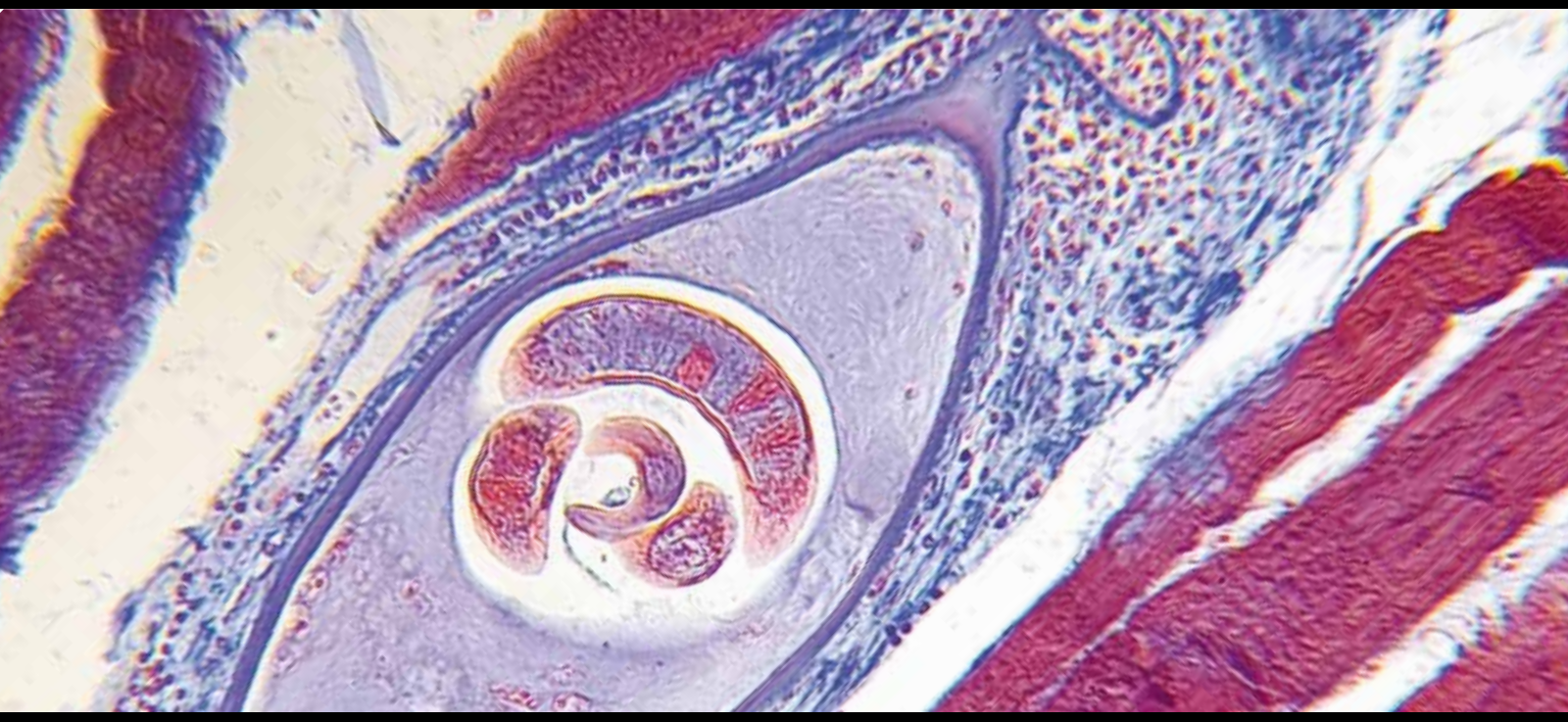
Gastroenterology Research and Practice

Endoscopic Ultrasound

Guest Editors: Salem Omar, Manoop S. Bhutani, Kenjiro Yasuda, and Ang Tiing Leong



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Editorial Board

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Editorial
Endoscopic Ultrasound

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There is now considerable interest in the clinical practice of EUS. Over the decades, EUS has evolved from diagnostic imaging and tissue acquisition to EUS-guided interventions. Technological advances have improved the EUS image quality and in recent years, image enhancement using contrast and elastography have also become more widely available. In this special issue that focuses on EUS, five papers explored various diagnostic and therapeutic aspects of EUS. Three papers examined the impact of EUS in cancer T-staging. Two other papers dealt with the issue of EUS-guided therapeutics. One explored the role of EUS-guided radiofrequency ablation (RFA) in an animal model while the other are concerned with EUS-guided biliary access and drainage.

In the first paper entitled "*Accuracy of endoscopic ultrasonography for determining the treatment method for early gastric cancer,*" K. Mandai and K. Yasuda examined the value of EUS in determining the therapeutic strategy for early gastric cancer. They found excellent correlation (92.8%) between EUS assessment of mucosa/sm1 involvement and histology. However the accuracy was reduced in the context of ulcerated lesions and lesions larger than 2 cm.

In the second paper entitled "*Comparison of diagnostic accuracies of various endoscopic examination techniques for evaluating the invasion depth of colorectal tumours,*" S. Haruki et al. assessed the clinical value of magnifying endoscopy combined with EUS for estimating the invasion depth of colorectal tumours. They concluded that when it was difficult to evaluate the invasion depth of colorectal tumours on conventional endoscopy alone, the additional use of EUS may enhance diagnostic accuracy.

In the third paper entitled "*Endoscopic ultrasound-guided radiofrequency ablation (eus-rfa) of the pancreas in a porcine model,*" S. Gaidhane et al. evaluated the use of a prototype monopolar probe inserted through the EUS-needle to perform EUS-RFA in the porcine pancreas. They found that EUS-guided RFA of the pancreatic head was well tolerated with minimal amount of pancreatitis. Recent studies have shown the feasibility of RFA in patients with stage III pancreatic cancer in open, percutaneous, or laparoscopic setting. This study offers the promise of a less invasive means of performing RFA of unresectable pancreatic cancer.

In the fourth paper entitled "*Evaluation of endoscopic ultrasound image quality is necessary in endosonographic assessment of early gastric cancer invasion depth,*" S. Yamamoto et al. evaluated whether EUS image quality affected the accuracy of diagnosing the vertical invasion depth of early gastric cancer. They reported that low-quality EUS images led to an incorrect diagnosis of invasion depth of early gastric cancer, independent of tumour location and size.

In the fifth paper entitled "*The spectrum of endoscopic ultrasound intervention in biliary diseases: a single centre's experience in 31 cases,*" S. Attasaranya et al. described the spectrum and experience of EUS-guided interventions in biliary diseases in a single-tertiary center. The overall technical success for EUS-guided biliary drainage was 77%; this was considerably higher in the last 2 years compared to the first 3 years (89% versus 61.5%), reflecting the effect of a learning curve in this challenging procedure, which may be associated with significant morbidity.

Acknowledgment

This special issue on endoscopic ultrasonography (EUS) is dedicated to the memory of our dear friend and colleague Associate Professor S. Omar from the Department of Medicine, Faculty of Medicine, University of Malaya, Malaysia. Dr. Omar was an expert endosonographer who received his training in EUS at the Department of Interdisciplinary Endoscopy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. Associate Professor Omar was the chief editor of this issue but unfortunately he passed away unexpectedly during the production of this issue.

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Clinical Study

Accuracy of Endoscopic Ultrasonography for Determining the Treatment Method for Early Gastric Cancer

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Background. Endoscopic resection (ER) for early gastric cancer (EGC) is a minimally invasive and curative treatment. The value of endoscopic ultrasonography (EUS) in determining the therapeutic strategy for EGC was assessed in this study. *Materials and Methods*. Pretreatment EUS was performed on 406 EGCs. The lesions were divided into the histological categories m/sm1 and sm2. The EUS-determined depths of invasion were classified as EUS-M/SM1, EUS-SM2, and EUS-MP or deeper. An analysis of the factors influencing the EUS-based depth determination was then conducted. *Results*. Most (92.8%) of the EUS-M/SM1 group belonged to the m/sm1 histological category. Ulcerated lesions, tumor size of larger than 2 cm, and the use of an ultrasound endoscope were independently associated with misdiagnosis of the depth of EGC by EUS. The ulcerated lesions had a significantly higher probability of overestimation. *Conclusions*. EUS is a useful method for determining the therapeutic strategy for EGC. Special attention should be paid not to overestimate the depth of cancer invasion when determining the ulcerated lesions and the type of curative procedure to be used.

1. Introduction

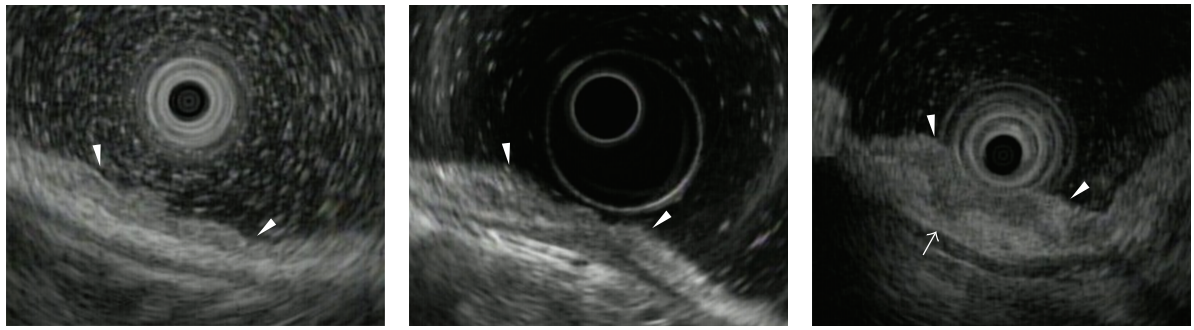
Endoscopic resection (ER) for the treatment of early gastric cancer (EGC) is currently accepted as a minimally invasive and curative treatment. According to the *Japanese Gastric Cancer Treatment Guidelines* [1], the indication for ER is a mucosal lesion, less than 2 cm in size, without ulceration. However, the guidelines have also expanded the indications for ER into the following categories that have very low possibilities of lymph node metastasis [1, 2]: (1) differentiated, mucosal cancer lesions, larger than 2 cm, without ulcerative findings [UL(−)]; (2) differentiated, mucosal cancer lesions ≤3 cm in size, with ulcerative findings [UL(+)]; (3) undifferentiated, mucosal cancer lesions ≤2 cm, UL(−); (4) differentiated lesions ≤3 cm in size, with submucosal invasion of less than 500 μm (sm1). Therefore, accurate determination of the depth of gastric cancer invasion is increasingly important to the determination of the therapeutic strategy.

Endoscopic ultrasonography (EUS) is one of the diagnostic methods for determining the depth of gastric cancer invasion. In this study, EUS was evaluated for its utility in determining the depth of gastric cancer invasion, and for its necessity in determining therapeutic strategy.

2. Materials and Methods

Pretreatment EUS was performed on 406 EGCs with histologically proven mucosal and submucosal cancer lesions between January 2006 and December 2009 at Kyoto Second Red Cross Hospital (Kyoto, Japan). Endoscopic mucosal resection (EMR) was performed on 18 lesions; endoscopic submucosal dissection (ESD) was performed on 202; 186 lesions were treated surgically. The results of these treatments were retrospectively reviewed.

Based on the classification system of the Japanese Gastric Cancer Association [3], the locations of the stomach lesions were divided into the upper, middle, and lower thirds of the stomach; each lesion was classified as either differentiated or undifferentiated, based on a histological assessment. The macroscopic features of the lesions were diagnosed by endoscopic findings and were classified as elevated type (0-I and 0-IIa), UL(−) type (0-IIb and 0-IIc without ulcerative



(a) (b) (c)

Figure 1: Endoscopic ultrasonography images of early gastric cancer. (a) EUS-M/SM1, type 0-IIc: there is no destruction in the first and second layers. The third layer looks normal. (b) EUS-M/SM1, type 0-IIc + III: the third layer shows smooth tapering and convergence. (c) EUS-SM2, type 0-IIa: a hypoechoic tumor shows the submucosal invasion. (white arrow).

Table 1: Macroscopic classification of early gastric cancers [3].

Type 0-I (protruding)	Polypoid tumors
Type 0-IIa (superficial elevated)	Slightly elevated tumors
Type 0-IIb (superficial flat)	Tumors without elevation or depression
Type 0-IIc (superficial depressed)	Slightly depressed tumors
Type 0-III (excavated)	Tumors with deep depression

findings), and UL(+) type (0-IIc with ulcerative findings, and 0-III) according to the classifications described in Table 1 and based on whether or not they were ulcerated.

The depth of cancerous invasion was histologically classified as follows: lesion confined to mucosal layer (m); <500 μm invasion into the submucosal layer (sm1); >500 μm deep invasion into the submucosal layer (sm2). The lesions were divided into the histological m/sm1 group, for which ER may be suitable, and the sm2 group, for which surgery was indicated.

EUS was used to determine the depth of cancer invasion. Two EUS devices were used: the ultrasound probe (US-probe; UM-3R, 20 MHz, Olympus, Tokyo, Japan) was selected for use with smaller or flat lesions, and the ultrasound endoscope (US-endoscope; GF-UM-2000, Olympus) was selected for use with larger or deep, depressed lesions. The EUS-determined depths of invasion were classified as lesions with no abnormality in the submucosal layer or smooth tapering of the submucosal layer (EUS-M/SM1) (Figures 1(a) and 1(b)); lesions with irregularity of the submucosal layer (EUS-SM2) (Figure 1(c)); lesions with an abrupt interruption of the submucosal or deeper layer (EUS-MP or deeper).

The location, macroscopic features, tumor size, histological type, and EUS type were analyzed to determine if they influenced the EUS diagnosis of the depth of cancer invasion. "Dr. SPSS II for Windows" was used for statistical analysis. A Chi-square test was used for the univariate analyses, and logistic regression was used for multivariate analyses.

3. Results and Discussion

3.1. Accuracy of EUS and Risk Factors for Misdiagnosis of the Depth of Cancer Invasion. Of the 406 lesions evaluated, 52 were located in the upper third of the stomach; 45, in the middle third; 309, in the lower third. Morphologically, 152 lesions were classified as the elevated type; 171, the UL(−) type; 83 as the UL(+) type. Histologically, 314 lesions were the differentiated type and 92 lesions were the undifferentiated type. The US-probe was used to evaluate 298 lesions, and the US-endoscope was used in the remaining 108 lesions.

Previous reports have indicated that depth determination accuracy, by EUS, in EGC may range from 67%–90% [4–9]. In this study, when the lesions were divided into the histological m/sm1 and sm2 categories, the overall diagnostic accuracy of EUS was 74.6% (303/406) (Table 2).

Depending on the macroscopic features, the tumor size, and the histological type, the accuracy of EUS varied widely. The accuracy also varied depending on the ultrasound instrument that was used, with the US-probe and US-endoscope having accuracies of 85.2% and 45.3%, respectively. The univariate analysis showed that the accuracy was significantly lower for the UL(+), the tumor size of larger than 2 cm, and the undifferentiated types of lesions as well as for those diagnosed with the US-endoscope (Table 3). Multivariate analysis of these 4 factors showed that the UL(+) type (OR 8.573; 95% CI 4.632–15.867), the tumor size of larger than 2 cm (OR 2.071; 95% CI 1.149–3.731), and the use of US-endoscope (OR 2.472; 95% CI 1.330–4.593) were independently associated with misdiagnosis of the depth of EGC by EUS (Table 4).

In these risk factors for misdiagnosis, the UL(+) type and the use of US-endoscope had a significantly higher probability of overestimation (Table 5).

According to previous reports, lesions with ulcerous changes [8, 10] or lesions of the depressed [6, 11] or undifferentiated types [6, 9] or tumor size of larger than 3 cm [9] or lesions located in the upper third of the stomach [5, 11] were associated with incorrect depth determinations by EUS. These reported results are similar to our study.

Table 2: Accuracy of cancer invasion depth as determined by endoscopic ultrasound.

Histology	EUS				
	M/SM1	SM2	MP deeper	Total	Accuracy
m/sm1	**260**	56	11	327	79.5% (260/327)
sm2	20	**43**	16	79	54.4% (43/79)
PPV	92.8% (260/280)	43.4% (43/99)	—	—	

EUS: endoscopic ultrasonography; PPV: positive predictive value; M/SM1, SM2, and MP deeper are classifications of the depth of tumor invasion into the submucosa (see text for full description).

Table 3: Univariate analysis of factors affecting accuracy of determinations of the depth of cancer invasion.

	Correct (n)	Incorrect (n)	Accuracy (%)	P value	Odds ratio	95% CI (%)
Stomach location				0.802		
Upper third	40	12	76.9%		1	
Middle third	32	13	71.1%	0.514	1.354	0.54–3.37
Lower third	231	78	74.7%	0.738	1.112	0.56–2.25
Macroscopic features				**<0.001**		
Elevated type	131	21	86.1%		1	
UL(−) type	148	23	86.5%	0.924	0.969	0.51–1.83
UL(+) type	24	59	28.9%	**<0.001**	**15.33**	**7.91–29.71**
Tumor size				**<0.001**		
≤2 cm	217	36	85.7%		1	
>2 cm, ≤3 cm	52	32	61.9%	**<0.001**	**3.709**	**2.11–6.52**
>3 cm	34	35	49.2%	**<0.001**	**6.205**	**3.44–11.18**
Histology						
Differentiated	254	60	80.8%		1	
Undifferentiated	49	43	53.2%	**<0.001**	**3.715**	**2.26–6.10**
EUS type						
US-probe	254	44	85.2%		1	
US-endoscope	49	59	45.3%	**<0.001**	**6.951**	**4.23–11.41**

UL(+): ulcerated; UL(−): nonulcerated; EUS: endoscopic ultrasonography; US: ultrasound; ER: endoscopic resection.

Table 4: Multivariate analysis of factors affecting accuracy of the determination of the depth of cancer invasion.

	P value	Odds ratio	95% CI (%)
UL(+) type	**P < 0.001**	**8.573**	**4.632–15.867**
Tumor size >2 cm	**P = 0.015**	**2.071**	**1.149–3.731**
Undifferentiated	$P = 0.108$	1.664	0.895–3.093
US-endoscope	**P = 0.004**	**2.472**	**1.330–4.593**

Another report showed that the accuracy of US-probe was significantly higher than that of US-endoscope [4]. In our study, one of the risk factors for misdiagnosis of the depth of EGC was also associated with the use of the US-endoscope. The US-probe is particularly suitable for the determination of the depth of EGC because the frequency of the US-probe is higher than that of the US-endoscope, allowing the US-probe to have a higher resolution within the shallower layers. However, the selection of the type of ultrasound instrument used to make the depth determination was based on the endoscopic appearance of the tumor, such as its size, height of elevation, and depth of depression. The US-probe was used for smaller lesions or lesions with shallower depressions that were easy to diagnose as mucosal cancer, whereas the US-endoscope was used for lesions with a deep ulceration that were difficult to distinguish between a benign fibrosis and a cancerous invasion. This selection bias could explain why the accuracy of the US-probe was higher than that of the US-endoscope.

3.2. Therapeutic Strategy of EGC. In this study, most of the EUS-M/SM1 group lesions belonged to the histological m/sm1 category (Table 2: 92.8%, 260/280). Therefore, ER is appropriate for lesions determined to be EUS-M/SM1. On the other hand, the EUS-SM2 group included many histological m/sm1 lesions (Table 2: 56.5%, 56/99) for which ER, especially ESD, might be a curative treatment. However, most of these lesions have ulcerative changes (Table 6) which are predictive of difficult dissections during ESD. Therefore, although ESD might be considered for lesions determined to be EUS-SM2 or deeper, surgery is also an appropriate treatment for these lesions.

Table 5: The tendency of misdiagnosis in the risk factors for misdiagnosis of the depth of cancer invasion.

	Overestimation (n)	Underestimation (n)	P value	Odds ratio	95% CI (%)
Macroscopic features					
UL(+) type	56	3	**<0.001**	**11.753**	**3.17–43.57**
Non-UL(+) type	27	17			
Tumor size					
>2 cm	56	11	0.294	1.697	0.62–4.58
≤2 cm	27	9			
EUS type					
US-endoscope	55	4	**<0.001**	**7.858**	**2.39–25.73**
US-probe	28	16			

Table 6: Causes of m/sm1 cancer being classified as EUS-SM2 or deeper.

	67 lesions
Wrong evaluation of ulcerative change	44 (65.6%)
Presence of cystic change beneath the lesion	2 (3.0%)
Unknown	21 (31.3%)

m/sm1 refers to histologically determined depths and EUS-SM2 or deeper refers to depths of EGC invasion determined by EUS (see text for full description).

4. Conclusions

EUS is a useful tool for determining the therapeutic strategy for EGCs. However, EUS is not the best method to correctly determine the depth of the EGC invasion, in the cases of UL(+) lesions or tumor size of larger than 2 cm. Special attention should be paid not to overestimate the depth of cancer invasion when determining the UL(+) lesions and the type of curative procedure to be used. ER should be performed for lesions classified as EUS-M/SM1, whereas surgery is an appropriate treatment for EUS-SM2 lesions.

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Research Article

Comparison of Diagnostic Accuracies of Various Endoscopic Examination Techniques for Evaluating the Invasion Depth of Colorectal Tumors

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This study was designed to assess the clinical value of magnifying endoscopy combined with EUS for estimating the invasion depth of colorectal tumors. We studied 168 colorectal adenomas and carcinomas that were sequentially examined by conventional endoscopy followed by magnifying endoscopy and EUS in the same session to evaluate invasion depth. Endoscopic images obtained by each technique were reassessed by 3 endoscopists to determine whether endoscopic resection (adenoma, mucosal cancer, or submucosal cancer with slight invasion) or colectomy (submucosal cancer with massive invasion or advanced cancer) was indicated. The accuracy of differential diagnosis was compared among the examination techniques. The rate of correct differential diagnosis according to endoscopic examination technique was similar. The proportion of lesions that were difficult to diagnose was significantly higher for EUS (15.5%) than for conventional endoscopy and magnifying endoscopy. Among lesions that could be diagnosed, the rate of correct differential diagnosis was the highest for EUS (89.4%), but did not significantly differ among three endoscopic examination techniques. When it is difficult to evaluate the invasion depth of colorectal tumors on conventional endoscopy alone, the combined use of different examination techniques such as EUS may enhance diagnostic accuracy in some lesions.

1. Introduction

Endoscopic examinations have an important role in the differential diagnosis of benign and malignant colorectal tumors (adenomas and carcinomas), as well as in accurate estimation of the depth of invasion and selection of the treatment. In particular, "early" colorectal cancer with invasion confined to the mucosa or the submucosa is a borderline lesion for the selection of either endoscopic resection or colectomy. It is thus essential to accurately evaluate the depth of tumor invasion on the basis of endoscopic findings.

The invasion depth of colorectal cancer is basically estimated on conventional endoscopy combined with chromoendoscopy, as needed. If the depth of tumor invasion is difficult to estimate on conventional endoscopy alone, however, additional examinations such as magnifying endoscopy to assess pit patterns and endoscopic ultrasonography (EUS) are performed. However, few studies have examined the extent to which these detailed examination techniques improve the accuracy of estimating the depth of invasion. We studied colorectal tumors that were sequentially examined by conventional endoscopy followed by EUS and magnifying endoscopy in the same session to evaluate invasion depth. The accuracy of evaluating the depth of tumor invasion was then compared among these endoscopic examination techniques to determine whether the additional use of in-depth procedures improved the accuracy of estimating the depth of tumor invasion, thereby facilitating the selection of treatment.

2. Methods

2.1. Patients. From January 2002 through April 2007, we sequentially examined 168 colorectal tumors (166

patients) by conventional endoscopy, followed by magnifying endoscopy to evaluate the pit pattern, and EUS to estimate the depth of tumor invasion at the request of the patients' attending physicians. After endoscopic resection or surgical operation, the invasion depth of all lesions was determined histopathologically. Lesions that were difficult to assess on conventional endoscopy because of factors such as inadequate bowel preparation and high-grade intestinal peristalsis were excluded.

The invasion depth of the colorectal tumors was classified according to the Japanese classification of colorectal carcinoma, issued by the Japanese Society for Cancer of the Colon and Rectum [1]. There were 44 adenomas, 66 carcinomas with invasion confined to the mucosa (mucosal cancer), and 54 carcinomas with invasion of the submucosa (submucosal cancer) (Table 1). Among submucosal cancers, 15 lesions had a submucosal invasion depth of less than 1000 μm (slight invasion), and 39 had an invasion depth of 1000 μm or greater (massive invasion). The most common lesion location was the rectum (74 lesions), followed by the sigmoid colon, transverse colon, and ascending colon. The macroscopic type of the tumors was classified according to the Paris endoscopic classification [2] and system reported by Kudo et al. [3]. Laterally spreading tumors (LST) were most common (131 lesions, 78%) and included 57 granular-type LST and 74 nongranular-type LST. About half of all tumors (82 lesions, 49%) had a diameter of 20 mm or greater, and the mean tumor diameter was 24.1 ± 14.2 mm. As for treatment, 55 lesions were treated by endoscopic resection, 85 by colectomy, and 28 by transanal local resection or transanal endoscopic microsurgery. Colectomy was additionally performed to treat 2 lesions with massive submucosal invasion that initially underwent endoscopic resection.

Table 1: Clinical characteristics of the study subjects.

(1) Histology	
Adenoma	44 (26%)
M ca†	66 (39%)
SM-S ca‡	15 (9%)
SM-M ca¶	39 (23%)
MP ca# or over	4 (3%)
(2) Location	
Rectum	74 (44%)
Sigmoid	34 (20%)
Descending	10 (6%)
Transverse	21 (13%)
Ascending	20 (12%)
Cecum	9 (5%)
(3) Morphology	
Protruded	20 (12%)
Superficial	13 (8%)
LST* granular	57 (34%)
LST* nongranular	74 (44%)
Others	4 (2%)
(4) Size (mm)	
~9	14 (8%)
10~19	55 (33%)
20~	82 (49%)
unknown	17 (10%)

† M ca: mucosal cancer, ‡SM-S ca: submucosal slight invaded cancer.
¶SM-M ca: submucosal massive invaded cancer.
#MP ca: muscularis propria invaded cancer, *LST: laterally spreading tumor.

2.2. Colonoscopic Examination. For bowel preparation before colonoscopy, oral intestinal lavage (polyethylene glycol) was mainly performed. As premedication, scopolamine butylbromide (10 mg) or glucagon (1 mg) was given intramuscularly to suppress intestinal peristalsis. We used colonoscopy with magnifying function (PCF-Q240ZI or CF-2TQ240ZI, Olympus, Tokyo, Japan). All colonoscopic examinations, including magnifying endoscopy and EUS, were performed by a single endoscopist who had at least 20 years of experience in colonoscopy. The number of years of experience in detailed evaluations was 17 for EUS and 7 for magnifying endoscopy. During conventional endoscopy, most lesions were also examined by chromoendoscopy, performed by spraying the mucosa with 0.2% indigo carmine dye. Before colonoscopy, patients were given a detailed explanation of the examination objectives, methods, and possible complications. Written-informed consent for colonoscopic examination was obtained from all patients.

2.3. Methods for EUS. After the completion of conventional endoscopy, the intestine near the tumor was filled with deaerated water that had been warmed to about body temperature, and EUS was performed to evaluate the depth of invasion. An ultrasound probe with a frequency of 20 MHz (UM-3R; Olympus, Tokyo, Japan) or a 3-dimensional ultrasound probe with a frequency of 20 MHz (UM DP20-25R; Olympus, Tokyo, Japan) was used.

On EUS, the normal wall of the colon is basically visualized as a 5-layer structure. From the luminal side, the hyperechoic first layer and hypoechoic second layer correspond to the mucosa, the hyperechoic third layer to the submucosa, the hypoechoic fourth layer to the muscularis propria, and the hyperechoic fifth layer to the subserosa or serosa (adventitia) [4]. The invasion depth of the colorectal carcinomas and adenomas on EUS was evaluated to be the deepest layer that showed narrowing or rupture of the wall structure due to the tumor. The resolution of currently available EUS devices precludes adequate visualization of the thin muscularis mucosae of the colonic wall and accurate measurement of the depth of submucosal invasion by carcinomas [5]. Submucosal carcinomas were classified into two subgroups on the basis of the degree of submucosal invasion on EUS. If the superior margin of the third layer was slightly narrowed by the tumor, submucosal cancer with slight invasion was diagnosed. If the third layer was severely narrowed or ruptured, but the fourth layer remained intact, submucosal cancer with massive invasion was diagnosed.

2.4. Magnifying Endoscopy. After the completion of conventional endoscopy and EUS, magnifying colonoscopic examination was performed to evaluate pit patterns. The tumor was washed with water to remove any mucus, sprayed with 0.2% indigo carmine dye, and examined by magnifying endoscopy at a magnification of 80 to 100 times to evaluate pit patterns. If pit patterns could not be accurately evaluated on indigo carmine staining alone, 0.05% crystal violet stain was concurrently applied. Pit patterns of the colorectal tumors were evaluated according to Kudo's classification [6]. Type V_I pit patterns were further classified as mildly irregular or severely irregular on the basis of structural and arrangement irregularities of pits, pit density, and stromal staining between pits. On the basis of the results of previous studies examining the relation between pit patterns and tumor invasion depth [6–10], tumors with type IIIs, III_L, IV, or V_I mildly irregular pit patterns were considered to be indicated for endoscopic resection (adenoma, mucosal cancer, and submucosal cancer with slight invasion). Tumors with type V_I severely irregular or type V_N pit patterns were considered to be indicated for colectomy (submucosal cancer with massive invasion and advanced cancer).

2.5. Evaluation of Invasion Depth. Three endoscopists who had no information on the histopathological findings of tumors reassessed the invasion depth of the colorectal tumors. All 3 endoscopists had at least 10 years of experience in colonoscopy and at least 5 years of experience in EUS and magnifying endoscopy. The number of years of experience did not differ appreciably according to examination technique among the 3 endoscopists. Conventional endoscopic, magnifying endoscopic, and EUS images were reviewed for lesions presented in random order. The lesions were divided into 2 groups on the basis of the estimated depth of invasion: lesions for which endoscopic resection was indicated (adenoma, mucosal cancer, and submucosal cancer with slight invasion) and those for which colectomy was indicated (submucosal cancer with massive invasion and advanced cancer). If the evaluation made by each endoscopist was consistent with the histopathological diagnosis for the resected specimen, the endoscopic diagnosis was classified as a correct diagnosis. If the evaluation did not agree with the histopathological diagnosis, the endoscopic diagnosis was classified as a misdiagnosis. If the invasion depth was difficult to evaluate on the basis of the presented endoscopic images, the endoscopic diagnosis was classified as a misdiagnosis. If at least 2 endoscopists made the same diagnosis, that diagnosis was considered the final diagnosis for the lesion. The accuracy of differential diagnosis and the frequency of difficult-to-diagnose lesions were retrospectively compared among conventional endoscopy, magnifying endoscopy, and EUS. For lesions that were considered by all 3 endoscopists to have an assessable invasion depth, the diagnostic accuracy was compared among the examination techniques. Our institutional review board approved the study protocol.

2.6. Statistical Analysis. Numerical data are expressed as means ± standard deviation. The chi-square test and Fisher's exact test were used to compare frequencies among groups. *P* values of less than 0.05 were considered to indicate statistical significance. StatView software (version 5.0 for Windows, SAS Institute Inc., Cary, NC) was used for statistical analysis.

3. Results

3.1. Accuracy of Differential Diagnosis according to Examination Technique. The rate of correctly diagnosing lesions for which endoscopic resection was indicated (i.e., adenoma, mucosal cancer, and submucosal cancer with slight invasion) was 83.2% (104/125 lesions) on conventional endoscopy, 83.2% (104/125) on magnifying endoscopy, and 81.6% (102/125) on EUS. The rate of correctly diagnosing lesions for which colectomy was indicated (i.e., submucosal cancer with massive invasion and advanced cancer) was 76.7% (33/43 lesions) on conventional endoscopy, 79.1% (34/43) on magnifying endoscopy, and 79.1% (34/43) on EUS. The overall accuracy of differential diagnosis was similar for conventional endoscopy (81.5%), magnifying endoscopy (82.1%), and EUS (81.0%) (Table 2).

3.2. Frequency of Difficult-to-Diagnose Lesions. The percentage of lesions that were evaluated by at least 1 of the 3 endoscopists to be difficult to diagnose on endoscopic images was 3.0% for conventional endoscopy, 4.8% for magnifying endoscopy, and 15.5% for EUS (Table 3). The frequency of difficult-to-diagnose lesions was significantly higher for EUS than for conventional endoscopy and magnifying endoscopy.

3.3. Comparison of Diagnostic Accuracy among Lesions Able to Be Diagnosed. The number of lesions for which the invasion depth was considered assessable by all 3 endoscopists was 163 for conventional endoscopy, 160 for magnifying endoscopy, and 142 for EUS. The rate of correct diagnosis among lesions with assessable endoscopic images was highest for EUS (89.4%), followed by magnifying endoscopy (85.6%) and conventional endoscopy (82.8%). The diagnostic accuracy of EUS was the highest, but did not significantly differ among three endoscopic examination techniques (Table 4).

3.4. Lesions for Which Magnifying Endoscopy and EUS Were Useful for Diagnosis. Endoscopic examination of a nongranular-type LST after spraying the tumor with 0.2% indigo carmine dye showed that the extensibility of the tumor on insufflation was relatively good, and all 3 endoscopists considered endoscopic resection to be indicated for treatment (Figure 1(a)). However, magnifying endoscopy after the application of 0.05% crystal violet stain showed pits with an amorphous structure (type V_N pit pattern) in part of the tumor (Figure 1(b)). On EUS, the third layer of the wall was severely narrowed in part of the tumor (Figure 1(c)). On the basis of the magnifying endoscopic and EUS findings, all 3 endoscopists judged that colectomy was indicated for treatment. Histopathological examination of the surgically resected specimen revealed a well-differentiated tubular adenocarcinoma invading the middle layer of the submucosa (Figures 1(d) and 1(e)). The vertical depth of invasion in

Table 2: Comparison of diagnostic accuracy among 3 different endoscopic techniques (conventional endoscopy, magnifying endoscopy, and EUS).

	Correct	Error	Accuracy
Conventional endoscopy	137	31	81.5%[A]
Magnifying endoscopy	138	30	82.1%[B]
EUS	136	32	81.0%[C]

$P = 0.8875$ (A versus B), $P = 0.7785$ (B versus C), $P = 0.8888$ (A versus C).

Table 3: Comparison of the frequencies of lesions with endoscopic images those were difficult to diagnosis among 3 different endoscopic techniques (conventional endoscopy, magnifying endoscopy, and EUS).

	Inadequate imaging		Frequency of inadequate imaging lesions
	Yes	No	
Conventional endoscopy	5	163	3.0%[A]
Magnifying endoscopy	8	160	4.8%[B]
EUS	26	142	15.5%[C]

$P = 0.3961$ (A versus B), $P = 0.0011$ (B versus C), $P < 0.0001$ (A versus C).

Table 4: Comparison of diagnostic accuracy among 3 different endoscopic techniques after excluding lesions with inadequate images.

	Correct	Error	Accuracy
Conventional endoscopy	135	28	82.8%[A]
Magnifying endoscopy	137	23	85.6%[B]
EUS	127	15	89.4%[C]

$P = 0.4897$ (A versus B), $P = 0.3188$ (B versus C), $P = 0.0978$ (A versus C).

the submucosa was 1850 μm. There was no evidence of lymphovascular invasion or lymph-node metastasis.

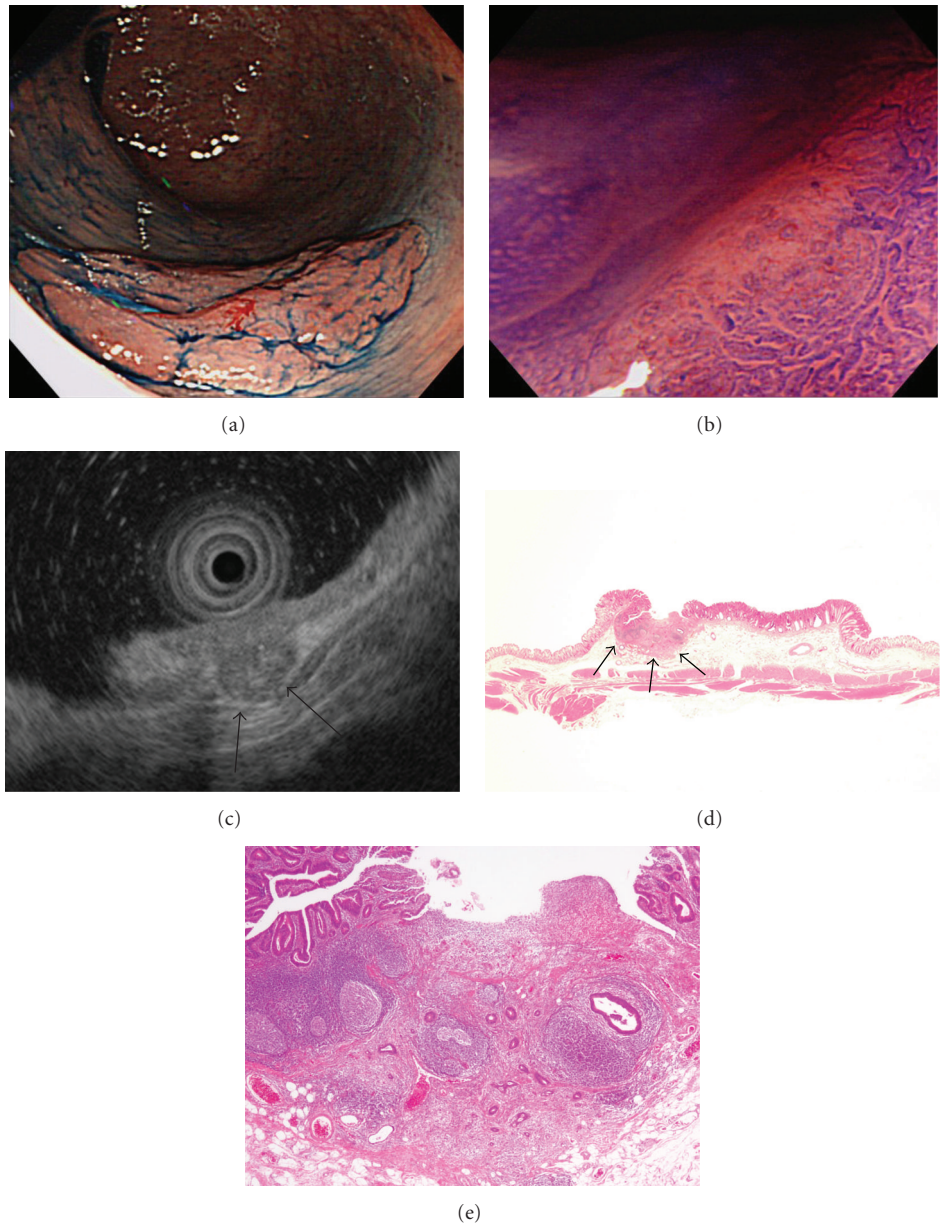
4. Discussion

Among colorectal cancers, mucosal cancer can be resected endoscopically because there is no risk of metastasis. In particular, the recent development of techniques such as endoscopic submucosal dissection and endoscopic piecemeal mucosal resection has enabled the endoscopic resection of even large lesions [11–13]. Submucosal cancers have a risk of metastases to lymph nodes and other organs [14–17]. However, tumors with slight submucosal invasion depth of less than 1000 μm are very rarely associated with metastasis; endoscopic resection is thus indicated for the treatment of such lesions [14]. In contrast, tumors with massive submucosal invasion of 1000 μm or deeper carry a risk of metastasis and must therefore be treated by colectomy with lymph-node dissection. Early colorectal cancer should therefore be differentially diagnosed according to the depth of invasion as either mucosal cancer or submucosal cancer with slight invasion or as submucosal cancer with massive invasion. The most appropriate treatment method (endoscopic resection or colectomy) should then be selected.

The invasion depth of colorectal cancer is generally evaluated on endoscopic examination. The basic procedure is conventional endoscopy. The depth of invasion is estimated on the basis of tumor diameter and macroscopic findings, as well as other characteristics of the tumor surface, such as a cracked or distended appearance, friability, spread, and fold convergence [18, 19]. As for the macroscopic findings, the frequency of submucosal cancer is higher among superficial-type tumors than elevated-type tumors [18]. Saitoh et al. [19] reported that a distended appearance, a deep depression, an uneven depressed surface, and convergent folds are important endoscopic findings that suggest a depressed-type, early colorectal cancer deeply invading the submucosa. They also reported that mucosal cancer or submucosal cancer with slight invasion could be differentiated from submucosal cancer with massive invasion on conventional endoscopy combined with chromoendoscopy for more than 90% of lesions. However, if the diagnosis is equivocal on conventional endoscopy, a number of additional examinations have been recommended, such as the evaluation of pit pattern of the tumor surface on magnifying endoscopy and the assessment of EUS findings, vascular patterns on narrow band imaging [20, 21], and non-lifting signs before endoscopic mucosal resection [22].

The evaluation of pit patterns on magnifying endoscopy is useful for differentiating neoplastic from nonneoplastic colorectal polyps [23, 24], as well as for estimating the invasion depth of early colorectal cancers [7–10]. Pit patterns of colorectal polyps on magnifying endoscopy are most often evaluated according to the classification of Kudo et al. [6]. Pit patterns of types I and II are associated with a high frequency of nonneoplastic lesions; type III_S, III_L, and IV with adenomatous polyps; and type V with cancer. Type V pit patterns can be further classified into type V_I and type V_N. Intype V_N, the pit structure has been lost and is amorphous, suggesting submucosal cancer with massive invasion [6]. Type V_I is subclassified into type V_I with mild irregularity and type V_I with severe irregularity on the basis of findings such as narrowed pit lumens, irregular margins,unclear outlines, and decreased or absence of stromal staining between pits [10]. The former suggests mucosal cancer or submucosal cancer with slight invasion, whereas the latter suggests submucosal cancer with massive invasion [7–10]. In our study, type V_I pit patterns were subdivided into type V_I with mild irregularity and type V_I with severe irregularity. The presented tumors were then reevaluated to decide whether endoscopic resection (adenoma, mucosal cancer, or submucosal cancer with slight submucosal invasion) or colectomy (submucosal cancer with massive invasion or advanced cancer) was indicated.

Many studies have reported that EUS is useful for estimating the invasion depth of colorectal cancer [25–30]. In particular, the advent of ultrasound probes able to be inserted through the forceps channel of an endoscope has allowed lesions to be evaluated by EUS after conventional endoscopy, greatly simplifying the endoscopic procedure [25]. We previously studied the diagnostic usefulness of EUS with respect to the selection of treatment for early colorectal cancer. The rate of correctly differentiating mucosal cancer



(a) (b) (c) (d) (e)

Figure 1: (a) Colonoscopic images after spraying with 0.2% indigo carmine dye, showing a nongranular LST in the rectum. The surface showed mild redness. Extensibility of the tumor on insufflation was relatively good. (b) Magnifying endoscopic images after the application of 0.05% crystal violet stain, showing a type V_N pit pattern characterized by an amorphous structure of part of the tumor. (c) EUS images, showing severe narrowing of the third layer in part of the tumor (arrow). Cancer with deep submucosal invasion was diagnosed. (d) and (e) Histopathological findings of the surgically resected specimen. (d) The longest diameter of the tumor was 20 mm. Although most of the tumor was confined to the mucosa, part of the lesion invaded the middle layer of the submucosa (arrow). The diagnosis was a well-differentiated tubular adenocarcinoma. (e) The intramucosal part of the tumor had become detached at the site of submucosal invasion.

and submucosal cancer with slight invasion from submucosal cancer with massive invasion was 90%, indicating good diagnostic accuracy [26].

Pit patterns on magnifying endoscopy and EUS findings have been confirmed to be useful for evaluating the invasion depth of colorectal tumors. However, few studies have compared the diagnostic accuracy of conventional endoscopy, magnifying endoscopy, and EUS in large numbers of lesions. Some studies have reported that the diagnostic accuracy of EUS is superior to that of magnifying endoscopy [31, 32], whereas others have shown that the diagnostic accuracy is similar [33]. Consensus has thus not been reached. One prospective study comparing magnifying endoscopy with EUS in patients with submucosal cancer [32] showed that EUS has a significantly higher diagnostic accuracy than magnifying endoscopy.

The present study compared the diagnostic accuracies of conventional endoscopy, magnifying endoscopy, and EUS

by reviewing endoscopic images to estimate the invasion depth of mainly early colorectal tumors and thereby select the treatment method. Because the macroscopic appearance and disease stage of tumors can differ on endoscopic examinations performed at different times, we only studied lesions that were sequentially examined by conventional endoscopy, magnifying endoscopy, and EUS in the same session. Moreover, to ensure that invasion depth was objectively evaluated, 3 endoscopists who were blinded to the histopathological diagnosis of the tumors reviewed the endoscopic images.

When only lesions with interpretable endoscopic images as assessed by all 3 endoscopists were evaluated, the diagnostic accuracy of EUS was the highest, but did not differ from that of magnifying endoscopy and tended to be higher than that of conventional endoscopy ($P = 0.0978$). Among gastrointestinal endoscopic examinations, the depth of invasion is estimated on the basis of changes of the tumor surface on conventional endoscopy and magnifying endoscopy. In contrast, with EUS the entire lesion can be visualized in vertical slices, allowing the invasion depth to be objectively evaluated on the basis of changes in wall structure.

However, the diagnosis of colorectal tumors on EUS has several limitations. Histologically, the presence of inflammation or fibrosis around the tumor invasion front may lead to overestimation of the depth of invasion [34]. In addition, clear ultrasonographic images are occasionally precluded by factors such as the macroscopic type and location of tumors. In our study, although examinations were performed by an endoscopist who had more than 15 years of experience in EUS of the colorectum, about 15% of lesions were difficult to diagnose on EUS, which was significantly higher than percentages of difficult-to-diagnose lesions on conventional endoscopy and magnifying endoscopy. Matsunaga et al. [35] reported that 12% of early colorectal cancers were difficult to clearly visualize on EUS. Colorectal tumors arising in the colonic flexure, on folds, or near the anus are often difficult to visualize. Inadequate filling of the colon with deaerated water caused by intestinal peristalsis may also adversely affect the visualization of tumors. We previously reported that many lesions difficult to visualize on EUS are located in the proximal colon, associated with marked haustral thickening and frequent intestinal peristalsis [26]. Devices and examination techniques for EUS should therefore be further refined. Even on magnifying endoscopy, an appreciable number of lesions were difficult to diagnose because of factors such as mucus adhering to the tumor surface or bleeding.

This study compared the accuracy of estimating the invasion depth of mainly colorectal LST among 3 different endoscopic techniques. The invasion depth was correctly diagnosed on conventional endoscopy combined with chromoendoscopy for more than 80% of lesions. The relatively high diagnostic accuracy of conventional endoscopy may be attributed to the following factors: a high proportion of lesions were adenomas and mucosal cancers, for which it is relatively easy to estimate the invasion depth; the endoscopists who performed the examinations and estimated the invasion depth were well experienced. Because many conventional endoscopic findings used to evaluate invasion depth are subjective, diagnostic accuracy may largely depend on the knowledge and experience of the endoscopist. A previous study has reported that the accuracy of estimating the invasion depth of colorectal cancer on conventional endoscopy is negatively affected if the examination is performed by an inexperienced endoscopist [35].

Among in-depth evaluations of colorectal tumors, the assessment of pit patterns on magnifying endoscopy, especially the classification of type V_I pit patterns [10], is often difficult for inexperienced physicians. The most important endoscopic findings at the time of evaluation remain controversial among specialists. Another problem is the high proportion of difficult-to-diagnosis lesions, even on EUS. However, when the depth of tumor invasion is difficult to estimate on conventional endoscopy, the results of our study suggest that the concurrent use of in-depth examinations such as EUS may be useful for diagnosis in some lesions. In our study, the years of experience of the endoscopist who performed all colonoscopic examinations was longer for EUS than for magnifying endoscopy. Such differences in the number of years of experience may have influenced the diagnostic outcomes of these examination techniques. Further prospective multicenter studies may be needed to compare the diagnostic accuracies of various endoscopic techniques and to establish new strategies for the endoscopic diagnosis of colorectal cancer.

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Research Article

Endoscopic Ultrasound-Guided Radiofrequency Ablation (EUS-RFA) of the Pancreas in a Porcine Model

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Backgrounds. Limited effective palliative treatments exist for pancreatic cancer which includes surgery or chemotherapy. Radiofrequency ablation (RFA) uses high frequency alternating current to ablate diseased tissue and has been used to treat various tumors. In this study, we evaluated a prototype probe adjusted to the EUS-needle to perform EUS-RFA to permit coagulative necrosis in the pancreas. *Methods*. Five Yucatan pigs underwent EUS-guided radiofrequency ablation of the head of their pancreas. Using an EUS-needle, RFA was applied with 6 mm and then 10 mm of the probe exposed at specific wattage for preset durations. *Results*. Only one pig showed moderate levels of pancreatitis (20% proximal pancreatitis). The other animals showed much lower areas of tissue damage. In 3 of the 5 pigs, the proximal pancreas showed greater levels of tissue injury than the distal pancreas, consistent with the proximity of the tissue to the procedure site. In 1 pig, both proximal and distal pancreas showed minimal pancreatitis (1%). There was minimal evidence of fat necrosis in intra-pancreatic and/or extra-pancreatic adipose tissue. *Conclusion*. EUS-guided RFA of the pancreatic head with the monopolar probe through a 19-gauge needle was well tolerated in 5 Yucatan pigs and with minimal amount of pancreatitis.

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the USA [1]. The 5-year survival rate is only 3% with a median survival of less than 6 months [2]. Conventional treatment approaches, such as surgery, radiation, chemotherapy, or combinations of these, have little impact on the course of this aggressive cancer [3]. Within months of completing chemoradiation, patients frequently have evidence of local tumor progression (biliary or gastric outlet obstruction) or new metastatic disease [3]. Radiofrequency (RF) ablation has been widely used in oncology but not in the pancreas because of its high operative risks [4]. Recent studies have shown the feasibility of monopolar RF ablation in patients with stage III pancreatic cancer in open, percutaneous, or laparoscopic setting [5, 6]. Ablating with endoscopic ultrasound (EUS) guidance allows real-time imaging into the deeply located pancreas [4]. Radiofrequency ablation (RFA) works by emitting energy that uses heat to produce coagulative necrosis in the surrounding tissue [7, 8]. There is a growing interest and need of RFA of the pancreas [4] and it appears that RFA in unresectable pancreatic carcinoma is feasible with acceptable mortality but high morbidity [5, 6, 8–11]. The objective of the study was to report safety and efficacy of EUS-guided transduodenal RF ablation of porcine pancreas using a new well-shaped monopolar probe (Habib EUS RFA, EMcision Ltd., London, UK) that fits better into the EUS needle. The improved needle design should hypothetically permit coagulative necrosis of larger areas of the pancreas, while still minimizing the risk of damage to the intestinal mucosa.

2. Procedure

Five Yucatan pigs (30–35 kgs) were acclimated in the vivarium for 3 days after arrival. On day 4, the procedure was effected. Animals were premedicated intramuscularly

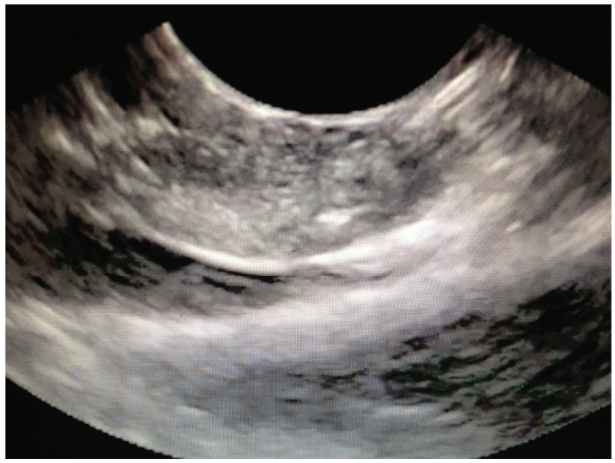


Figure 1: Endoscopic Ultrasound view of the EUS-RFA probe inserted into the porcine pancreas.

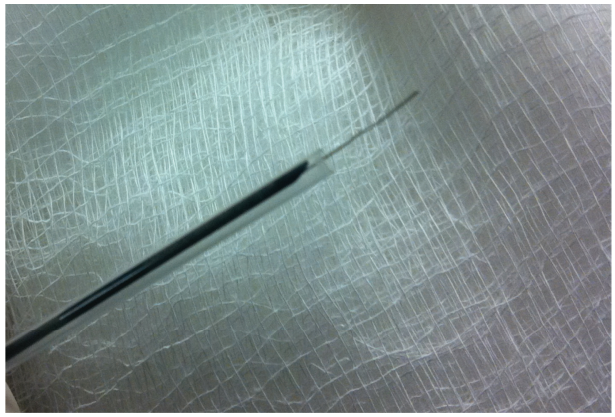


Figure 2: Habib EUS RFA probe.

with atropine sulphate (0.04 mg/kg) and anesthesia was induced with intramuscular Telazol/Xylazine 4–6/2 mg/kg. The animals were placed in recumbence on their left side on a fluoroscopy table. Vital signs (heart rate, respiratory rate, and anesthetic depth) were continuously monitored during the procedure. Prophylactic antibiotic Enrofloxacin 2.5 mg/kg was administered intramuscularly before the procedure, after anesthesia.

The porcine pancreatic tissue was ablated with RFA after placing an EUS guided 19 gauge Wilson Cook needle into the pancreas in a transduodenal approach. The echoendoscope (Linear Endoscope (EG-3870UTK) 3.8 mm, Pentax Montvale, NJ, USA) was advanced through the mouth to the duodenal bulb and observed by ultrasonography of the pancreas. A 19-gauge needle (Wilson Cook, Winston-Salem, NC, USA) was inserted through the working channel of the endoscope into the pancreas (Figure 1). The needle was used to puncture the pancreas and the stylet was removed. The pilot RFA probe connected to RITA (Electrosurgical RF Generator) was then advanced through the needle into the pancreas. The pilot Habib EUS RFA probe (EMcision LTd., London, UK) is a 1 Fr wire (0.33 mm, 0.013″) and has a working length of 190 cm (Figure 2).

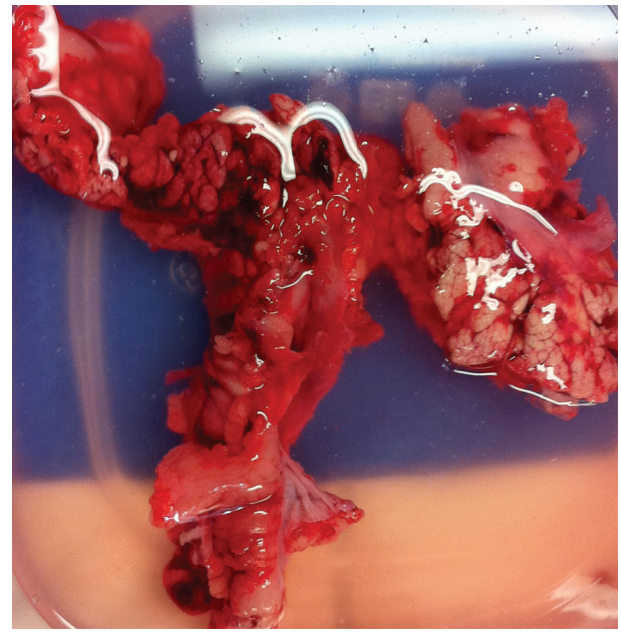


Figure 3: Excised porcine pancreas after euthanization.

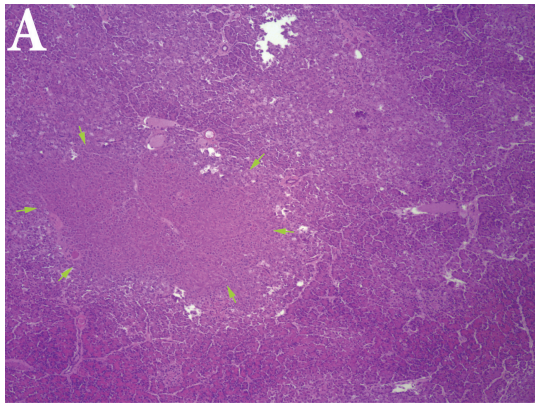
The RFA probe was applied with 6 mm of the probe exposed at 4 watts for 300 seconds (5 mins), 5 watts for 54 seconds (0.9 mins), and 6 watts for 12 seconds (0.2 mins). Then with 10 mm of the probe exposed in the pancreas, RFA was affected at 4 watts for 258 seconds (4.3 mins), 5 watts for 84 seconds (1.4 mins), and 6 watts for 48 seconds (0.8 mins). The wattage and exposure time was predetermined based on in vitro testing with a generator.

After procedure, yohimbe 0.3 mg/kg was given intravenously to hasten recovery from anesthesia and a fentanyl patch was given for analgesia.

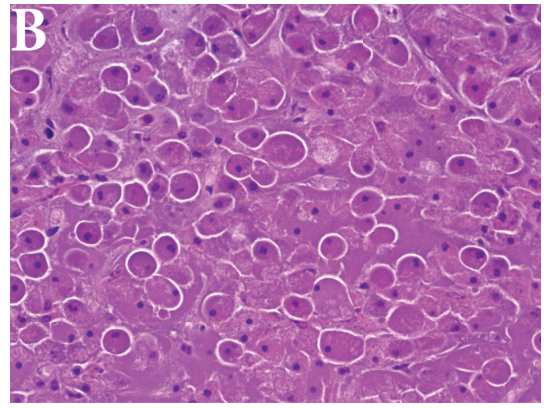
Three days after procedure, blood was drawn to evaluate total bilirubin, alkaline phosphatase, cell blood count, and amylase. On the 6th day after procedure, the pigs were euthanized. The pancreas of the pigs were immediately excised surgically for gross examination of damage, tissue response, and histological analysis (Figure 3).

3. Pathologic Examination

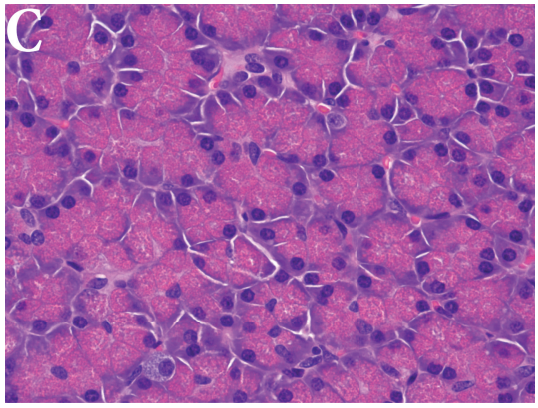
3.1. Histopathological Assessment. Pancreata were excised and fixed in neutral buffered formalin. The organs were serially sectioned at 3 mm intervals by a dedicated GI pathologist blinded to the procedure performed. Cross-sections were taken from the proximal pancreas (2-3 cm from the ampulla) and from the distal pancreas (2-3 cm from the tail end) by the pathologist. The sections were subjected to routine processing and paraffin embedding. Four-micron histologic sections were stained with hematoxylin and eosin (H&E). The presence of acute pancreatitis (cell necrosis) was assessed as an estimate of the percent area of acinar pancreatic tissue involved.



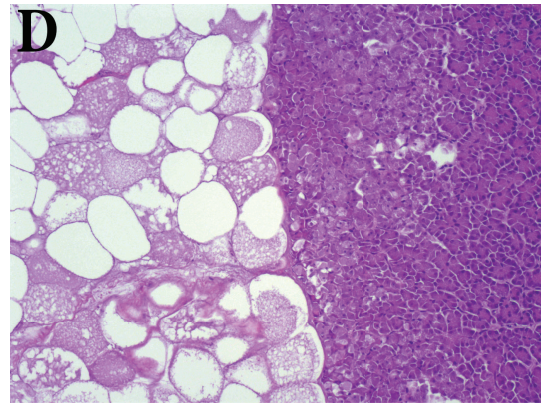
(a) Representative image of proximal pancreas of animal no. 1, showing a localized area of tissue necrosis consistent with acute pancreatitis (arrows). (H&E, original magnification 40x)



(b) Higher power image of pancreatitis showing histologic evidence of cellular apoptosis and necrosis consistent with cell death (shrunken fragmented nuclei and dissolution of cell membranes). (H&E, original magnification 400x)



(c) Adjoining area of pancreas showing normal histology of acinar cells with no evidence of pancreatitis or other cellular injury. (H&E, original magnification 400x)



(d) Example of fat necrosis (left side of image) in adjacent extrapancreatic adipose tissue from the proximal potion of animal no. 5. (H&E, original magnification 100x)

Figure 4: Pancreatic histology.

4. Results

All 5 Yucatan pigs tolerated the RFA. The pigs did not display any abnormal behavior or signs of complications after procedure.

Due to inadequate EUS visualization of the pancreas and repositioning difficulties with the probe in pig 1, the pancreas was ablated once for 5 minutes at 4 watts with 6 mm of the probe exposed. In pig 2, with 10 mm of the probe exposed, it was activated for 84 seconds (1.4 mins) at 5 watts; 48 seconds (0.8 mins) at 6 watts; twice for 258 seconds (4.3 mins) at 4 watts. The probe was activated 7 times instead of 6 times (10 mm, 4.3 minutes at 4 watts) in pig 2 to test for efficacy at a different site within the pancreas.

4.1. Lab Results and Complications Assessment. Three days after procedure, blood was drawn to evaluate total bilirubin, alkaline phosphatase, cell blood count, and amylase. The values were within normal range, and the pigs did not display any symptoms or abnormal behavior.

4.2. Tissue Analysis. No gross abnormalities were noted during the serial sectioning of the pancreata. Examination of the representative histologic sections showed focal areas of acute pancreatitis as evidenced by necrotic change of acinar pancreatic tissue (Table 1 and Figure 4). Only one animal (no. 1) showed moderate levels of pancreatitis, with involvement of 20% of the proximal pancreatic tissue. The other animals showed much lower areas of tissue damage. In 3 of the 5 animals, the proximal pancreas showed greater levels of tissue injury than the distal pancreas, consistent with the proximity of the tissue to the procedure site. In one animal (no. 4), there was minimal (1%) pancreatitis in both the proximal and distal pancreas, and in one animal (no. 3), slightly more injury was seen in the distal pancreas versus the proximal pancreas (4% versus 1%). In all tissue sections examined, there was evidence of fat necrosis in intrapancreatic and/or extrapancreatic adipose tissue (Figure 4(d)). In pigs no. 3 and no. 5, fat necrosis around their pancreases was seen, indicating pancreatitis. However, the pigs had normal lab values and did not display any symptoms or abnormal behavior.

Table 1: Scoring of histologic injury.

Animal #	Location	% acute pancreatitis	Fat necrosis
1	Proximal	20	Present
1	Distal	2	Present
2	Proximal	7	Present
2	Distal	0	Present
3	Proximal	1	Present
3	Distal	4	Present
4	Proximal	1	Present
4	Distal	1	Present
5	Proximal	5	Present
5	Distal	2	Present

5. Discussion

Radiofrequency ablation (RFA) uses high-frequency alternating current to destroy solid tumors [9]. When attached to a generator, RF current is emitted from the exposed portion of the electrode and this current translates into ion agitation within the surrounding tissue, which is converted by friction into heat and induces cellular death by means of coagulation necrosis [12, 13]. Its minimally invasive approach and good tolerability are the advantages of using RFA [9].

RFA of the bile duct during endoscopic retrograde cholangiography (EndoHPB probe, London, UK) was used in 2 studies [8, 14] and seems to be efficacious and well tolerated. Also, percutaneous RF-induced tissue coagulation has been used in early clinical trials for the management of hepatocellular carcinoma [15] and hepatic [15, 16] and cerebral metastases [17].

EUS has been increasingly used for therapeutic purposes as it allows precise measurement of the location and size of the pancreatic masses and can be used to follow the area of ablation and help avoid surrounding structures. The potential advantage of ablation with EUS is the guidance by real-time imaging into a deeply located target such as the pancreas, which is extremely difficult to reach percutaneously [4]. EUS-RFA is a safe, effective, and well-recognized modality for the treatment of focal malignant diseases [18, 19].

In the studies of Wu et al., Van Goethem et al., and Lee et al, the bipolar probe was found to ablate with less collateral thermal damage than the monopolar system but with less efficiency overall [5, 20, 21]. A hybrid cryotherm probe (CTP) combines the bipolar RF ablation with cryotechnology [4] increasing RF-induced interstitial devitalization [22]. Carrara et al. [4] utilized the EUS-guided CTP in pigs and found the longer the application time, the greater the variation in lesion size; an application of 900 seconds induced a high complication rate in the healthy pancreas. The mean size of the ablation zone obtained in this experiment with the bipolar probe and a 300-second application was about twice as big as the ablation zone obtained with the monopolar system at 360 seconds [13]. The mortality was zero while the morbidity was significant with one (7%) symptomatic necrotic pancreatitis with peritonitis, one burn of the gastric wall, and four (28.5%) adhesions between the pancreas and the gut. The burn of the gastric wall was thought to be due to incomplete probe penetration of the gastric mucosa, which is thicker in pigs than humans.

Similar complications were seen in Goldberg et al. [13], where EUS-RF was applied for 6 minutes to normal pancreatic tissue of 13 Yucatan pigs with specifically modified 19-gauge needle electrodes (285 ± 120 mA) via a transgastric approach. One pig had mild hyperlipasemia, a focal zone of pancreatitis (<1 cm), and later a pancreatic fluid collection. Other complications included three gastric and one intestinal burn caused by improper electrode placement. In pigs killed immediately and 1 to 2 days after ablation, pathological examination showed discrete, well-demarcated spherical foci of coagulation necrosis measuring 8 to 12 mm in diameter surrounded by a 1 to 2 mm rim of hemorrhage.

The complications seem to be associated with the duration of the ablation. The pancreas is very thermosensitive biological tissue and the thermal ablation of normal pancreas leads to an inflammatory response with edema and fibrotic and sometimes cystic transformation [4]. A major risk of massive necrosis seems to be related to multiple ablations that are in close proximity during the same treatment [5, 9].

The monopolar system was chosen in our EUS-guided ablation experiment over the bipolar due increased efficiency overall. This is remarkable considering that our ablation target was the head of the pancreas, where the sequelae of ductal trauma may be more significant [4]. Prior studies have shown that achieving maximum coagulation diameter in the liver, muscle, and intrahepatic tumor requires 6 minutes of RF application [23]. Thus, we aimed at concentrating around this duration time in our experiment. Currently achievable coagulation diameter is between 8 to 10 mm [4, 24–27] and so larger tumors might necessitate multiple needle insertions and RF applications [4]. Varadarajulu et al. in 2009 [28] achieved a complete coagulation necrosis of 2.6 cm diameter in the liver of 5 Yucatan pigs without damage to the surrounding parenchyma or vasculature utilizing EUS-RFA with a 19-gauge FNA needle fitted with an umbrella-shaped retractable needle electrode array. Noteworthy, this electrode array prototype with an umbrella diameter of 2 cm may be too large for the pancreas and even other organs [28].

In our study, there was evidence of fat necrosis in intrapancreatic and/or extrapancreatic adipose tissue. In two pigs (no. 3 and no. 5), fat necrosis around their pancreases was seen, indicating pancreatitis. However, in two of the pigs, EUS visualization was suboptimal; this may be due to a duodenal view of the pancreatic head not being very feasible in pigs because the stomach is longer than in humans and the pyloric muscle is very thick and difficult to pass [4]. In addition, a two-dimensional (2D) endosonography was used whereas a 3D ultrasound picture would improve the accuracy of the positioning of the probe [4] and potentially the visualization of the ablation site. Pancreatitis was achieved in both the proximal and distal pancreas even though our ablation target was the proximal pancreas. Therefore, some of the inflammatory changes of the pancreas could have been attributed to the needle insertion and not ablation alone. Pancreatitis was not detected between the proximal and distal sections of the porcine pancreas which may be related to the

anatomy of the porcine pancreas. The area of necrosis could not be measured due to the limited necrosis induced.

EUS-guided RFA appears to be well tolerated and most complications due to initial technical problems or differences between porcine and human anatomy [13]. RFA has been effective in the treatment of unresectable hepatic tumors and promising results have been obtained in tumors of the lung, bone, kidney, brain, breast, and prostate [9]. Thus, other applications of RFA exist but further studies in animals are needed to investigate the radiofrequency ablation of pancreatic tumor tissue with the monopolar probe prior to its use for palliation of unresectable malignant tumors of the pancreas. Additional modification of existent technology likely is needed to allow coagulation of greater volumes of tissue [13].

In conclusion, EUS-guided radiofrequency ablation of the pancreatic head with the monopolar probe through a 19-gauge needle was well tolerated in 5 Yucatan pigs and with minimum amount of pancreatitis. Contrary to the previous study conducted in porcine pancreas, our study has demonstrated that RFA can be delivered via EUS with minimal pancreatitis. Although the safety of EUS-RFA has been proven, the effectiveness of the monopolar probe in EUS-guided RFA in pancreatic cancer remains to be determined. Future refinements of the device with better visualization and higher energy should allow for greater ablation effectiveness without jeopardizing safety.

Acknowledgment

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Research Article

Evaluation of Endoscopic Ultrasound Image Quality Is Necessary in Endosonographic Assessment of Early Gastric Cancer Invasion Depth

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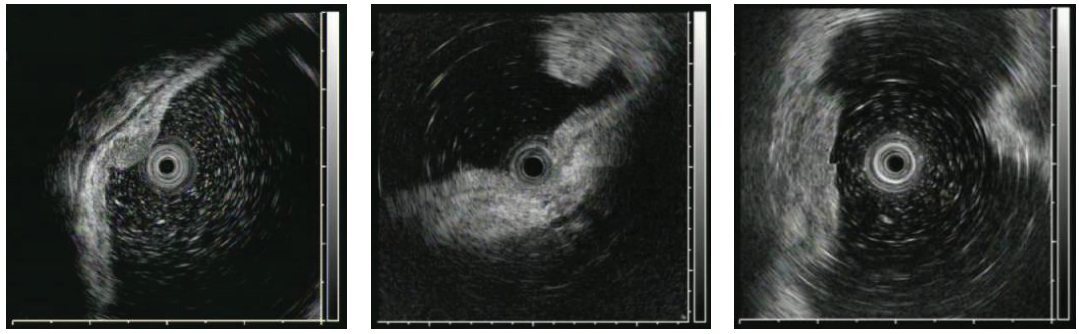
We evaluated whether endoscopic ultrasonography (EUS) image quality affects the accuracy of diagnosing the vertical invasion depth of early gastric cancer (EGC). A total of 75 lesions in 75 patients suspected of having EGC were enrolled. All patients underwent EUS examination. Findings of EUS were compared with histopathologic results. We evaluated the effect of the following clinicopathologic factors: location, diameter, surface pattern, concomitant ulceration, histology type, and EUS image quality score. EUS image quality was scored based on detection repeatability, appropriate probe placement, and clarity of the five gastric wall layers including the lesion. Sixty-three lesions (84%) were pathologically mucosal and 12 lesions (16%) were submucosal cancer. Overall accuracy was 82.7%. Significantly more lesions in the upper and middle portions of the stomach were incorrectly diagnosed than in the lower portion ($P = 0.0019$). Lesion diameter was significantly larger among incorrectly diagnosed lesions ($P = 0.0257$). Low-quality images were significantly more often associated with incorrectly diagnosed lesions than with correctly diagnosed lesions ($P = 0.0001$). Multivariate analysis revealed that EUS image quality was associated with EUS staging accuracy (odds ratio, 21.8; 95% confidence interval, 4.5–137.6). Low-quality EUS images led to an incorrect diagnosis of invasion depth of EGC, independent of tumor location or size.

1. Introduction

Pretherapeutic diagnosis based on the invasion depth of early gastric cancer (EGC) has become increasingly important with the development of endoscopic submucosal dissection (ESD) techniques. Although endoscopic ultrasonography (EUS) is considered useful for diagnosing the vertical cancer invasion depth, there are contradictory reports on the role of EUS in diagnosing EGC [1, 2]. Clinicopathologic factors of tumors, including the size [3, 4] and location of the lesion [3, 5, 6], gross morphologic type [5, 6], concomitant ulceration [4, 7], and histologic type [3], are reported to affect the diagnostic performance of EUS. Factors influencing the accuracy of EUS-based diagnosis, however, differ among studies and a consensus has not yet been reached [2, 3, 6, 8]. In addition, endoscopic skill or practical technical difficulties also influence the ability to make an accurate diagnosis. We considered that practical technical difficulties of achieving adequate EUS images such as probe placement and scanning at a constant distance from the lesion might influence diagnostic performance. It is difficult to evaluate technical problems or skill quantitatively, but we hypothesized that the quality of the EUS images is important to eliminate the factors of technical problems or skill that may affect the diagnosis. Measuring the depth of EGC using poor-quality EUS images might lead to incorrect results, irrespective of tumor-related factors such as tumor location and size. We hypothesize that the EUS image quality affects the diagnostic



(a) (b) (c)

Figure 1: Representative EUS images for evaluating EUS image score. (a) An EUS image fulfilling the three characteristics, including "repeatability of detection," "appropriate probe placement," and "clarity of the five layers of the gastric wall including the lesion"; (b) Inappropriate placement of the probe. The EUS probe is pressed on the lesion; (c) the five layers of the gastric wall including the lesion are not clear.

accuracy of EUS regarding the EGC invasion depth. To the best of our knowledge, there are no reports on this aspect. The aim of the present study was to elucidate the influence of the quality of EUS images on the diagnostic accuracy of EUS for assessing vertical invasion of EGC.

2. Patients and Methods

2.1. Patients and Lesions. A total of 77 lesions in 77 consecutive patients suspected for EGC endoscopically from April 2007 to July 2008 were retrospectively investigated. We excluded two lesions because one was considered advanced cancer before analysis and the other was in a reconstructed gastric tube following esophageal cancer. Thus, a total of 75 lesions were enrolled and analyzed in this study. All patients underwent EUS examination with an endosonography catheter probe before treatment at Osaka University Hospital, Osaka, Japan. The patients were then treated by ESD or gastrectomy in our hospital based on the endoscopic diagnosis. ESD was basically indicated according to the criteria of node-negative EGC established by Gotoda et al. [9] and gastrectomy was indicated if the EGC was more advanced than allowed by the ESD criteria. All the patients provided written informed consent before undergoing examination and treatment.

2.2. EUS Diagnosis. We used a 2.5 mm diameter miniature ultrasonic probe UM-2R or 3R (Olympus, Tokyo, Japan) in the study. The UM-2R or UM-3R ultrasonic probe incorporated a radial scanning system with a frequency of 12 MHz or 20 MHz, respectively. These were connected to an endoscopic ultrasonic observation unit (EU-M2000; Olympus, Tokyo, Japan). Nonaerated water was instilled to improve transmission of the ultrasound beam. EUS examinations were performed by 4 investigators (S.Y, M.K, Y.H, and T.K) whose years of EUS experience were 3, 3, 2, and 5 years, respectively. We classified the findings of the EUS images of tumor lesions into EUS-M and EUS-SM according to the method by Yanai et al. and Mouri et al. with some modification [10, 11]. EUS-M was defined to include pathologic, minute (500 μm) invasive cancer (sm1) in the submucosa because differentiating "sm1" from "m" is very difficult and the therapeutic strategy is very similar. If the lesion was confined within sonographic layers 1 and 2, we considered the lesion as EUS-M. Lesions with obvious irregular narrowing or budding into sonographic layer 3 were defined as EUS-SM. After treatment, we histologically examined specimens that were resected endoscopically or surgically, and compared EUS findings with histologic findings if the pretherapeutic diagnosis was correct. The lesions were defined as sm1 in cases of histologic invasion within 500 μm beyond the mucosa and sm2 in cases of histologic invasion of more than 500 μm. Sensitivity was defined as the proportion of lesions defined as sm2 relative to those defined as EUS-SM. Specificity was defined as the proportion of lesions with less than sm1 relative to those defined as EUS-M. Accuracy was defined as the proportion of the number of true diagnoses divided by the total number of patients.

To determine the factors that influenced the diagnostic accuracy of EUS, we evaluated the following clinical and histologic parameters; location (upper, middle, and lower third of the stomach), tumor size (mm), gross morphologic type (elevated or depressed), concomitant ulceration (endoscopic presence or absence), histologic type (intestinal-type or diffuse-type), and quality of the EUS images. To investigate the influence of the EUS image quality, one of the authors (a physician, S.Y.) retrospectively reviewed and evaluated all EUS images of the lesions based on the following parameters in the blinded manner of pathologic results, and scored them as follows: (1) repeatability of detection (presence [1] or absence [0]), (2) appropriate placement of the probe (ensuring the proper spacing between the probe and the lesion [1]) or impingement of the probe (probe was positioned too close to the lesion; [0]), and (3) clarity of the five layers of the gastric wall including the lesion (clear [1] or unclear [0]). The scores were summed (total ranged from 0 to 3) to calculate the quality of the EUS image of each lesion. The score was stratified as either a low score (scores 0 and 1) or a high score (scores 2 and 3). Typical images of each factor are shown in Figure 1. Finally, multivariate logistic regression analysis was performed to identify the variables among these clinicopathologic factors.

Table 1: Characteristics of the included lesions.

Characteristics	No. (%)
Location	
Upper third	14 (18.4)
Middle third	32 (42.1)
Lower third	29 (38.2)
Tumor size (mean ± SD, mm)	17.6 ± 11.5
Gross morphologic type	
Depressed	38 (51)
Elevated	37 (49)
Concomitant ulceration	
Present	17 (23)
Absent	58 (77)
Histologic type	
Intestinal	68 (91)
Diffuse	7 (9)
EUS image quality	
0	3 (4)
1	11 (14.7)
2	15 (20)
3	46 (61.3)

2.3. Statistical Analysis. All continuous variables were expressed as mean ± standard deviation (SD). For two-group comparisons, continuous variables were analyzed using Student's t-test, and categorical variables using the Fisher's test. Data analysis including multivariate logistic regression analysis was performed with the JMP 8-statistical package (Statistical Analysis Systems Inc, Cary, NC). A P value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patients and Lesions. A total of 75 lesions were included in this study (62 men and 13 women; mean age: 67 years; range: 41–86 years). ESD was selected to treat 59 lesions and surgery was selected to treat 16 lesions. Analysis of the resected specimens revealed that 63 lesions (84%) were pathologically mucosal and 12 lesions (16%) were submucosal cancer. Location, tumor size, gross morphologic type, concomitant ulceration, histologic type, and EUS image quality of all lesions are shown in Table 1.

3.2. EUS Diagnosis. Among the 75 lesions, the overall accuracy of the EUS assessment of the tumor invasion depth was 82.7% (62 of 75 lesions). Sensitivity and specificity were 37.5% (6 of 16 lesions) and 94.9% (56 of 59 lesions), respectively. Among the 13 incorrectly diagnosed lesions, 5.1% (3 of 59 EUS-M lesions) were underdiagnosed and 62.5% (10 of 16 EUS-SM lesions) were overdiagnosed ($P < 0.0001$; Table 2).

The EUS accuracy was not different according to the gross morphologic type, concomitant ulceration, or histologic type of EGC. The EUS accuracy was decreased for lesions in the upper part of the stomach, larger lesions, and lower-quality EUS images (Table 3). The association between the quality of EUS images and the proportions of correct diagnosis are shown in Figure 2. There were five "sm1" lesions in this study. Among them, 3 were diagnosed as EUS-M (correct; image quality score was 3 in all 3 cases), and other 2 were diagnosed as invading over 500 μm by EUS (the score of one case was 1 and that of the other was 2).

Table 2: Comparison of EUS and pathologic staging.

	Pathologic m/sm1	Pathologic sm2 or more
EUS-M	56	12
EUS-SM	3	4

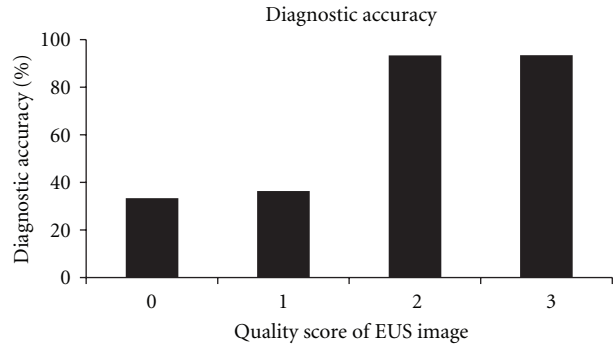


Figure 2: Association between the quality of EUS images and diagnostic accuracy.

Multivariate analysis using six parameters (location, tumor size, gross morphology type, concomitant ulceration, histology type, and EUS image quality) revealed that EUS image quality was an independent factor with a significant effect (odds ratio, 21.8; 95% confidence interval, 4.5–137.6).

4. Discussion

In the present study, the overall accuracy of EUS assessment of tumor depth invasion was 82.7% and the location of the lesion and tumor size were the major factors influencing the diagnostic performance of EUS, similar to previously reported findings [3, 4, 7, 8, 12–14]. Tsuzuki et al. reported that the submucosal layer is relatively thin and tends to have fibrosis and many vessels in the upper third of the stomach, making signs of submucosal invasion difficult to detect and leading to incorrect staging [6]. Our results slightly differed from previous reports, however, in that lesions in the middle third as well as the upper third of the stomach were at high risk for incorrect staging compared to the lower third. We considered the following three explanations. First, in the upper and middle third of the stomach, adequate filling with water is often difficult and may result in an unclear EUS image. Second, progression of atrophic or metaplastic gastritis surrounding the tumor might affect tumor appearance in EUS images. Third, it is technically difficult to precisely horizontally place EUS probes in lesions in the inferior wall in the body or in the lesser curvature in the angle of the stomach, which results in unclear or inaccurate EUS images. In this study, overstaging was the

Table 3: Univariate analysis of clinicopathologic factors for diagnostic accuracy of EUS.

Characteristics		N (%) of correct diagnosis	P value
Location	Upper, middle, lower	6/14 (42.9), 25/32 (78.1), 28/29 (96.6)	0.0019
Tumor size	Correct/incorrect (mm)	16.2 ± 10.0 (62)/24.0 ± 15.7 (13)	0.0257
Gross morphologic type	Depressed/elevated	32/38 (84.2)/30/37 (81.1)	0.7204
Concomitant ulceration	Present/absent	13/17 (76.5)/49/58 (84.5)	0.4428
Histologic type	Intestinal/diffuse	57/68 (83.8)/5/7 (71.4)	0.4094
Quality of EUS images	Low (0,1)/high (2,3)	5/14 (35.7)/57/61 (93.4)	<0.0001

major cause of our incorrectly staged lesions. Yanai et al. reported that EUS tended to result in overstaging while observation under white light endoscopy tended to result in understaging [15, 16]. In addition, incorrect staging is reported to be caused by inflammation associated with ulcers, benign cystic glands in the submucosal layer, and attenuation of the high-frequency ultrasound beam [16].

To clarify the factors influencing inaccurate diagnosis by EUS in this study, we investigated the EUS image quality in addition to the well-known clinicopathologic factors assessed to determine the invasion depth of EGC using a high-frequency EUS probe. Although it was difficult to evaluate technical problems or skills quantitatively and to eliminate the subjective view of the operator, which may strongly affect the EUS diagnosis, we considered that we were able to evaluate the impact of technical problems or skills by assessing the quality of EUS images. We found that the EUS image quality was an independent factor that affected diagnosis accuracy. To the best of our knowledge, this is the first study to evaluate EUS image quality. We chose the following three factors to evaluate EUS image quality: (1) repeatability of detection, (2) appropriate probe placement, and (3) the clarity of the five layers of the gastric wall including the lesion, because we considered that these factors could be not difficultly and objectively assessed. Based on our results, EUS images with a score of 1 or lower may be insufficient for making an accurate diagnosis of the invasion depth of EGC. The advantage of using an EUS image score is that the usefulness of each EUS image can be objectively assessed, in addition to factors such as tumor location or size. Among tumors with image quality scores of 3, however, three (6.5%) were incorrectly staged (2 lesions were overstaged and 1 was understaged). A strict and highly structured technique may improve the accuracy [17]. Well-experienced endosonographers might be able to produce endoscopic ultrasound images with better quality and to increase diagnosis accuracy. However, we think that the results by average endoscopists in this study may be rather practical. Whether comprehensive diagnosis can be made with EUS and conventional endoscopy must be confirmed in future studies, and may provide helpful information for the staging [18, 19].

The present study has several limitations due to the fact that, was a retrospective study. First, to some extent, there was a potential selection bias, but this type of bias may have been minimized by the consecutive patient enrollment. Next, only one investigator judged the EUS score to avoid bias in this study. In the future, evaluation of the EUS scores should be made in concordance with several physicians. Other limitations were the small number of patients and the lack of comparison data with other diagnostic modalities for EGC, especially conventional endoscopy. The importance of using EUS images to evaluate the diagnostic accuracy of invasion depth of EGC must be prospectively confirmed in future studies.

In conclusion, we elucidated that high-quality EUS images increased the diagnostic accuracy of EGC invasion depth. Thus, lower-quality EUS images may lead to an inaccurate diagnosis and this finding should be taken into account in the evaluation.

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Clinical Study

The Spectrum of Endoscopic Ultrasound Intervention in Biliary Diseases: A Single Center's Experience in 31 Cases

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Background and Aim. EUS-guided intervention (EGI) for biliary therapy has been increasingly used in recent years. This report aims to describe the spectrum and experience of EUS-guided interventions in biliary diseases in a single-tertiary center. *Methods.* All patients with EGI were analyzed retrospectively by retrieving data from a prospectively stored endoscopic database between January 2006 and September 2010. *Results.* There were 31 cases with EGIs (17 female, 14 male) with a mean age ± SD of 58.03 ± 16.89 years. The majority of cases (17/31; 55%) were ampullary or pancreatic cancers with obstructive jaundice. The major indications for EGI were obstructive jaundice ($n = 16$) and cholangitis ($n = 9$). The EGIs were technically successful in 24 of the 31 cases (77%). The success rate for the first 3 years was 8 of 13 procedures (61.5%) as compared to that of the last 2 years (16/18 procedures (89%); $P = 0.072$). Twenty-three of the 24 cases (96%) with technical success for stent placement also had clinical success in terms of symptom improvement. The complications were major in 4 (13%) and minor in 7 (23%) patients. *Conclusion.* The EUS-guided drainage for biliary obstruction, acute cholecystitis, bile leak, and biloma was an attractive alternative and should be handled in expert centers.

1. Introduction

Endoscopic ultrasound (EUS) guided cholangiography was firstly reported in 1996 [1]. EUS-guided interventions (EGIs) have been increasingly used in recent years [2, 3]. Many reports pertaining to EUS-guided biliary drainage in patients with failed ERCP, acute cholecystitis, and bilomas are available in the literature [4–36]. This report describes the spectrum and experience of EUS-guided interventions in biliary diseases in our center.

2. Methods

This is a retrospective analysis of a prospectively stored endoscopic database from 2006 till September 2010. The study was approved by our institutional ethics committee. All of the endoscopic reports of EUS-guided interventions in biliary diseases were retrieved, and all of the endoscopic reports and medical records were reviewed. Data regarding the demographic profiles, indications, procedure types, technical success, clinical success, complications, and outcome of patients were analyzed.

The main indications for EGIs of biliary diseases included patients with failed ERCPs for biliary therapy, patients with surgically altered anatomy preventing accessible ERCP, the unfit-for-surgery patients with cholecystitis not responding to medical treatment, and one patient with biloma requiring drainage. The EUS-guided intervention was performed using the Olympus EUS scope (GF-UCT160OL5, Olympus Medical, Tokyo, Japan) with a 3.7 mm working channel by

two authors (S. Attasaranya and B. Ovartlarnporn). All of the procedures were carried out under conscious sedation with midazolam and pethidine supplemented with propofol where necessary, except one case (an 11-year-old girl) under general anesthesia. The common bile duct (CBD) was preferred as an access route in patients with distal bile duct obstruction, while the left intrahepatic duct was selected as an access point in patients with hilar obstruction, surgically altered anatomy, or narrowing of the pylorus preventing the EUS scope from passing into the proper position in the duodenum. The bile duct was punctured using a 19-gauge needle (Echotip Wilson-Cook Medical, Winston-Salem, NC). After confirmation of the proper position of the needle in the bile duct by aspiration for bile and contrast injection, a 0.035″-guidewire (Jagwire Boston Scientific, Miami, FL) was inserted through the needle until several loops of the wire were coiled in the bile duct. The needle was removed, and the needle tract was dilated using an ERCP catheter followed by 6 Fr and 7 Fr dilating catheters (Soehendra dilation catheter, Wilson-Cook Medical) over the guidewire. A 7 Fr double-pigtail plastic stent (Zimmon biliary stent, Wilson-Cook Medical) or a partially covered metallic stent (Wallstent, Boston Scientific) was then inserted. If the needle tract dilatation using an ERCP catheter was unsuccessful, a needle knife (Microknife, Boston Scientific, Spencer, IN) using the endocut mode (VIO 300D, ERBE Elektromedizin GmbH, Tübingen, Germany) over the wire, was then introduced into the bile duct, and the tract was further dilated with 6 Fr and 7 Fr dilating catheters or an 8 mm biliary dilation balloon (Hurricane balloon catheter, Boston Scientific, Cork, Ireland). The procedures were performed in an out-patient setting in 4 cases and in an in-patient setting in 27 cases.

The technical success was defined as a successful procedure with a properly placed stent, whereas the clinical success as the improvement of the symptoms intended to be treated by the procedure. The reduction of serum bilirubin level by a value greater than 50% measured after 2 weeks after the procedure as compared to the baseline value was defined as successful drainage for patients with obstructive jaundice.

The complications that required surgical interventions were defined as major complications, and those that recovered spontaneously or responded to medical therapy or minimally invasive procedures were defined as minor complications.

3. Results

A total of 31 cases (17 female and 14 male) underwent EUS-guided interventions during the period under investigation. The mean age ± SD was 58.0 ± 16.9 years, with a range of 11 to 88 years. The median follow-up time in the 28 patients with available follow-up data was 3.4 months, with a range of 0.3–21.5 months. Fourteen patients died, ten patients were still alive, and seven patients defaulted during the followup.

The diagnoses of the patients comprised periampullary or pancreatic cancer in 17, gastric cancer in 1, duodenal cancer in 1, pancreatic inflammatory pseudotumor in 1, metastatic cancer in 2, choledochojejunostomy stenosis in 3, gallstone with cholecystitis in 1, post ERCP cholecystitis in 1, CBD stone in 1, bile leak in 1, hilar cholangiocarcinoma in 1, and biloma with postlaparoscopic cholecystectomy bile leak in 1.

Table 1: Indications for EUS-guided interventions.

Indication	Number of cases
Obstructive jaundice	16
Cholangitis	9
Cholecystitis	2
Choledochojejunostomy stenosis	1
PTBD replacement[f]	1
Bile leak	1
Biloma	1

[f]Percutaneous transhepatic biliary drainage.

Table 2: Type of drainage, success rate, and type of stent inserted.

Type of procedure	No.	Success
Hepaticogastrostomy	16	13
Choledochoduodenostomy	9	5
Cholecystoduodenostomy	4	3
Biloma drainage	1	1
Antegrade placement of metallic stent in CBD through the duodenal wall	1	1
Total	31	24
Type of stent		
Plastic, double pigtail	22	
Metallic, partially covered	4	

The indications for endoscopic drainage were obstructive jaundice in 16, cholangitis in 9, cholecystitis in 2, choledochojejunostomy stenosis in 1, replacement of percutaneous transhepatic biliary drainage (PTBD) in 1, bile leak in 1, and biloma in 1 (Table 1). The reasons for EUS-guided drainage were failed ERCP for biliary cannulation in 14, inaccessible ERCP due to luminal stenosis secondary to tumor invasion of gastric antrum or duodenum in 10, surgically altered anatomy in 4, acute cholecystitis with unfit condition for surgery in 2, and biloma in 1.

The EUS-guided interventions (EGIs) were technically successful in 24 of 31 (77%) cases. Twenty-three (96%) of those with technical success for EGIs had clinical success in terms of symptoms improvement also. There were 16 hepaticogastrostomies (HG) with 3 failures, 9 choledochoduodenostomies (CD) with 3 failures, 4 cholecystoduodenostomies (CHD) with 1 failure, 1 antegrade placement of metallic stent in CBD through the duodenal wall, and 1 biloma drainage performed. Covered metallic stents were inserted in 4 patients and plastic stents in 22 others (Table 2). The failure rates in the HG and non-HG procedures were 3 in 16 (19%) and 4 in 15 (27%), respectively, but the difference was not statistically significant. There were 5 failures out of 13 procedures done in the first 3 years (38%) and 2 failures out of 18 procedures in the last 2 years (11%); the difference was not significant ($P = 0.072$). The mean hospital stay in the

Table 3: Complications, treatment, and outcomes.

	Number	Outcome
Major complications in technical success		
Stent slipped off 2 days later	1	Surgery done, recovered
Major complications in technical failure		
Metallic stent deployed outside gastric wall	1	Surgery done, recovered
Duodenal perforation	1	Surgery done, recovered
Bile peritonitis	1	Surgery done, deteriorated
Total major complications	4	
Minor complications in technical success		
Severe abdominal pain	1	Resolved with medical treatment
Postprocedure fever	2	Recovered with antibiotics
Mild abdominal pain	1	Recovered
Retrogastric collection	1	Recovered with PCD[+]
Minor complications in technical failure		
Bleeding	1	Stopped spontaneously
Postprocedure fever	1	Recovered with antibiotics
Total minor complications	7	
Total overall complications	11	10 with recovery

[+]Percutaneous drainage.

27 patients on whom procedures were performed in an inpatient basis was 16.8 ± 28.6 days. In the subgroup analysis to compare the mean hospital stay between the patients with successful ($N = 20$) and those with failed procedures ($N = 7$), no statistical difference between the two groups was observed (17.3 ± 33.3 versus 15.1 ± 6.3 days; $P = 0.78$).

There were 11 complications in the 31 procedures (35%) as shown in Table 3. The complications were major in 4 (13%) and minor in 7 (23%) cases. In subgroup analysis, 2 major and 2 minor complications occurred in the patients with EUS-guided CD, while 1 major and 5 minor complications occurred in those with EUS-guided HG. There was no statistical difference of complication rate between the two groups ($P = 0.527$). The four major complications included delayed migration of the stent out of the bile duct leading to bile peritonitis requiring surgery for biliary diversion in 1, malposition of stent deployment resulting one tip of the stent located in intraperitoneum requiring surgery to retrieve the stent into a proper position in 1, perforation induced by the EUS scope requiring surgical repair in 1, and bile peritonitis after failed EUS-guided CHD requiring surgical intervention in 1. All but one patient recovered following surgical intervention. The patient with bile peritonitis after the failed EUS-guided CHD had a stormy, deteriorating postoperative course. The patient was eventually referred to a local facility for best supportive care in accordance with the patient and his family's wish. The minor complications included severe abdominal pain with pneumoperitoneum that subsided with conservative treatment in 1, postprocedure fever in 3, minor abdominal pain in 1, infected retrogastric collection resolved by medical therapy with percutaneous drainage in 1, and self-limited bleeding at the puncture site in 1. The complication rate for the first 3 years was 7 of 13 procedures (54%), which trended to be higher than that for the last two years (4 of 18 procedures; 22.2%) but with no statistical insignificance ($P = 0.087$).

Stent exchange was required in 3 patients during the followup. One patient with metastatic gastric cancer had the stent occluded at 3-month intervals and required another EUS-guided metallic stent placement. Another patient with recurrent pancreatic cancer after Whipple's operation underwent a biliary plastic stent exchange 2 months after the procedure. The third patient with a stricture during hepaticojejunostomy was treated with percutaneous placement of a metallic stent elsewhere, but the stent was blocked, leading to cholangitis. The stent was partially removed using single-balloon enteroscopy followed with EUS-guided HG with a metallic stent placement. Cholangitis resolved, but the new stent was occluded 3 weeks later. The repeated endoscopy revealed that the tip (gastric side) of the stent was found to be too long and submersed under gastric juice. Trimming of the stent tip with argon plasma was performed, and the stent was then cleaned by repeated balloon sweeping. However, multiple episodes of stent occlusion still recurred, requiring additional plastic stent insertion. The patient defaulted after a 9-month followup following the first procedure. Three patients, two with acute cholecystitis and one with biloma, had their stents removed after the resolution of symptoms. All of the stents in the remaining 17 patients with successful procedures were still functioning at the time of the last followup.

4. Discussion

The EUS-guided interventions for biliary diseases were demonstrated to be an attractive alternative in our report. The overall technical success rate in our study was in the boundary of the 50–100% range that is reported in the literature [4–36]. In the study by Itoi et al. [16], the technical success rate for EUS-guided HG ranged from 91–100%, and the success rate of EUS-guided CD ranged from 50–100%. The 81% success rate for the former and the 67% success rate for the latter in our series were similar to the data reported in the literature. The higher success rate for EUS-guided HG suggested that it may be easier to perform than EUS-guided CD, which was in agreement with other reports [34]. The failure rate of 38% in the initial 3 years compared with that of 11% in the last 2 years suggested that a learning curve period was required to improve technical skill. Notably, our success

rate of 89% in the last 2 years was comparable to the ranges reported in other series [16].

The EUS-guided drainage of the gallbladder (GB) in our report showed the potential use of this approach in treating selected patients with acute cholecystitis. Only a few reports with a small number of patients have reported the utility of EUS-guide drainage of the GB in cholecystitis [21–24, 32, 33]. In the literature review by Itoi et al. [22], 24 cases were reported with EUS-guided drainage of the GB in acute cholecystitis, with clinical success in all cases and a 25% complication rate. Recently, Itoi et al. have reported a case series of 5 patients with acute cholecystitis successfully treated via EUS-guided GB drainage using novel fully covered metallic stents designed to have bilateral anchor flanges [37]. Interestingly, the stent stayed fully patent for 12 months in a patient whose GB stent remained dwelling. The benefit of long-term GB stenting in this setting, however, needs to be determined by further study.

The EUS-guided drainage of the GB without acute cholecystitis was performed on 2 patients in our report. One patient with failed ERCP intervention causing subsequent bile leak showed resolution of the leakage following EUS-guided GB drainage. The other patient with obstructive jaundice from malignant distal bile duct stricture, whose HG and CD could not be performed due to the small degree of upstream duct dilation, failed the EUS-guided drainage of the GB and developed bile leak from the punctured GB leading to a dismal outcome. In detail, the failure in this patient occurred due to the dislodgement of the proximal tip of the stent out of the GB during stent deployment. Subsequent attempts at EUS-guided puncturing of the GB for another stent placement were unsuccessful presumably due to the collapsed GB following the leak. To the best of our knowledge, there has been no report regarding EUS-guided drainage of the GB without acute cholecystitis. For noninflamed GB, EUS-guided drainage should be done with caution since the GB is mobile; thus, the procedure may be more challenging, and the risk of bile leakage into the peritoneum is theoretically higher than that involving cases of inflamed GB, in which the surrounding adhesion may prevent bile leakage into the peritoneal cavity. Further refinement regarding the techniques and development of accessories for the procedure are needed before EUS-guided drainage of the GB can be accepted as a standard option.

EUS-guided drainage of the bile duct in patients with surgically altered anatomy was carried out in 4 patients and all of them experienced technical success. One of our patients had an ERCP performed using a single balloon enterosope, but only partial removal of the blocked metallic stent was accomplished. The EUS-guided drainage provided some additional treatment, but it did not completely solve the problem of recurrent stent occlusion. Two of our patients underwent EUS-guided bile duct drainage for anastomosis stricture. In one of the two patients, the stricture was dilated with a biliary balloon, and a concomitant bile duct stone was successfully pushed through the anastomosis into the jejunal limb using a balloon resulting in improved symptoms. Another patient underwent an HG and waited for the tract to mature before tract dilatation to deal with the stricture. In another patient, the EUS-guided drainage was used to replace the preexisting PTBD to improve quality of life, but the stent became malfunctional at 4 weeks after insertion. A PTBD was eventually required for biliary drainage. The ultimate role of EUS-guided drainage in patients with surgically altered anatomy as compared with ERCP by a balloon enteroscope or a percutaneous approach needs further study for clarification.

One patient with biloma was successfully drained by the EUS-guided approach in this report. Shami et al. has reported on EUS-guided drainage of biloma with a clinical response in 5 patients [31]. EUS-guided drainage of bilomas is technically feasible, appears safe, and provides an attractive alternative to other treatment modalities.

The overall complication rate of EUS-guided intervention of 35% in this report was within the range reported in the literatures [4–36]. However, the complication rate of 0–36.3% reported in the literatures may be an under estimation, since series with unfavorable outcome are more likely to be unreported. Most of the complications in our series were minor, but the 4 (13%) major complications are of concern. Three out of 4 major complications occurred following technical failure (Table 3). Notably, two of the major complications were related to stent displacement; one was related to delayed dislodgment of a double-pigtail plastic stent out of the common bile duct in the patient undergoing an EUS-guided CD, and the other was related to the improperly placed metallic stent with the proximal end dislodged into the intra-abdominal cavity. In order to prevent stent dislocation/migration, some experts have suggested that a relatively longer plastic stent is preferable, particularly when placing via a HG approach. The shortening ratio of the metallic stent should also be taken into account when placing the braided-type metallic stent [38].

The complication rate declining from 53% in the first 3 years to 22% in the last 2 years might imply that more experience resulted in a more favorable outcome.

The longer-than expected hospital stay (mean 16.8 ± 28.6 days) in our study was due to multiple contributing factors mostly unrelated to the procedures per se. Most patients required concomitant therapy for their underlying medical conditions as well as chemotherapy for the underlying malignancies.

In conclusion, our data suggest that EUS-guided biliary intervention is feasible and an attractive alternative tool providing biliary drainage in selected patients and should be performed by experienced endoscopists.

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