicated
[b]Versus lolal 93%, $p < 0.001$
CI, confidence interval; EGC, early gastric cancer; EUS-AD, arch-shaped hypoechoic area spreading to the muscularis propria; EUS-M·SM1, hypoechoic area limited to the mucosal layer or a fan-shaped hypoechoic area in the submucosal layer; EUS-SM2, aroh-shaped hypoechoic area in the submucosal layer; M, mucosal; SM1, penetration into submucosal layer ≤ 500 μm from the muscularis mucosae; SM2, penetration into submucosal layer ≥ 500 μm from the muscularis mucosae

Table 2. High-frequency ultrasound probe sonograpy for determining depth of early gastric cancer according to histologic type and ulcerative status

	Histologic diagnosis		
	M, SM1	SM2	Total
Differentiated			
Accuracy (95% CI)	93 (89–96)	61 (39–80)	90 (85–94)
Case/patients	216/2.52	14/23	230/255
Undifferentiated			
Accuracy (95% CI)	94 (79–99)	63 (24–91)	88 (73–96)
Cases/patients	30/32	5/8	35/40
UL^-			
Accuracy (95% CI)	97 (94–99)	63 (38–84)	94 (90–97)
Cases/patients	192/198	12/19	204/217
UL^+			
Accuracy (95% CI)	82 (70–90)	58 (28–85)	78 (67–86)
Cases/patients	54/66	7/12	61/78

[a]Versus UL^+, $p < 0.001$
CI, confidence interval; M, mucosal; SM1, penetration into submucosal layer ≤ 500 μm from the muscularis mucosae; SM2, penetration into submucosal layer ≥ 500 μm from the muscularis mucosae; UL^+, ulceration or scarring present in lesion; UL^- ulceration or scarring absent in lesions

Discussion

EGCs controllable by EMR are now widely diagnosed in Japan owing to several factors including mass screening for EGC, advances in endoscopic technology, and the low cost of measuring serum pepsinogens [12]. In addition, gastric cancer lesions are often found in elderly patients and in patients with underlying disease for whom surgery would be risky. Thus, it is important to make an accurate preoperative determination of depth of cancer invasion to determine whether EMR is indicated. According to the Japanese Gastric Cancer Association, EMR is indicated for patients with differentiated mucosal cancer smaller than 2 cm in diameter [1]. In a previously reported study, none of the differentiated adenocarcinomas smaller than 30 mm in diameter without lymphatic or venous permeation were associated with lymph node metastasis, provided that invasion was shallower than 500 μm into the submucosa [3]. In our institute, no well-differentiated adenocarcinomas have been associated with lymph node metastasis, provided that invasion was shallower than 400 μm into the submucosa [2].

The gastrointestinal wall is visualized as a five-layered structure on conventional EUS images, and these layers correspond to the histologic layers [13, 14]. The EUS pattern of fibrosis is used to determine the depth of invasion and peptic ulceration in the tumor focus [15]. The fibrosis spreads in the shape of a fan within the stomach walls, and the cancer spreads in the shape of an arch within the stomach walls. However, resolution of the conventional echoendoscope is not sufficient for diagnosing EGC, and obtaining accurate scanning of small lesions is difficult [16]. With the miniprobe, it is very easy to depict small lesions, and operability is improved. Moreover, the image of the surface layer is more detailed with high-frequency ultrasound. High-frequency imaging separates the normal gastrointestinal wall into 9 or 11 layers, thus providing detailed observation of lesions. We interpreted the layered structure according to the guidelines of the Japan Gastroenterological Endoscopy Society, i.e., 5 to 13 layers [7]. When determining the depth of submucosal invasion, it is important to obtain an image of the muscularis mucosae, which is a clinically important border between the mucosa and the submucosa. In an ex vivo study with a 30-MHz miniprobe, the muscularis mucosae was clearly defined in all normal gastric wall specimens [17]. In our in vivo study, we were able to visualize the gastrointestinal wall as a structure with more than nine layers that included the muscularis mucosae in 63% (186 of 295) of EGC cases. EUS is limited in its resolution and ability to diagnose minimal invasion [18]. In an *ex vivo* study, submucosal invasion (<200 μm) was undetectable by HFUPS with a 30-MHz miniprobe, but submucosal invasion deeper than 500 μm below the level of the muscularis mucosae was clearly visualized [17]. We used the ROC curve, which graphically assesses the tradeoff between sensitivity and specificity, over all cutoff points to determine the limitation in visualizing the depth of submucosal cancer by HFUPS. On the basis of our present findings and the ROC curve in particular, we determined that submucosal invasive cancer can be diagnosed in vivo by HFUPS to a depth of about 600 μm. There was no case in which invasion deeper than 1000 μm was diagnosed as EUS-M·SM1.

In this study, according to indications for EMR, we compared M and SM1 cancers with EUS-M·SM1 cancers and SM2 cancers with EUS-SM2 cancers [1–3]. With EUS, the overall accuracy rate for EGC, the accuracy rate for M plus SM1, and the accuracy rate for SM2 were 90%, 93%, and 61%, respectively. Diagnoses of M and SM1 EGCs were accurate, but diagnosis of SM2 EGC was significantly low in accuracy. This is because diagnosis of SM2 EGC requires visualization of malignant changes on HFUPS images. Overcoming this problem may require improved equipment or enhanced performance of the equipment. The multibending endoscope may enhance performance of the miniprobe by providing for an ultrasonographic scanning plane perpendicular to the area of interest within the focal zone [19].

The differentiated type of gastric cancer tends to be characterized by expansion of the tumor nodule or mass, and the undifferentiated type tends to be characterized by diffuse infiltration of tumor cells individually or in small nests [20, 21]. However, according to our data, accuracy of HFUPS in diagnosing undifferentiated EGC did not differ significantly from accuracy in diagnosing differentiated EGC, possibly because, even in undifferentiated EGC, the entire cancer does not consist of infiltration of tumor cells. The accuracy for diagnosis of UL^- EGC was 94%, which was significantly better than the 78% accuracy for UL^+ EGC. Even if the pattern analysis method and miniprobe are used, it is difficult to distinguish ulcer fibrosis from submucosal invasion.

Although HFUPS is limited in its diagnostic ability with respect to minimal submucosal invasion and the presence of UL, it is advantageous because it can directly visualize submucosally invasive cancer. HFUPS provides high accuracy in predicting the depth of invasion of gastric cancer, and surgeons should consider HFUPS examination when determining whether EMR is indicated.

Acknowledgment. This work was performed at the Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan.

References

1. Nakajima T (2002) Gastric cancer treatment guidelines in Japan. Gastric Cancer 5:1–5
2. Nishida T, Tanaka S, Haruma K, et al. (1995) Histologic grade and cellular proliferation at the deepest invasive portion correlate with the high malignancy of submucosal invasive gastric carcinoma. Oncology 52:340–346
3. Gotoda T, Yanagisawa A, Sasako M, et al. (2000) Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 3:219–225
4. DiMagno EP, Buxton JL, Regan PT, et al. (1980) Ultrasonic endoscope. Lancet 1:629–631
5. DiMagno EP (1984) Endoscopic ultrasonography. In: Bolondi L, Gandolfi L, Labo G. (eds) *Diagnostic ultrasound in gastroenterology*. Bologna: Piccin/Butterworths, pp 523–539
6. Silverstein FE, Martin RW, Kimmey MB, et al. (1989) Experimental evaluation of an endoscopic ultrasound probe: in vitro and in vivo canine studies. *Gastroenterology* 96:1058–1062
7. Yamanaka T (2002) JGES consensus meeting report in DDW—Japan 2000, Kobe: interpretation of the layered structure of gastrointestinal wall with endoscopic ultrasonography. Dig Endosc 14:39–40
8. Japanese Gastric Cancer Association (1998) Japanese classification of gastric carcinoma, 2nd English edition. Gastric Cancer 1:10–24

9. Japanese Gastric Cancer Association (1999). Japanese classification of gastric carcinoma, 13th ed [in Japanese] Tokyo: Kanehara
10. Metz CE (1986) ROC methodology in radiologic imaging. Invest Radiol 21:720–733
11. Metz CE (1978) Basic principles of ROC analysis. Semin Nucl Med 8:283–298
12. Yoshihara M, Sumii K, Haruma K, et al. (1998) Correlation of ratio of serum pepsinogen I and II with prevalence of gastric cancer and adenoma in Japanese subjects. Am J Gastroenterol 93:1090–1096
13. Aibe T (1984) A study on the structure of layers of the gastrointestinal wall visualized by means of ultrasonic endoscope [in Japanese with English abstract]. Gastroenterol Endosc 26:1447–1473
14. Kimmey MB, Martin RW, Haggitt RC, et al. (1989) Histologic correlates of gastrointestinal ultrasound images. Gastroenterology 96:433–441
15. Kida M, Tanabe S, Watanabe M, et al. (1998) Staging of gastric cancer with endoscopic ultrasonography and endoscopic mucosal resection. Endoscopy 30(suppl 1):A64–A68
16. Maruta S, Tsukamoto Y, Niwa Y, et al. (1994) Evaluation of upper gastrointestinal tumors with a new endoscopic ultrasound probe. Gastrointest Endosc 40:603–608
17. Sabet EA, Okai T, Minamoto T, et al. (2003) Visualizing the gastric wall with a 30-MHz ultrasonic miniprobe: ex vivo imaging of normal gastric sites and sites of early gastric cancer. Abdom Imaging 28:252–256
18. Matsumoto Y, Yanai H, Tokiyama H, et al. (2000) Endoscopic ultrasonography for diagnosis of submucosal invasion in early gastric cancer. J Gastroenterol 35:326–331
19. Yoshida S, Tanaka S, Kamino D, et al. (2004) Initial experience with catheter probe US when using a multibending endoscope. Gastrointest Endosc 59:889–894
20. Ming SC (1998) Cellular and molecular pathology of gastric carcinoma and precursor lesions: a critical review. Gastric Cancer 1:31–50
21. Sugano H, Nakamura K, Kato Y (1982) Pathological studies of human gastric cancer. Acta Pathol Jpn 32(suppl 2):329–347