



A forward-viewing radial-array echoendoscope is useful for diagnosing the depth of colorectal neoplasia invasion

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Abstract

Background It is important to accurately diagnose the depth of colorectal neoplasia invasion. We aimed to evaluate the usefulness of a new forward-viewing radial-array echoendoscope (FRE), relative to the pit pattern method.

Methods In this prospective study, the invasion depth of suspected early-stage carcinoma was diagnosed using the pit pattern and FRE methods. The diagnoses were classified as T1a (submucosal invasion distance < 1,000 μm) or shallower and T1b (≥ 1,000 μm) or deeper. Pathological diagnoses were used to compare the diagnostic capabilities of the two methods.

Results The final analyses included 110 lesions. The FRE was successfully inserted to the lesion in all cases. There were no significant differences between the two methods regarding the correct prediction rate (79.1% vs. 75.5%, $P=0.57$), accuracy (81.3% vs. 79.0%, $P=0.68$), specificity (81.3% vs. 70.8%, $P=0.135$), positive predictive value (65.0% vs. 60.4%, $P=0.649$), negative predictive value (91.0% vs. 98.1%, $P=0.108$), or frequency of unevaluable cases (2.7% vs. 4.5%, $P=0.471$). The correct prediction rate was calculated by adding the number of unevaluable cases to the denominator of accuracy. Relative to the pit pattern method, the FRE method offered significantly higher sensitivity for predicting T1b or deeper invasion (81.3% vs. 97.0%, $P=0.048$). The pit pattern method had significantly poorer accuracy for large lesions (> 36 mm) than for smaller lesions (≤ 36 mm). In contrast, the accuracy of the FRE method did not differ significantly with lesion size. When using the FRE method, no cases were unevaluable because of attenuation. The FRE method provided correct diagnoses in 2 of 3 cases that were unevaluable using the pit pattern method.

Conclusions The pit pattern and FRE methods offered similar diagnostic performance for invasion depth. Furthermore, the FRE method may be used to correctly diagnose cases that are unevaluable using the pit pattern method.

Keywords Pit pattern method · Forward-facing radial-array echoendoscope · Colorectal neoplasia · Invasion depth

Endoscopic treatments for early colorectal cancer have recently improved after the application of endoscopic submucosal dissection (ESD) in the colorectum [1–6]. These improvements have allowed more lesions to be treated endoscopically, although more precise pre-treatment diagnosis of invasion depth is needed to select the treatment strategy for colorectal neoplasia. For example, endoscopic treatment is used for adenoma and intramucosal cancers, which have no possibility of metastasis, while the treatment strategies

for T1 cancer are determined based on the submucosal (SM) invasion distance. In T1a cases (SM invasion distance of < 1000 μm), endoscopic treatment is performed because of the very low probability of lymph node metastasis, while T1b cases (SM invasion distance of ≥ 1000 μm) are typically treated surgically, given the occurrence of lymph node metastasis in approximately 10–15% of cases [7, 8]. Surgical treatment is also selected for cases with a T2 or deeper classification. Therefore, it is very important to preoperatively distinguish between T1a or shallower cases and T1b or deeper cases.

There are several methods for diagnosing the depth of invasion for colorectal neoplasia. Endoscopic ultrasonography (EUS) is an established method with good accuracy. For example, Mukae et al. reported that the diagnostic accuracy of EUS was 89% (excluding difficult to evaluate

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cases) [9]. During EUS, the depth of invasion is typically evaluated using a high-frequency ultrasound probe (HFUP) or an oblique-viewing echoendoscope. However, because an HFUP has high frequency, attenuation can lead to cases being considered unevaluable [9, 10], which has led to some studies only targeting non-polypoid lesions [11–13]. Moreover, it can be difficult to deeply insert an oblique-viewing echoendoscope [14], and some studies have only targeted left colonic and rectal lesions [15]. Another approach to diagnose the depth of invasion is the pit pattern method, which is widely used, especially in Japan. Shimura et al. have reported that the pit pattern method has 71.2% accuracy [12].

Few reports have described the evaluation of invasion depth using a forward-viewing radial-array echoendoscope (FRE), although Kongkam et al. reported that the FRE is a feasible tool for determining T and N classifications for colon cancers beyond the rectum [14]. However, no reports have described using FRE to differentiate between T1a or shallower cases and T1b or deeper cases. In this context, we hypothesized that FRE might help to address the issues regarding ultrasound attenuation and deep insertion of the endoscope, which might make it a useful tool for determining the depth of invasion for colorectal neoplasia and differentiating between T1a or shallower cases and T1b or deeper cases. Therefore, this study aimed to prospectively evaluate the diagnostic performance of the pit pattern and FRE methods, as well as the insertability and related adverse events of the FRE.

Patients and methods

Study design and patients

This prospective single-center study was conducted at Nagoya University Hospital in Japan between August 2017 and June 2019 and was carried out in accordance with the principles of the Declaration of Helsinki. Patient data, including their general characteristics, were obtained from the medical records of our hospital. All patients provided written informed consent before their enrollment. The study's protocol was approved by our institutional review board (2015–0381) and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000028059).

The inclusion criteria were (1) age of > 20 years, (2) suspected early-stage carcinoma (intramucosal cancer and T1) based on conventional endoscopic observation using white-light imaging (WLI), (3) planned treatment using endoscopy or surgery, and (4) written informed consent. Patients were excluded when they had (1) a history of chemotherapy or radiation therapy; (2) an inappropriate lesion for study entry

as judged by the investigators, such as a pedunculated lesion, a scarring lesion, or a lesion in ulcerative colitis; or (3) no final histology results for the lesion because lung metastases were detected using computed tomography after the endoscopy.

Study protocol

The study included patients with suspected early-stage carcinoma based on WLI findings, and chromoendoscopy with a 0.2% indigo-carmin solution was added in some cases to clarify the morphology (Fig. 1A). The WLI observation was performed by an independent physician who did not participate in the pit pattern or FRE evaluations. Before the pit pattern method was applied, enrolled patients were sedated using 5-mg midazolam intravenously (the dose was adjusted as needed), and an antispasmodic agent (such as intravenous 20-mg scopolamine butylbromide or 1-mg glucagon) was administered to all patients without contraindications or comorbidities. Invasion depth was first evaluated using the pit pattern method, and the results were recorded by one physician. The FRE evaluation was subsequently performed by another physician who was blinded to the pit pattern evaluation, in order to avoid bias related to the order of the evaluations. The insertion time of FRE and the procedure time for each method was measured. The participating physicians were four expert endoscopists who had each performed > 3000 pit pattern evaluations and > 100 conventional EUS evaluations. The pathological diagnosis of invasion depth was based on the surgical or endoscopic specimen to evaluate the accuracies of the pit pattern and FRE methods. Because the FRE evidence was insufficient for definitively diagnosing the depth of colorectal neoplasia invasion, the attending physician (no a study investigator) selected the treatment plan (endoscopic or surgical treatment) by combining all evaluation results from the WLI, pit pattern, and FRE evaluations, with the pit pattern set as the gold standard. We also evaluated the insertability and related adverse events of the FRE.

Pit pattern diagnosis

All lesions were sprayed with a solution containing 0.05% crystal violet and then evaluated under $\times 80$ magnification using a magnifying colonoscope (EC-L600ZP7; FUJIFILM CO., Tokyo, Japan) (Fig. 1B). The results were classified according to Kudo et al.'s pit patterns [16]. Types III_L, III_S, IV, V_I, and V_N were considered neoplastic patterns, including adenoma and cancers. Type V_I was subdivided into type V_I-h (highly irregular) and type V_I-s (slightly irregular). Type V_I-h was defined as a pit pattern with a narrowing pit, irregular edges, unclear outline, decline or loss of stromal area, or scratch signs. Type V_I-s did not have any of these

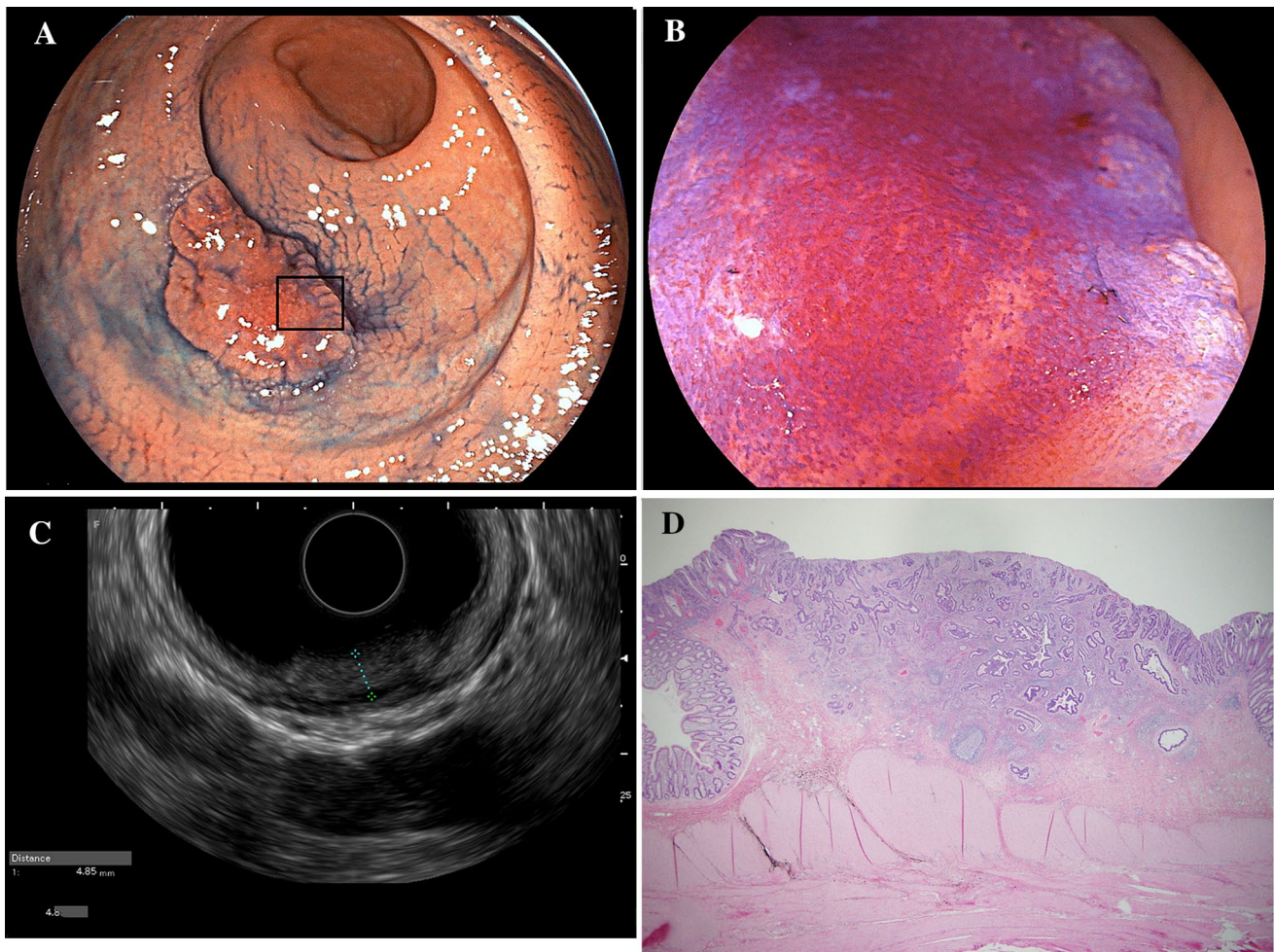


Fig. 1 Representative images. **A** Conventional colonoscopy revealed a laterally spreading tumor in the rectum with a central depression (size: 25 mm). Chromoendoscopy with a 0.2% indigo-carmin solution helped clearly visualize the morphology. **B** Magnifying colonoscopy of the boxed area in **(A)** using a 0.05% crystal violet solution revealed the V_N pit pattern. **C** The forward-viewing radial-array echendoscope revealed a hypoechoic mass extending into the middle of

characteristics. For the present study, we assumed that types III_L , III_s , IV , and V_I -s corresponded to an invasion depth of T1a or shallower and that types V_I -h and V_N corresponded to an invasion depth of T1b or deeper.

FRE diagnosis

All lesions were observed using an FRE (EG-580UR; FUJIFILM CO., Tokyo, Japan) (Fig. 1C). The FRE was inserted to the lesion, and the lumen of the colon was filled with distilled water. The balloon was not used to capture the endosonographic images. The available frequencies were 5, 7.5, 10, and 12 MHz, which were optimized for each case. In cases with a FRE diagnosis of a T1 lesion, the SM invasion distance was measured from the lower end of the

the submucosal layer. The position of the muscularis mucosa could not be identified; thus, the submucosal invasion distance was measured from the lesion's surface layer (4850 μ m). **D** The histological assessment revealed that the cancer had invaded to the submucosal layer. The position of the muscularis mucosa could not be identified; thus, the submucosal invasion distance was measured from the lesion's surface layer (4000 μ m). The histological diagnosis was pT1b

muscularis mucosae (where identifiable) to the deepest part of the lesion. If the muscularis mucosae could not be identified or approximated, the invasion distance was measured from the surface of the lesion. The depth of invasion based on FRE was also classified as T1a (SM invasion distance of < 1000 μ m) or shallower and T1b (SM invasion distance of \geq 1000 μ m) or deeper.

Pathological assessment

To determine the invasion depth, the surgical or endoscopic specimen was evaluated by a pathologist who was blinded to the pre-treatment diagnosis (Fig. 1D). Similar to the FRE evaluation, in pathological (p) T1 cases, SM invasion distance was measured from the lower end of the muscularis

mucosae (where identifiable) to the deepest part of the lesion. If the muscularis mucosae could not be identified or approximated, the invasion distance was measured from the surface of the lesion. The pathological diagnosis of pT1 was classified as pT1a (SM invasion distance of < 1000 μm) or pT1b ($\geq 1000 \mu\text{m}$) [8].

Objectives and outcome measures

The primary study objective was to compare the pit pattern and FRE methods' abilities to predict T1b or deeper invasion. The following measures of diagnostic performance were evaluated: correct prediction rate, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. The correct prediction rate was defined as (true positive cases + true negative cases)/(positive cases + negative cases + unevaluable cases). The correct prediction rate was calculated by adding the number of unevaluable cases to the denominator of accuracy. On the other hand, accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated according to the standard definitions after excluding all unevaluable cases. In addition to these, the procedure time was also evaluated. The procedure time in the pit pattern was the time from spraying the crystal violet to diagnosing with magnification. That in the FRE was the time from the beginning of the filling of the distilled water to evaluating the tumor depth. The secondary study objective was to perform risk analyses for incorrect diagnoses of invasion depth using the pit pattern and FRE methods. The risk analyses were only performed for evaluable cases. We also performed analyses for the following: (1) insertability and related adverse events of FRE, (2) detailed pathological assessments of FRE diagnoses in evaluable cases, and (3) cases that could not be evaluated using the pit pattern or FRE method.

Statistical analysis

In some papers, the accuracy using EUS was about 90% [17–19]. We estimated that the FRE diagnosis would increase the correct prediction rate for diagnosing invasion depth to 90% (vs. 75% for the pit pattern diagnosis). Based on a power of 80% and a two-sided test with a significance level of 5%, 100 patients would be needed. Thus, we targeted 120 patients to account for potential dropouts.

Univariate analyses were performed using the McNemar's test, the χ^2 test, Fisher's exact probability test, or Wilcoxon signed-rank test. Multivariate analyses were performed using logistic regression. All analyses were performed using IBM SPSS software (version 24; IBM Corp., Armonk, NY, USA), and a P value < 0.05 was considered statistically significant.

Results

We enrolled 120 patients with 120 lesions, although 10 patients and 10 lesions were subsequently excluded (Fig. 2). Thus, data for 110 lesions were included in the final analysis. Table 1 shows the characteristics of the 110 lesions in the 110 patients. The mean lesion size was 36.0 mm, and all lesions had sizes of > 10 mm. Twenty-eight lesions were polypoid (25.5%) and 45 lesions (40.9%) were located at the proximal colon. The FRE was successfully inserted to evaluate all lesions and there were no adverse events related to the use of the FRE. The median time taken for FRE insertion to the lesions located in the cecum was 10.0 min.

After endoscopic or surgical treatment with final histology evaluations, 77 lesions (70.0%) were classified as pT1a or shallower (adenoma, intramucosal cancer, and pT1a) and 33 lesions (30.0%) were classified as pT1b or deeper (pT1b, pT2, and pT3).

Comparison of evaluability

When we compared the pit pattern and FRE methods, there was no significant difference in the frequencies of unevaluable cases (2.7% [3 cases] vs. 4.5% [5 cases], $P = 0.471$). All 3 cases (2.7%) that were unevaluable using the pit pattern method were related to insufficient staining on the lesion surface due to mucus. Among the cases that were unevaluable using the FRE method, 2 cases (1.8%) were related to peristalsis, 2 cases (1.8%) were related to location on the fold, and 1 case (0.9%) was related to

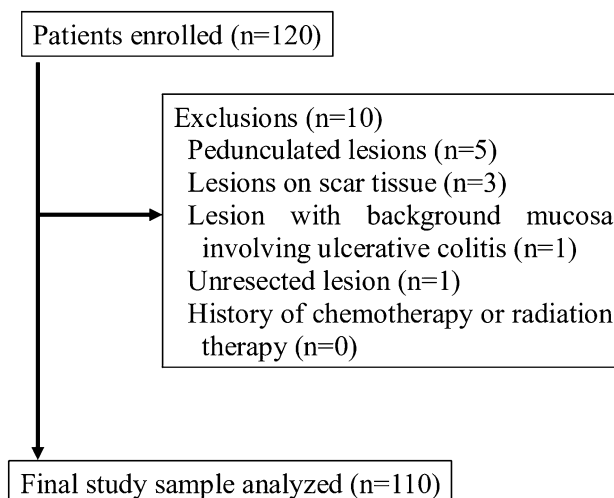


Fig. 2 Study flowchart. Data for 110 lesions were included in the final analysis

Table 1 Patient characteristics

Age in years, mean (SD)	68.0 (11.5)
Sex	
Male	64 (58.2%)
Female	46 (41.8%)
Size in mm, mean (SD)	36.0 (16.9)
Growth pattern	
Polypoid lesion	28 (25.5%)
Flat lesion	82 (74.5%)
Location	
Proximal colon	45 (40.9%)
Cecum	11 (10.0%)
Ascending colon	16 (14.5%)
Transverse colon	18 (16.4%)
Distal colon	65 (59.1%)
Descending colon	4 (3.6%)
Sigmoid colon	19 (17.3%)
Rectum	42 (38.2%)
Insertion time of the FRE in minutes, median (interquartile range)	
Cecum	10.0 (7.1–18.3)
Ascending colon	6.5 (5.0–10.0)
Transverse colon	3.2 (2.0–5.8)
Descending colon	7.8 (2.5–12.6)
Sigmoid colon	2.0 (1.0–2.5)
Rectum	0.1 (0.1–0.2)
Treatment	10.0 (7.1–18.3)
Endoscopic resection	76 (69.1%)
EMR	5 (4.5%)
ESD	71 (64.5%)
Surgical resection	27 (24.5%)
Surgical resection after ESD	7 (6.4%)
Histological diagnosis	
pT1a or shallower	77 (70.0%)
Adenoma	7 (6.4%)
Intramucosal cancer	59 (53.6%)
pT1a	11 (10.0%)
pT1b or deeper	33 (30.0%)
pT1b	15 (13.6%)
pT2	14 (12.7%)
pT3	4 (3.6%)

SD standard deviation, FRE forward-viewing radial-array echoendoscope, EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection

insufficient water retention. Polypoid lesions accounted for approximately 25% of all cases, although attenuation did not interfere with the ability to evaluate these lesions using the FRE.

Table 2 Comparisons of diagnostic performance for assessing T1b or deeper depth of invasion

	Pit pattern	FRE	<i>P</i> value
Correct prediction rate, % (n)	79.1% (87/110)	75.5% (83/110)	0.57*
Accuracy, % (n)	81.3% (87/107)	79.0% (83/105)	0.68**
Sensitivity, % (n)	81.3% (26/32)	97.0% (32/33)	0.048***
Specificity, % (n)	81.3% (61/75)	70.8% (51/72)	0.135**
PPV, % (n)	65.0% (26/40)	60.4% (32/53)	0.649**
NPV, % (n)	91.0% (61/67)	98.1% (51/52)	0.108***
Procedure time in minutes, median (interquartile range)	5.4 (3.2–8.9)	5.6 (2.7–11.2)	0.218****

FRE forward-viewing radial-array echoendoscope, PPV positive predictive value, NPV negative predictive value

**P* values were calculated using McNemar's test

***P* values were calculated using the chi-squared test

****P* values were calculated using Fisher's exact probability test

*****P* values were calculated using Wilcoxon signed-rank test

Comparisons of diagnostic performance

Table 2 shows the correct prediction rate (which includes cases that were judged unevaluable), accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for diagnostic predictions of T1b or deeper invasion that were obtained using the pit pattern and FRE methods. The pit pattern and FRE methods provided similar correct prediction rates (79.1% vs. 75.5%, $P=0.57$). In addition, no significant differences were observed between the two methods in terms of accuracy (81.3% vs. 79.0%, $P=0.68$), specificity (81.3% vs. 70.8%, $P=0.135$), positive predictive value (65.0% vs. 60.4%, $P=0.649$), or negative predictive value (91.0% vs. 98.1%, $P=0.108$). The FRE method had significantly higher sensitivity than the pit pattern method (81.3% vs. 97.0%, $P=0.048$).

No significant difference was observed between the two methods in terms of procedure time (5.4 min [3.2–8.9] vs. 5.6 min [2.7–11.2], $P=0.218$).

Risk factors for incorrect diagnosis

Tables 3 and 4 show the risk analyses for incorrect diagnoses of invasion depth that were obtained using the pit pattern and FRE methods. All of the risk analyses were limited to the evaluable cases. The univariate analyses of the pit pattern and FRE methods did not reveal any significant risk factors for incorrect diagnosis. All of the characteristics that were evaluated in the univariate analyses were included in the multivariate analyses of the two methods. For the pit pattern method, the multivariate

Table 3 Risk analysis for incorrect diagnoses using the pit pattern method

	Accuracy of the pit pattern method, % (n)	Univariate analysis <i>P</i> value	Multivariate analysis	
			<i>P</i> value	Odds ratio (95% confidence interval)
Age				
≤ 68 years	87.0% (40/46)	0.193	0.171	2.155 (0.719–6.460)
> 68 years	77.0% (47/61)			
Sex				
Male	82.3% (51/62)	0.767	0.532	1.388 (0.497–3.873)
Female	80.0% (36/45)			
Size				
≤ 36 mm	87.3% (55/63)	0.057	0.031	3.233 (1.115–9.373)
> 36 mm	72.7% (32/44)			
Growth pattern				
Polypoid lesion	81.5% (22/27)	0.979	0.566	0.701 (0.209–2.353)
Flat lesion	81.3% (65/80)			
Location				
Proximal colon	78.6% (33/42)	0.559	0.415	0.637 (0.215–1.887)
Distal colon	83.1% (54/65)			

P values on univariate analysis were calculated using the chi-squared test

Table 4 Risk analysis for incorrect diagnoses using the FRE method

	Accuracy of the FRE method, % (n)	Univariate analysis <i>P</i> value	Multivariate analysis	
			<i>P</i> value	Odds ratio (95% confidence interval)
Age				
≤ 68 years	80.9% (38/47)	0.683	0.545	1.355 (0.506–3.627)
> 68 years	77.6% (45/58)			
Sex				
Male	80.3% (49/61)	0.704	0.689	1.216 (0.466–3.176)
Female	77.3% (34/44)			
Size				
≤ 36 mm	78.7% (48/61)	0.915	0.802	0.880 (0.324–2.390)
> 36 mm	79.5% (35/44)			
Growth pattern				
Polypoid lesion	78.6% (22/28)	0.942	0.940	1.043 (0.345–3.156)
Flat lesion	79.2% (61/77)			
Location				
Proximal colon	83.3% (35/42)	0.378	0.322	1.703 (0.594–4.882)
Distal colon	76.2% (48/63)			

P values on univariate analysis were calculated using the chi-squared test

FRE forward-viewing radial-array echoendoscope

analysis revealed that a lesion size of > 36 mm (mean tumor size) was an independent risk factor ($P=0.031$, odds ratio: 3.233, 95% confidence interval: 1.115–9.373). In contrast, analyses of the FRE method showed that diagnostic accuracy did not differ significantly with lesion size. The FRE method provided similar accuracies for polypoid lesions and flat lesions.

Detailed pathological assessment of FRE diagnoses in evaluable cases

Table 5 summarizes the detailed pathological assessments of FRE diagnoses in evaluable cases. The pathological assessments revealed that the FRE method of predicting

T1b or deeper invasion was more likely to overestimate depth than to underestimate depth (21 cases vs. 1 case).

Using FRE in cases unevaluable using the pit pattern method

Table 6 shows the FRE diagnoses of the cases that were unevaluable using the pit pattern method. In the first case, an FRE diagnosis was also impossible because of peristalsis. In the second case, the FRE diagnosis was T1a or shallower, and the pathological diagnosis was intramucosal cancer. In the third case, the FRE diagnosis was T1b or deeper, and the pathological diagnosis was pT1b. Thus, in the two cases for which FRE was possible, the FRE diagnosis matched the pathological diagnosis.

Table 5 Detailed pathological assessments of FRE diagnoses in evaluable cases

FRE diagnosis	Pathological assessment					
	Adenoma	Intramucosal carcinoma	pT1a	pT1b	pT2	pT3
T1a or shallower n=52	5 (9.6%)	40 (76.9%)	6 (11.5%)	1 (1.9%)	0 (0%)	0 (0%)
T1b or deeper n=53	1 (1.9%)	16 (30.2%)	4 (7.5%)	14 (26.4%)	14 (26.4%)	4 (7.5%)

FRE forward-viewing radial-array echoendoscope

Table 6 FRE diagnoses in cases where mucus obscured the pit pattern diagnosis

Age (years)	Sex	Size (mm)	Growth pattern	Location	Forward-viewing radial-array echoendoscope diagnosis	Histological diagnosis
75	Male	30	Flat lesion	Ascending colon	Could not be evaluated because of peristalsis	Adenoma
66	Female	15	Polypoid lesion	Ascending colon	cT1a or shallower	Intramucosal carcinoma
77	Male	20	Flat lesion	Transverse colon	cT1b or deeper	pT1b

FRE forward-viewing radial-array echoendoscope

Table 7 Pit pattern diagnoses in cases unevaluable using FRE

Age (years)	Sex	Size (mm)	Growth pattern	Location	Pit pattern diagnosis	Histological diagnosis
70	Male	25	Flat lesion	Transverse colon	Type V _I -h	Intramucosal carcinoma
75	Male	30	Flat lesion	Ascending colon	Could not be evaluated because of peristalsis	Adenoma
78	Male	30	Flat lesion	Ascending colon	Type V _I -h	Intramucosal carcinoma
72	Female	20	Flat lesion	Sigmoid colon	Type V _N	pT1a
70	Female	25	Flat lesion	Sigmoid colon	Type V _I -s	Intramucosal carcinoma

FRE forward-viewing radial-array echoendoscope

Using the pit pattern method in cases unevaluable using FRE

Table 7 shows the pit pattern diagnoses of the cases that were unevaluable using the FRE method. In one of them, the pit pattern diagnosis was also impossible due to the presence of mucus. Three of them could not be diagnosed correctly by the pit pattern diagnosis, while one of them could be diagnosed correctly.

Discussion

The present study evaluated whether FRE could be used to accurately diagnose the depth of colorectal neoplasia invasion and differentiate between cases with invasion depths corresponding to T1a or shallower and T1b or deeper. An HFUP or oblique-viewing echoendoscope is typically used

during EUS to diagnose invasion depth, although these tools are associated with several issues. For example, the high frequency of HFUPs (mainly 12–20 MHz) leads to issues with echo attenuation, which can make a case unevaluable, particularly when an HFUP is used for polypoid lesions. In contrast, the FRE we evaluated uses a frequency of 5–12 MHz, which should be associated with less attenuation, even for polypoid lesions. The images of HFUP and FRE in the evaluation of polypoid lesions are shown in Fig. 3. Since we did not include HFUP observations in the protocol of this study, we prepared the HFUP image of another polyp with size and morphology similar to the polyp presented in FRE. As shown in Fig. 3A, when HFUP with a frequency of 20 MHz was used to observe a polyp with a height of about 15 mm, it was difficult to evaluate the deep portion, due to attenuation. Conversely, in Fig. 3B, when FRE with a frequency of 7.5 MHz was used to observe a similar polyp with a height

of about 15 mm, it was possible to evaluate the invasion depth of the polyp without attenuation. In this FRE image, the lesion did not invade the submucosa and was diagnosed as intramucosal cancer. It is highly likely that FRE could make it possible to estimate the tumor depth that could not be evaluated by HFUP.

Conventional echoendoscopes in the colon are oblique-viewing, which sometimes makes them difficult to insert into the deep colon. In contrast, the FRE's forward view addresses this issue and improves insertability because we could successfully insert the FRE to all lesions, including the lesions in the proximal colon, which accounted for approximately 40% of the overall study cohort. The median time taken for insertion to the lesions in the cecum by FRE was 10.0 min. In a previous paper [20], the median insertion time to the cecum using the normal colonoscope (model CF260H or CF260HZ; Olympus Optical, Tokyo, Japan) by the attending physician (with > 2000 total career colonoscopies) was 11.8 min. Thus, the insertion time in this study and that in the previous study are similar. The working length of the FRE was 1250 cm, which is shorter than that of the intermediate-length colonoscope. However, the insertability of FRE is good, and it was possible to insert it into the proximal colon without forming a loop in most cases. Hence, there was little difficulty in insertion due to the shorter working length of FRE.

Several studies have compared the accuracies for diagnosing colorectal neoplasia invasion depth between EUS and magnifying chromoendoscopy methods, which include the pit pattern method. However, the results of these studies are conflicting [12, 13, 17–19, 21]. In addition, some of the studies did not include cases that were judged unevaluable using EUS, or did not describe the related results. Furthermore, other studies were biased by the order of the diagnostic methods.

In the present study, the pit pattern and FRE methods had similar correct prediction rates, accuracies, and frequencies of unevaluable cases. The FRE method also offered similar accuracies for polypoid and flat lesions. The FRE method had significantly higher sensitivity for predicting T1b or deeper invasion than the pit pattern method. Moreover, our assessments were blinded to avoid bias related to the order of the evaluation. These findings show that the FRE method has similar diagnostic performance and better sensitivity than the pit pattern method for diagnosing the depth of colorectal neoplasia invasion. The reason why the accuracy of FRE in this study was lower than that in previous EUS studies might be because the pit pattern and EUS were performed in an unblinded manner in some of these studies. However, in this study, FRE was performed by another endoscopist who did not know the result of the pit pattern.

With respect to procedure time, there was no significant difference between pit pattern and FRE evaluations. A

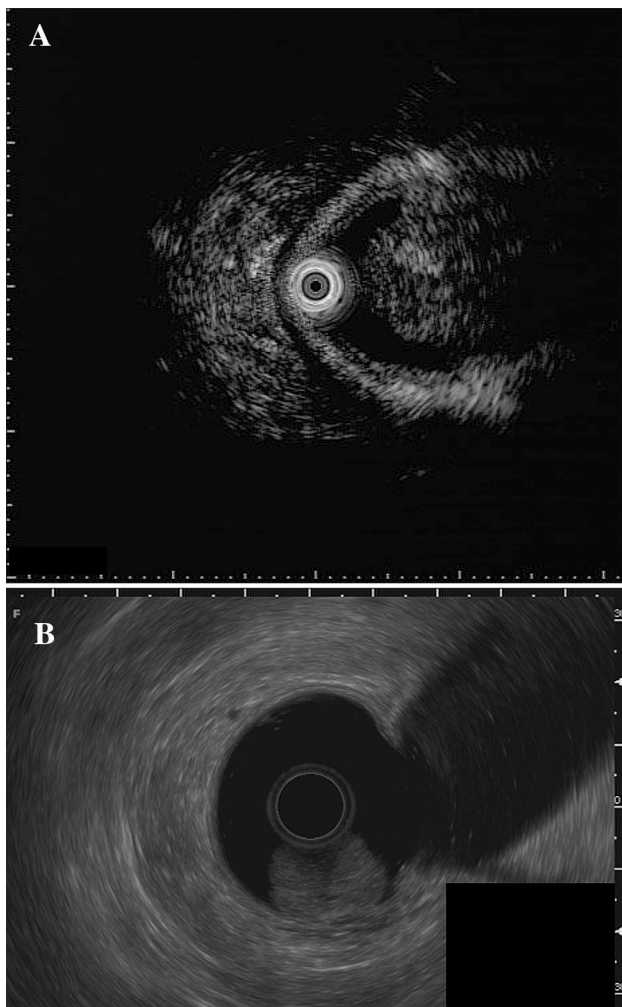


Fig. 3 Images of a high-frequency ultrasound probe and a forward-viewing radial-array echoendoscope in the evaluation of polypoid lesions. **A** It is difficult to evaluate the invasion depth due to attenuation. **B** It is possible to evaluate it without attenuation

previous report has indicated that the procedure time was longer for EUS than for magnifying chromoendoscopy [12]. Interestingly, there was no significant difference in the procedure times for the pit pattern and FRE evaluations in our study, despite the fact that the lesion size in our study was larger than that in the previous report [12]. In this context, magnifying chromoendoscopy requires a longer time to evaluate large lesions, while FRE has a broader evaluation range and does not require a prolonged time to evaluate even large lesions. This suggests that the burden on the patient's body while performing FRE is not much different than that while performing pit pattern diagnosis.

A lesion size of > 36 mm was an independent risk factor for incorrect diagnoses of invasion depth using the pit pattern method. Conversely, the lesion size in the FRE assessment was not associated with any significant difference in diagnostic accuracy. Our results show that the FRE method can be used to correctly diagnose the invasion depth, regardless of lesion size. When using the FRE method to diagnose the invasion depth of large lesions, we attempted to move the scope in all directions relative to the lesion, scan all parts of the lesion, and capture the deepest part of the lesion.

We also examined the detailed pathological assessments of FRE diagnoses in evaluable cases. The FRE method has the advantage of a high sensitivity for predicting T1b or deeper invasion. However, its specificity seemed to be lower than that of pit pattern diagnosis although the difference was not statistically significant. While using the FRE method, overestimation of invasion depth is more likely than underestimation of invasion depth. Overestimation of invasion depth is a concern because it may lead to unnecessary surgical management of the lesion. When the FRE indicate T1b or deeper images, the endoscopist must adopt the FRE result with caution. If necessary, it is better to perform another procedure to determine the treatment necessary to improve diagnostic reliability.

Most previous studies have distinguished between clinical T1a and T1b disease using EUS to evaluate the form of the SM layer, rather than making this distinction based on the invasion distance [10]. The form of the SM layer becomes slightly narrow in T1a cases, but distinctly thin or obscure in T1b cases. However, one study also reported a significant correlation between the histological and HFUP diagnoses of the SM invasion distance [22]. Thus, we evaluated the SM invasion distance using FRE in T1 cases and classified the results as T1a (< 1000 μm) or T1b (\geq 1000 μm) based on the distance from the lower end of the muscularis mucosa (or the lesion's surface layer) to the deepest part of the tumor. This method is similar to and complements the existing guidelines for pathological evaluations [8]. Although few reports have described using this technique, we believe it is useful based on the similar accuracies of the pit pattern and FRE methods.

Although the FRE did not significantly improve the correct prediction rate of invasion depth, it was similar to that for the pit pattern method. Furthermore, the FRE correctly diagnosed 2 of 3 cases that were unevaluable using the pit pattern method. Thus, FRE may be effective even in cases that are unevaluable using the pit pattern method (e.g., because of mucus). Because of the high sensitivity of FRE for predicting T1b or deeper invasion, we suggest that endoscopic treatment should be indicated for cases diagnosed as V₁-h using the pit pattern method, but as T1a or shallower using the FRE method.

The present study has two important limitations. The first limitation is that the patients received intravenous injections of scopolamine butylbromide or glucagon, which were followed by the pit pattern diagnosis and then the FRE diagnosis. Thus, peristalsis was more likely to occur during the FRE diagnosis and might have worsened the observation conditions. It might also be prudent to consider two groups of patients in future studies, with one group undergoing the pit pattern diagnosis first and the other group undergoing the FRE diagnosis first. The second limitation is the study's single-center design and small sample size. A larger multicenter study will be needed to validate our findings. It would also be useful to evaluate FRE performance in other countries. The third limitation was that the insertion time of FRE was compared with that reported in previous studies, not directly compared with the insertion time in this study of the magnifying colonoscope.

In conclusion, the present study revealed that the FRE method has similar ability to predict the depth of colorectal neoplasia invasion, relative to the pit pattern method. Furthermore, the FRE method remained useful in cases with polypoid lesions, lesions at the proximal colon, and larger lesions. Moreover, the FRE method may correctly diagnose cases that are unevaluable using the pit pattern method.

Compliance with ethical standards

Disclosures Drs. Takeshi Kuno, Takeshi Yamamura, Masanao Nakamura, Keiko Maeda, Tsunaki Sawada, Yasuyuki Mizutani, Masaya Esaki, Takuya Ishikawa, Kazuhiro Furukawa, Eizaburo Ohno, Hiroki Kawashima and Mitsuhiro Fujishiro have no conflicts of interest or financial ties to disclose.

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