ESDs were performed. Finally, there were no procedure-related mortalities at any of the institutions (**Tables 1** and **2**).

Independent risk factors for complications assessed by univariate and multivariate analysis

In the screening analysis for complication risk factors, tumor size, tumor location, macroscopic type, and histology had no significant association with the ESD complication rate (not significant), but there was a significantly decreased risk of complications corresponding to the increased number of ESDs performed at the 3 groups of institutions (group A, <50 ESDs, 17.6%; group B, ≥50 and <100 ESDs, 8.2%; and group C, ≥100 ESDs, 5.1%) ($P < .0001$) (**Table 3**). In the logistic regression models, the complication rate was independently higher for large tumors (≥50 mm) (multivariate analysis: odds ratio, 2.1; 95% confidence interval, 1.1-3.4; $P = .0198$), whereas the larger number of ESDs performed by groups B and C decreased the risk of complications (multivariate analyses: group B/group C: odds ratio, 0.4/0.2; 95% confidence interval, 0.2-0.9/0.1-0.5; $P = .0253/.0002$) (**Table 4**). There was no association, however, between the types of knives used during the ESDs and the complication rate (data not shown).

DISCUSSION

This is the first large prospective, multicenter cohort study of colorectal ESDs performed at specialized centers in Japan. There is increasing evidence of the effectiveness of colorectal ESD because the procedure makes it possible to treat large nongranular type LSTs (>20 mm) that had been treated by surgery in the past.[8] The longer procedure time and higher complication rate of ESD compared with conventional EMR have also been discussed previously.[36] In fact, a small number of analyses[12] conducted in an earlier Japanese multicenter study indicated a higher complication rate during colorectal ESDs and that standardization of the colorectal ESD procedure would be difficult.

This study is particularly important because more than 1000 colorectal ESD cases in 10 specialized centers were analyzed at a time when the use of colorectal ESD is spreading in Japan, and a number of trained endoscopists are starting to perform colorectal ESDs in Western countries as well.[21,22] The complication rate significantly decreased with the increased number of ESDs performed at an institution from 17.6% for group A (<50 ESDs) to 8.2% for group B (≥50 and <100 ESDs) to 5.1% for group C (≥100 ESDs), probably because of greater clinical experience in performing colorectal ESDs on a regular basis at group B institutions and even more so at group C institutions. There were no significant statistical differences for the mean procedure time, en bloc resection rate, and curative resection rate among the 3 groups, most likely because the mean tumor size was smaller and the locations differed as did the macroscopic types in group A,

TABLE 3. Risk factors for ESD complications

Risk factors	Complications		
	No	Yes	*P* Value
ESDs	1039	72	
Sex, male	639	42	.595
Age, y, mean ± SD	66.2 ± 10.5	64.8 ± 9.5	.273
Tumor size, mm			
<50	851	52	
≥50	188	20	.0316
Tumor location			
Cecum	93	10	
Right colon	384	24	
Left colon	249	14	
Rectum	313	24	.451
Macroscopic type			
LST-NG	397	22	
LST-G	501	36	
Depressed (IIc)	30	0	
Protruded (Is)	54	8	
Recurrent tumor	39	5	
Submucosal tumor	18	1	.075
Histology			
Non-neoplastic	3	1	
Adenoma	328	28	
Mucosal cancer	487	32	
SM1 cancer	106	6	
SM2 cancer	96	5	
Others	19	0	.45
Institutions (no. of ESDs)			
Group A (<50)	56	12	
Group B (≥50 and <100)	201	18	
Group C (≥100)	782	42	<.0001
Trend			<.0001

ESD, Endoscopic submucosal dissection; *LST-NG*, nongranular type laterally spreading tumor; *LST-G*, granular type laterally spreading tumor; *SD*, standard deviation; *SM1*, submucosal invasion less than 1000 μm from the muscularis mucosae; *SM2*, submucosal invasion 1000 μm or more from the muscularis mucosae.

TABLE 4. Risk factors for complications

	Univariate Analysis			Multivariate Analysis		
	OR	95 CI	*p* Value	OR	95 CI	*p* Value
Macroscopic Type						
LST-NG	1					
Recurrent Tumor	2.3	0.7-6.0	0.1088			
Others	1.3	0.8-2.3	0.2668			
Tumor Size						
<50 mm	1			1		
≥50 mm	1.7	1.0-2.9	0.0439	2.1	1.1-3.4	0.0198
Institutions (ESDs)						
A (<50)	1			1		
B (≥50, <100)	0.4	0.2-0.9	0.0351	0.4	0.2-0.9	0.0253
C (≥100)	0.3	0.1-0.5	0.0004	0.2	0.1-0.5	0.0002

CI, confidence interval; *OR*, odds ratio; *ESD*, endoscopic submucosal dissection.

suggesting that less-experienced endoscopists did not attempt to perform ESDs in more challenging cases.

To decrease the colorectal ESD complication rate in the future, it will be necessary to establish a learning curve based on the results of our large case series. In addition, conservative treatment of perforations should be possible in the future in those cases in which endoscopic clipping has already been shown to be effective.

The indications for ESD in this series were markedly different from those for conventional EMR,[17,36] and the overall perforation rate of 5.2% was higher compared with conventional EMR,[36] but considerably lower than the earlier Japanese multicenter analyses mentioned previously[12] in which delayed perforation cases were regarded as requiring emergency surgery because of the risk of peritonitis. Two of the 4 patients with delayed perforations in this series, however, were successfully treated conservatively as abdominal findings and inflammation changes based on laboratory data were slight. Taku et al[12] also reported that conservative treatment might be possible, even for cases of delayed perforation when abdominal findings and laboratory data are stable, but we must carefully follow patients with delayed perforation and continued close communication with consulting surgeons is essential because the number of such cases has been quite limited so far.

The other principal ESD complication involved postoperative bleeding, but the total postoperative bleeding rate was only 1.5%, and none of the 17 patients required a blood transfusion or emergency surgery. This relatively low rate of postoperative bleeding was probably a result of using the coagulation technique for exposed vessels during ESD procedures, and the incidence of postoperative bleeding also decreased as the total number of ESDs performed at the 3 respective groups of institutions increased.

Univariate and multivariate analysis revealed that large tumor size (≥50 mm) and less experience performing ESDs (group A, <50 cases) were independent risk factors for complications, so endoscopists should begin by performing colorectal ESDs on smaller lesions.

The mean ESD procedure time was considerably longer compared with that of conventional EMR,[36] but the indications for ESD and EMR were different, as were the tumor characteristics.[36] We should be comparing, therefore, the procedure times between ESD and surgery rather than ESD and EMR.

As for ESD devices, more than 2 knives were used in most institutions and CO_2 insufflation was used at 8 of the 10 institutions to reduce patient discomfort (Table 1). These factors also will need to be taken into account when considering costs in the future.

This was a prospective multicenter cohort study, but eligibility criteria for performing colorectal ESDs were sometimes unclear at some of the institutions. It will be necessary, therefore, to further assess the clinical outcome of using ESD for the treatment of large colorectal tumors in the future.

Another limitation of this study is that no long-term outcome data are available yet because a few of the institutions have only started performing colorectal ESDs in recent years. With more than 6 months of follow-up for cases at the National Cancer Center Hospital, there have been only 3 local recurrences (2%) in ESD cases (mean endoscopic follow-up period, 20.0 ± 12.9 months) compared with 33 recurrences (14%) in EMR cases (mean endoscopic follow-up period 25.9 ± 17.0 months).[36]

In conclusion, ESD performed by experienced endoscopists is a safe and very effective procedure for treating large superficial colorectal tumors such as nongranular type LSTs larger than 20 mm and granular type LSTs larger than 30 mm that would have previously been treated with surgery, as well as large villous tumors and intramucosal lesions, recurrent lesions, and residual mucosal lesions showing nonlifting sign after EMR.

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Endoscopic Submucosal Dissection of Non-Polypoid Colorectal Neoplasms

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KEYWORDS

- Endoscopic submucosal dissection
- Endoscopic mucosal resection
- Endoscopic piecemeal mucosal resection • Colorectum
- Laterally spreading tumor granular type
- Laterally spreading tumor nongranular type

Traditionally, endoscopic mucosal resection (EMR)[1–5] and surgery were the only available treatments for large colorectal tumors, even for those detected at an early stage. In Japan, EMR is indicated for the treatment of colorectal adenomas, intramucosal and submucosal superficial (invasion <1000 μm from the muscularis mucosae) cancers, because of its negligible risk of lymph node metastasis[6] and excellent clinical outcomes.[2–4]

The endoscopic submucosal dissection (ESD) technique, which enables en-bloc resection of large tumors, is accepted as a standard minimally invasive treatment for early gastric cancer in Japan.[7,8] However, it is not widely used to treat superficial colorectal cancer because of technical difficulty and the higher risk of complications. Conventional EMR, therefore, is used for the resection of non-polypoid colorectal neoplasms (NP-CRNs), including the large flat carpet lesions, called colorectal laterally spreading tumors (LSTs).[4,5] EMR, however, is not designed for en-bloc resection of LSTs larger than 20 mm. Piecemeal EMR is associated with the risks of incomplete removal and local recurrence[9] albeit most recurrences can be successfully treated by additional EMR and only a few cases require surgery.[9] ESD of LSTs larger than 20 mm is therefore an attractive treatment provided that it is safe to use in the colon and rectum.

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Based on the refinement of ESD instruments and progress in the development of ESD skills, the ESD technique has recently been reported to be useful in the treatment of large colorectal LSTs instead of EMR or surgery.[10–15] Herein, the authors describe their experience.

INDICATIONS FOR COLORECTAL ESD

The indication for colorectal ESD at the National Cancer Center Hospital (NCCH) in Tokyo, Japan, is a nongranular type LST (LST-NG) larger than 20 mm.[12]

Based on clinicopathologic analyses of LSTs,[4,16] LST-NGs, which are large (>1 cm) superficial elevated NP-CRNs with a smooth surface, have a higher rate of submucosal (sm) invasion, which can be difficult to predict endoscopically. About 30% of LST-NGs with sm invasions are multifocal, and such invasions are primarily superficial submucosal cancers (sm1s) and difficult to predict before endoscopic treatment.

Granular type LSTs (LST-Gs) have a lower rate of sm invasion, and most such invasions are found under the largest nodule or depression, which are easier to predict endoscopically.[4,16] LST-Gs larger than 20 mm can be treated by endoscopic piecemeal mucosal resection (EPMR) rather than by ESD, with the area that has the largest nodule resected before resection of the remaining tumor. LST-Gs larger than 30 mm or 40 mm are possible candidates for ESD because they have higher sm invasion rates and are more difficult to treat even by EPMR; so they have been treated by either EPMR or ESD, based on the individual endoscopist's judgment.

ESTIMATION OF THE DEPTH OF INVASION

A non-invasive pattern[17,18] should be verified in each lesion, indicating suitability for EMR or ESD: the estimated invasion depth should be less than that of superficial submucosal cancers (sm1s). No biopsy is performed before ESD because it can cause fibrosis and may interfere with submucosal lifting.

CESSATION PERIOD OF ANTICOAGULANT AND ANTIPLATELET BEFORE ESD

ESD is considered to be a high-risk procedure.[19] Most patients receiving aspirin or ticlopidine alone underwent ESD after a cessation period of 5 to 7 days and restarted the drugs after 7 days if possible. Patients receiving warfarin used intravenous heparin or subcutaneous low-molecular-weight heparin in the perioperative period and resumed warfarin after the ESD procedure.

ESD PROCEDURE AT NCCH

The procedures were primarily performed using a ball-tip bipolar needle knife (B-knife) (XEMEX Co, Tokyo Japan) (**Fig. 1**A)[20] and an insulation-tip (IT) electrosurgical knife (Olympus Optical Co, Tokyo, Japan) (see **Fig. 1**B) with carbon dioxide insufflations instead of air insufflation to reduce patient discomfort (see **Fig. 1**C).[11] After submucosal injection of 10% glycerin and 5% fructose (Glyceol, Chugai Pharmaceutical Co, Tokyo, Japan)[21] and 0.4% hyaluronic acid[14] (MucoUp, Seikakagu Co, Tokyo, Japan) (see **Fig. 1**D) into the sm layer, a circumferential incision was made using the B-knife and an ESD was then performed using the B-knife and IT knife (see **Fig. 1**A, B).

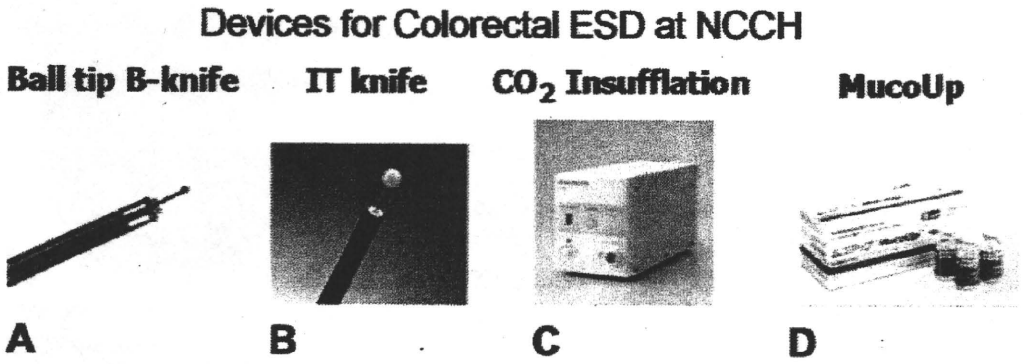

Fig. 1. The procedures were primarily performed using a B-knife (*A*) and an IT electrosurgical knife (*B*) with carbon dioxide insufflation (*C*) instead of air insufflation to reduce patient discomfort. After injection of Glyceol (Chugai Pharmaceutical Co, Tokyo, Japan) and MucoUp (Seikakagu Co, Tokyo, Japan) (*D*) into the sm layer, a circumferential incision was made using the B-knife and an ESD was performed using the B-knife and IT knife. (*From* XEMEX Co, Tokyo, Japan; with permission [*A*]; Olympus Optical Co, Tokyo, Japan; with permission [*B*]; and Seikakagu Co, Tokyo, Japan; with permission [*D*].)

SUBMUCOSAL INJECTION SOLUTION

A mixture of 2 solutions was prepared before the procedure to create a longer-lasting sm fluid cushion.

Solution 1: Indigo carmine dye (2 mL of 1% solution) and epinephrine (1 mL of 0.1% solution) were mixed with 200 mL Glyceol[21] in a container, which was then drawn into a 5-mL disposable syringe.

Solution 2: MucoUp was drawn into another 5-mL syringe with a smaller amount of indigo carmine dye and epinephrine. During the actual ESD procedure, a small amount of solution 1 was injected into the sm layer to confirm the appropriate sm layer elevation and then solution 2 was injected into the properly elevated sm layer. Finally, a small amount of solution 1 was injected again to flush out any residual solution 2.

DETAILED COLORECTAL ESD PROCEDURES

1. The margins of the lesion were delineated before ESD by spraying 0.4% indigo carmine dye (**Fig. 2**A). After creation of the submucosal fluid cushion, an initial incision was made with the B-knife at the oral side of the lesion (see **Fig. 2**B).[20] In colorectal cases, it was not necessary to actually mark around lesions because tumor margins can be visualized clearly with indigo carmine.
2. The B-knife was inserted into the initial incision, and an electrosurgical current was applied in endocut mode (50 W) using a standard electrosurgical generator (ICC 200, ERBE, Tubingen, Germany) to continue the marginal incision around the oral side of the lesion.
3. After partial resection of the margin on the oral side of the lesion to ensure adequate submucosal lifting, submucosal dissection was begun using the same B-knife in retroflex view (see **Fig. 2**B).
4. Additional resection of the margin on the anal side was performed using the B-knife in the straight view (see **Fig. 2**C).
5. After the lesion was partially dissected so that the sm layer could be visualized sufficiently, an IT knife (see **Fig. 2**D) was used to complete the dissection of the sm layer quickly and safely. The previously indicated solutions were injected

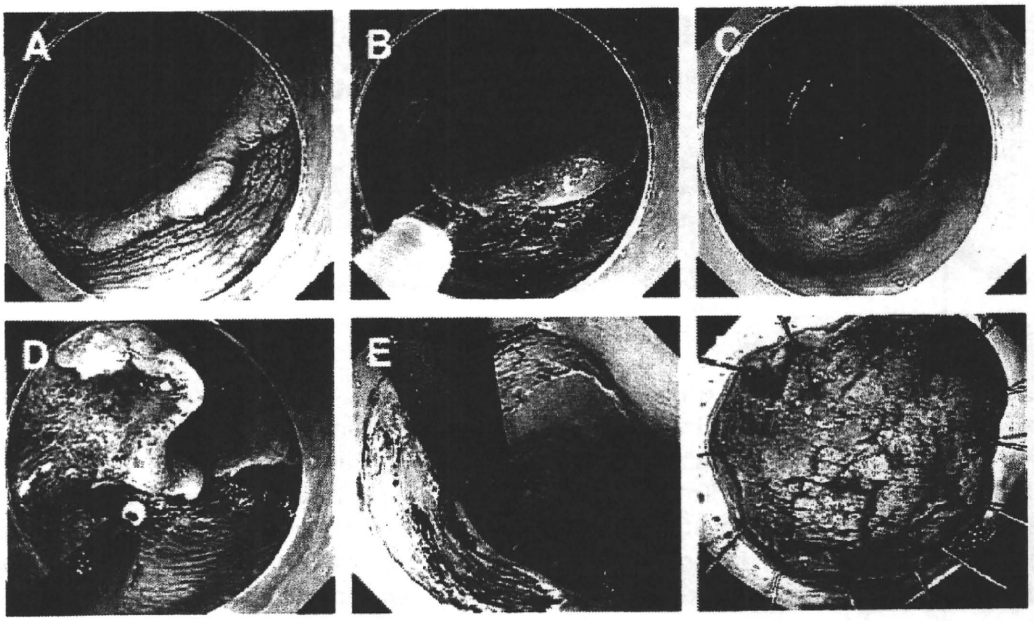

Fig. 2. ESD procedures. (*A*) An LST-NG type lesion 40 mm in size located in transverse colon (reverse view). Lesion margins delineated before ESD using 0.4% indigo carmine dye spraying. (*B*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, a half-circumferential incision (anal side) was performed using B-knife (retroflex view). After circumferential incision, sm dissection was performed using the same B-knife. (*C*) Straight view of the lesion after half-circumference marginal resection and sm dissection of the oral side. Additional resection of the margin on the anal side was performed using the B-knife in the straight view. (*D*) Dissection of the sm layer from outside to inside of the lesion is easily performed using the IT knife. (*E*) Ulcer bed after successful en-bloc resection in 1.5 hours. (*F*) Resected specimen was 40 × 30 mm in diameter and histologic findings revealed intramucosal cancer with tumor-free margin.

repeatedly into the sm layer to maintain the sm fluid cushion so as to minimize the risk of perforation.

6. Hemostatic forceps were used in soft coagulation mode (70–80 W) to control visible bleeding. The patient's position was sometimes changed to facilitate visualization of the tissue plane, and dissection continued until the lesion was completely excised.
7. After the colorectal ESD was completed, routine colonoscopic review to detect any possible perforation or exposed vessels was conducted and minimum coagulation was performed using hemostatic forceps on nonbleeding visible vessels to prevent postoperative bleeding (see **Fig. 2**E).
8. The resected specimen was stretched and fixed to the board using small pins (see **Fig. 2**F).

CLINICAL OUTCOME OF ESD AT NCCH

The en-bloc resection rate was 88% and the curative resection rate was 86% among 500 ESDs (**Table 1**). Of these, 127 were tubular adenomas, 315 were intramucosal cancers or minute sm cancers (sm1s), 55 were submucosal deep cancers (sm2s), 2 were carcinoid tumors, and 1 was mucosa-associated lymphoma tissue. The median operation time was 90 minutes, and the mean size of resected specimens was 40 mm (range, 20–150 mm).

COMPLICATIONS OF ESD AT NCCH

The postoperative bleeding rate for ESD was 1.0% (5 of 500), which is almost the same as that for conventional EMR (see **Table 1**). In contrast, the perforation rate for ESD

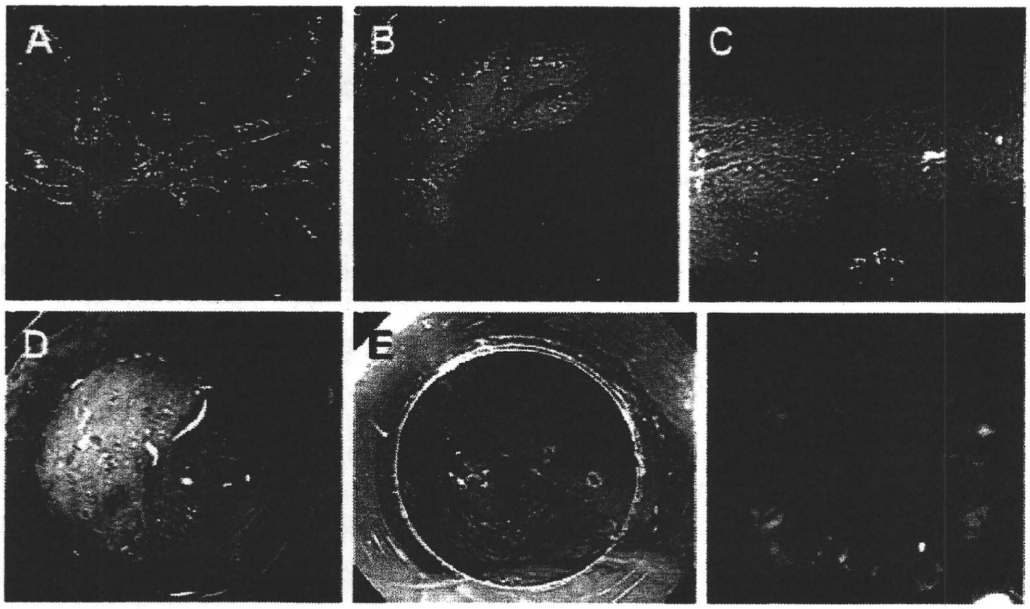

Fig. 3. ESD procedures for recurrent tumor. (*A*) A 20-mm flat-type lesion with ulcer scar was located in the transverse colon, and prominent fold convergences were noticed. (*B*) Lesion margins were delineated before ESD using 0.4% indigo carmine dye spraying. (*C*) Crystal violet (0.05%) staining clearly revealed IIIL and IIIs (non-invasive) pit pattern and indicated that this lesion was a good candidate for endoscopic treatment despite severe fibrosis and nonlifting sign. (*D*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, circumferential incision was performed using B-knife. After circumferential incision, sm dissection was performed using B-knife and IT knife. Severe sm layer fibrosis was visualized clearly due to the distal attachment, and the sm layer was carefully dissected just below this fibrosis. (*E*) Ulcer bed after successful en-bloc resection in 1 hour. (*F*) Resected specimen was 20 mm in diameter, and histologic findings revealed intramucosal cancer with tumor-free margin.

Table 1
Clinical outcomes of 500 colorectal ESDs at NCCH

Macroscopic Types	
LST-G/LST-NG	220/200
Depressed/Protruded	18/30
Recurrence	28
SMT	4
Location	C:35, Rt: 195, Lt: 130, R:140
Size of Resected Specimens [Mean±SD (range)]	40 ± 20 (20–150) mm
Pathology	Adenoma, 127; m-sm1, 315; sm2, approximately 55; Others, 3
Procedure Time	90 ± 73 (15–390) min
En-bloc Resection	88%
Curative Resection	86%
Complications	
Perforation	13[a] (2.6%)
Delayed Bleeding	5 (1%)

Abbreviations: C, cecum; Lt, left; m-sm1, intramucosal-submucosal superficial (invasive <1000 mm from the muscularis mucosae) cancer; R, rectum; Rt, right; sm2, submucosal deep; SD, standard deviation; SMT, submucosal tumor.

[a] All cases except 1 treated without surgery.

was 2.6% (13 of 500), which is considerably higher than that for conventional EMR (1.3%); only 1 perforation case needed emergency surgery because of ineffective endoscopic clipping. There have been no delayed perforations observed.

TECHNICAL PROGRESS OF COLORECTAL ESD

Until recently, colorectal ESDs have been performed mainly in Japan[10–15,22,23] because of the technical difficulty involved in the procedure. Also, the most frequent indication for ESD, early gastric cancer, is more common in Japan than in Western countries.[24] Some trained endoscopists, however, have started to do colorectal ESDs in Europe[25] and the United States.[26]

Given the thinness of the colonic wall, the use of specialized knives,[7,20] distal attachments,[14] and hypertonic solutions (Glycerol[21] and MucoUp[14]) that produce a longer-lasting and higher sm elevation cushion are necessary for safe ESD and to reduce the perforation rate. The B-knife[20] is safer because the electric current is limited to the needle and the bipolar system prevents electric current from passing to the muscle layer.

A noninvasive and simple tool that facilitates the direct visualization of the sm layer was needed to reduce the risk of perforations in colorectal ESD. As a result, the authors developed a sinker system for traction-assisted ESD[10] and more recently a thin-endoscope–assisted ESD.[27] In addition, Sakamoto and colleagues[28] reported the usefulness of a new traction device (S-O clip) for ESD of superficial colorectal neoplasms.

ESD enables us to treat recurrent lesions after incomplete endoscopic resections (see **Fig. 3; Fig. 4**) and large colorectal LSTs greater than 10 cm in diameter (**Fig. 5**). It is important, therefore, to diagnose the lesion carefully using chromomagnification colonoscopy[17,18] before treatment to reduce unnecessary noncurative resection for sm deep invasive cancers.[6]

COMPARISON BETWEEN ESD AND EMR

The primary advantage of ESD compared with EPMR is a higher en-bloc resection rate for large colonic tumors that had been treated by surgery previously. Consequently, ESD has a lower recurrence rate compared with EPMR (2% vs 14%) and also results

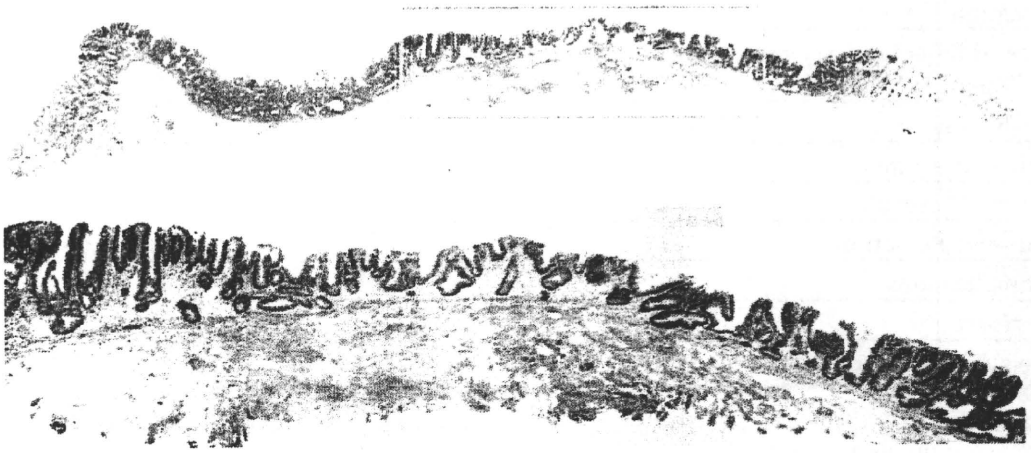

Fig. 4. Histologic findings revealed an intramucosal cancer with tumor-free margin. Severe fibrosis caused by previous EMR was observed at the center of this lesion.

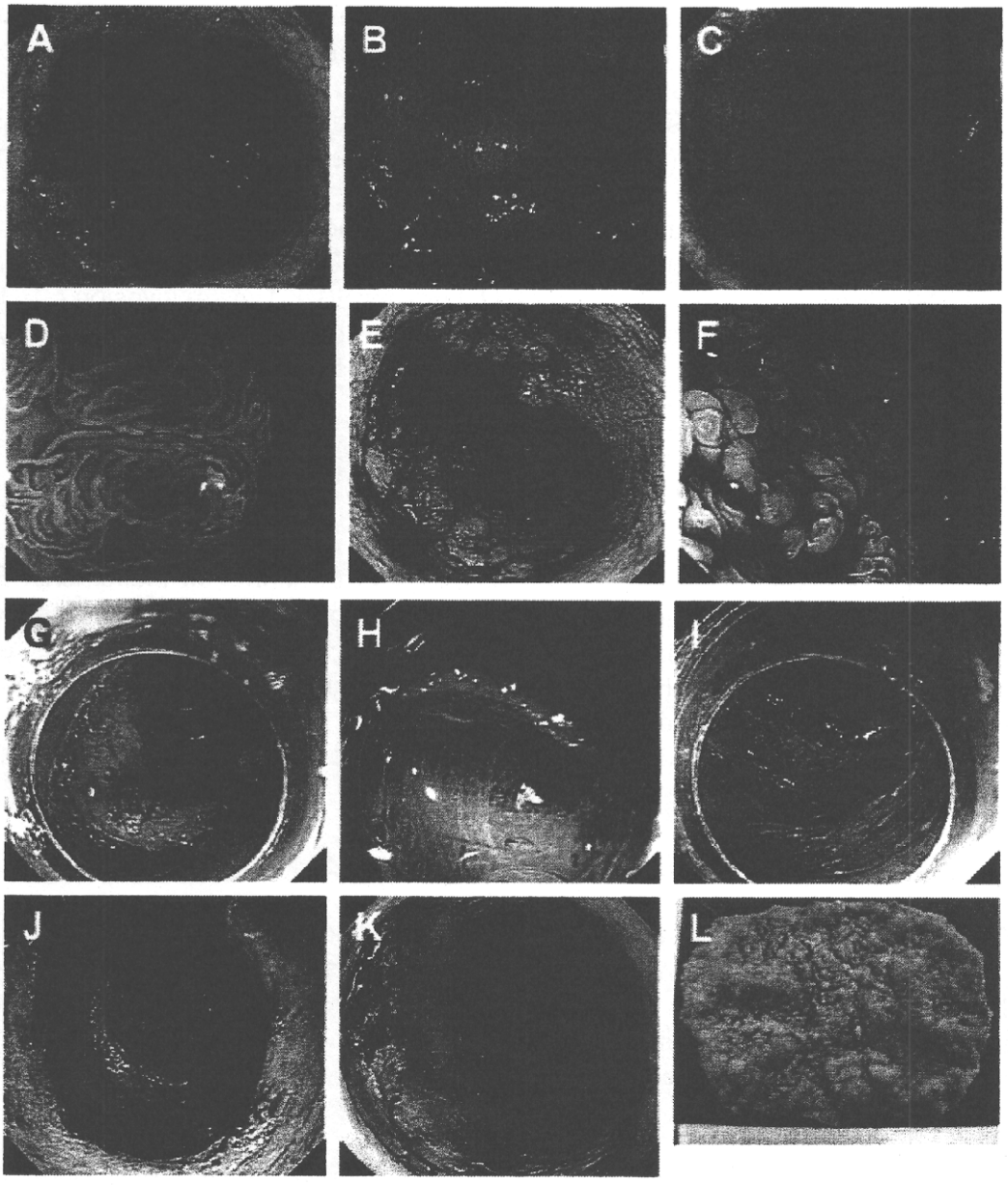

Fig. 5. ESD procedures for large LST-Gs. (*A*) An LST-G type lesion 100 mm in size located in the sigmoid colon. (*B*) A large nodule was identified in this LST-G. (*C*) Narrow-band imaging (NBI) revealed this LST-G lesion as brownish and the margin of this lesion became apparent. (*D*) NBI with magnification revealed a type II or IIIA Sano capillary pattern, suggesting intramucosal neoplastic lesion. (*E*) Lesion margins were delineated before ESD using 0.4% indigo carmine dye spraying. (*F*) Magnification colonoscopy with indigo carmine dye revealed non-invasive (IV) pit pattern at the elevated area of this lesion. (*G*) After injection of Glyceol and sodium hyaluronate acid solution into the sm layer, half-circumferential incision was performed using B-knife. (*H*) and (*I*) After circumferential incision, sm dissection was performed using B-knife and IT knife. Thickened sm layer was visualized as blue because of the distal attachment and indigo carmine. Sm dissection was performed carefully at this thickened sm layer above the muscle layer. (*J*) and (*K*) Ulcer bed after successful en-bloc resection in 2 hours. (*L*) Resected specimen was 100 mm in diameter, and histologic findings revealed intramucosal cancer with tumor-free margin.

in a better quality of life for patients compared with surgery. Future studies should be designed to compare the clinical outcomes of ESD and surgery but not of ESD and EMR because the indications for ESD and EMR are different as are the tumor characteristics.

Until now, EPMR had been considered a feasible treatment for colorectal LSTs. Low rates of local recurrence for such tumors and of repeat endoscopic resection were considered sufficient for most local recurrent tumors.[9]

In the authors' case series,[29] EPMR was also effective in treating many LST-Gs 20 mm or larger, but 3 cases (1.3%) required surgery after such piecemeal resections, including 2 cases of invasive recurrence.

Based on these results, cases for EPMRs in which accurate histologic evaluation would be difficult to make should be considered for ESD or laparoscopic surgery.

LST-Gs larger than 30 mm are good candidates for ESD. The sm invasion rate for such lesions was 16%, and multifocal invasion rate outside the large nodule or depression was 25%, which was more difficult to diagnose even using magnification colonoscopy.

INSTRUCTIONS ON POST-ESD CARE

From data analysis between ESD and EMR, follow-up endoscopy is recommended after 1 year for curative en-bloc ESD cases and after 6 months for piecemeal ESD cases considering local recurrence rates.[28] Even for pathologic curative resection cases, computed tomographic examination or endoscopic ultrasound imaging is recommended to examine lymph node metastasis or distant metastasis for sm1 cases and piecemeal resection cases.

Surgery is recommended for sm2s or cancers of deeper invasion or when lymphovascular invasion is diagnosed histologically.[6]

SUMMARY

ESD is a safe and effective procedure for treating colorectal LST-NGs larger than 20 mm and LST-Gs larger than 30 mm because it has a higher en-bloc resection rate and is less invasive than surgery. Establishment of a training system for technically more difficult colorectal ESD and further refinement of ESD instruments are encouraged for the increased use of colorectal ESD not only in Japan but also throughout the world.

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INDICATIONS FOR ENDOSCOPIC RESECTION OF COLORECTAL POLYPS AND SURVEILLANCE GUIDELINES

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We report three keynote lecture presentations from the Endoscopic Forum Japan 2009 at Otaru, Hokkaido, on 1–2 August 2009. We will discuss herein: (i) colorectal cancer screening focusing on a comparison between the National Polyp Study and the Japan Polyp Study; (ii) how to deal with small polyps <5 mm in diameter; (iii) the natural history of colorectal tumor development; (iv) the importance of follow up for local recurrence after endoscopic resection for colorectal polyps; and (v) screening for colorectal cancer using two new modalities, narrow-band imaging and autofluorescence imaging. A questionnaire was completed by everyone involved in the conference and the most important results were reported and then discussed by the participants.

Key words: colorectal cancer, surveillance guidelines, National Polyp Study, Japan Polyp Study, autofluorescence imaging, narrow-band imaging.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the USA and Japan. The 5-year survival rate for early-stage cancers is greater than 90%, whereas the 5-year survival rate for those diagnosed with advanced cancer is less than 10%.[1,2]

There is indirect evidence that most CRC develop from adenomatous polyps[3] and that it takes on average 10 years for a <1-cm polyp to be transformed into invasive CRC. The importance of the de novo cancer sequence, however, has been proposed and supported by not only Japanese, but also Western endoscopists based on their clinical experience.[4]

Given the findings that adenomatous polyps are precursors to cancer and that polyps and early cancers are usually asymptomatic, there is a strong rationale to support screening asymptomatic individuals for early colorectal cancer detection and prevention.

We report three keynote lecture presentations from the Endoscopic Forum Japan 2009 at Otaru, Hokkaido, on 1–2 August 2009. In this part of the program, we discussed the indications for endoscopic resection of colorectal polyps and surveillance guidelines.

Comparison of National Polyp Study and Japan Polyp Study

The National Polyp Study (NPS)[5] is used as the basis of recommendations for colonoscopic surveillance after polypectomy and it established an interval of 3 years after removal of newly diagnosed adenomas. The NPS was conducted, however, prior to recent epidemiological studies documenting the prevalence of non-polypoid lesions.[4] Thus, it was necessary to conduct a study similar to the NPS using Japanese-style colonoscopy, which consists of better bowel preparation using polyethylene glycol solution taken in the morning on the same day as colonoscopy and other techniques such as chromoendoscopy.

Matsuda *et al.* conducted a multicenter retrospective cohort study[6] to estimate the incidence of advanced neoplasia including the prevalence of non-polypoid lesions after initial colonoscopy using Japanese-style colonoscopy and to compare the differences among various risk groups. Their study group also started a multicenter prospective randomized controlled trial known as the Japan Polyp Study (JPS) in which the study design was similar to the NPS, but the concept was considerably different using Japanese-style chromoendoscopy.

How to deal with polyps <5 mm in diameter & natural history of colorectal polyp development

There is no question that all neoplastic lesions >5 mm in diameter should be resected endoscopically; however, the necessity of resection for small polyps <5 mm is still controversial.[7] The argument for not resecting colorectal polyps <5 mm is based on the hypothesis that such small lesions develop very slowly and need a long period to become invasive cancers.

Such small polyps, however, should be followed up endoscopically after several years. The natural history for the development of these colorectal polyps is still unclear because follow-up cases for such lesions without endoscopic

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resection are rare so far. A few reports are available from retrospective analysis of X-ray examinations.[8]

Until now, the adenoma–carcinoma sequence has been considered to be the main pathway for carcinogenesis, but the importance of the de novo cancer sequence has been proposed recently.

Follow up for local recurrence after endoscopic resection

Colorectal tumors >2 cm and suitable for endoscopic resection are usually superficial type lesions referred to as laterally spreading tumors (LST).[9,10] Such LST are treated with endoscopic mucosal resection (EMR), however, EMR for LST >2 cm occasionally result in piecemeal resection (EPMR).[11] The problem with EPMR is local recurrences and the difficulty of histological evaluation of the piecemeal resected specimens. There have been several reports of local recurrence after piecemeal resections, but the recurrence rate differed among the reports.[11,12] All of the previous reports were retrospective studies so a prospective study is necessary to establish the actual recurrence rate. In addition, endoscopic follow up is necessary within an appropriate period in order to manage local recurrence effectively.

Screening for colorectal cancer using two new modalities

For colorectal cancer screening, colonoscopy is considered the best method demonstrating the highest accuracy, sensitivity and specificity. High-definition colonoscopy[13] has been developed recently enabling colonoscopists to detect even small lesions, however, some flat and depressed lesions are still quite difficult to detect.

The autofluorescence imaging (AFI) (Olympus Medical Systems, Tokyo, Japan)[14] and narrow-band imaging (NBI) (Olympus Medical Systems) video endoscope systems[15–17] have recently been developed as non-invasive optical-digital techniques. It has been reported that both systems have an advantage over standard white light colonoscopy (WLC) and, therefore, may be more effective for the detection of colorectal adenomas.[16]

The AFI video endoscope system is an illumination method that allows for real-time WLC. Neoplastic areas involve a thickening of the mucosal layer and increased hemoglobin, so such areas emit weaker autofluorescence compared to non-neoplastic areas. Recently, the AFI system has been used to enhance detection of early neoplastic lesions in the esophagus, stomach and colon.

The NBI system is another novel optical-digital imaging process that uses special narrow-band filters in the endoscopic system to provide a more detailed visualization of the mucosal architecture and capillary pattern. As a result of the improved mucosal contrast provided by NBI, this technique also has the potential for improving the detection of colorectal lesions compared to standard WLC. NBI still remains somewhat controversial,[18,19] however, because some NBI reports from Japan and the UK have been positive but others from Western countries have been negative for polyp detection.

RESULTS OF QUESTIONNAIRE & DISCUSSION

Only one-third of the Japanese participants in the conference have guidelines for the resection of colorectal polyps <5 mm in diameter. Most participants resect such lesions case-by-case. In summary, it appears that there is no general agreement at the present time and this topic will require further study in the future before a consensus can be reached.

Sixty-three percent of the Japanese participants perform follow-up colonoscopy after 6 months for EPMR cases. In contrast, both of the Asian participants follow them up after 3 months (Fig. 1a). There is no definite evidence as to whether 3 months or 6 months is the better follow-up period. From our retrospective analysis, most recurrences were observed 6 months after EPMR and were treated successfully with repeat endoscopic resection.[12]

Concerning the treatment strategy for residual or recurrent tumors after EPMR, most participants chose endoscopic submucosal dissection (ESD)[20,21] or conventional EMR depending on the recurrent tumor characteristics with only one participant choosing surgery (Fig. 1b). Important factors for the treatment decision are tumor size, histology and tumor location. Appropriate colonoscopic follow up is necessary.

Most Japanese and Asian participants use NBI for targeted digital chromoendoscopy meaning that WLC is used for observation first and only when a polyp is detected, WLC is changed to the NBI mode and a detailed observation of the capillary pattern is performed. Interestingly, only 20% of the participants think that NBI will completely replace the role of indigo-carmine dye spraying (Fig. 1c).

For colorectal polyp detection, 25% of Japanese and 50% of Asian participants regarded NBI as useful in only some cases (Fig. 1d). Most Japanese participants regarded NBI as very useful for the differential diagnosis between non-neoplastic and neoplastic lesions, however, only one of two Asian participants regardeded NBI as being very useful for that purpose probably because NBI is not commonly used outside Japan at this time (Fig. 1e).

As for the possibility of estimating depth of diagnosis using NBI, the participants were undecided. Most participants thought NBI was useful for the depth of diagnosis of early colorectal cancer in some cases, but not for all cases (Fig. 1f). Five out of eight (63%) Japanese participants thought AFI was useful for polyp detection in some cases especially for flat lesions (Fig. 1g). Interestingly, five out of eight Japanese participants also thought AFI was useful for the differential diagnosis between non-neoplastic and neoplastic lesions. Unfortunately, AFI is only available in some Japanese institutions at this time so the data from the Asian participants was used only as a reference.

As for depth diagnosis, most participants thought AFI was not useful. NBI and AFI are considered very useful in some clinical settings, however, both will require further improvements and refinements in the future before widespread use not only in Japan, but also outside Japan.

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We would like to thank the doctors listed below for their excellent presentations and insightful scientific discussion.

In this preview, all reported information was based on an extensive questionnaire with data collected from the nine

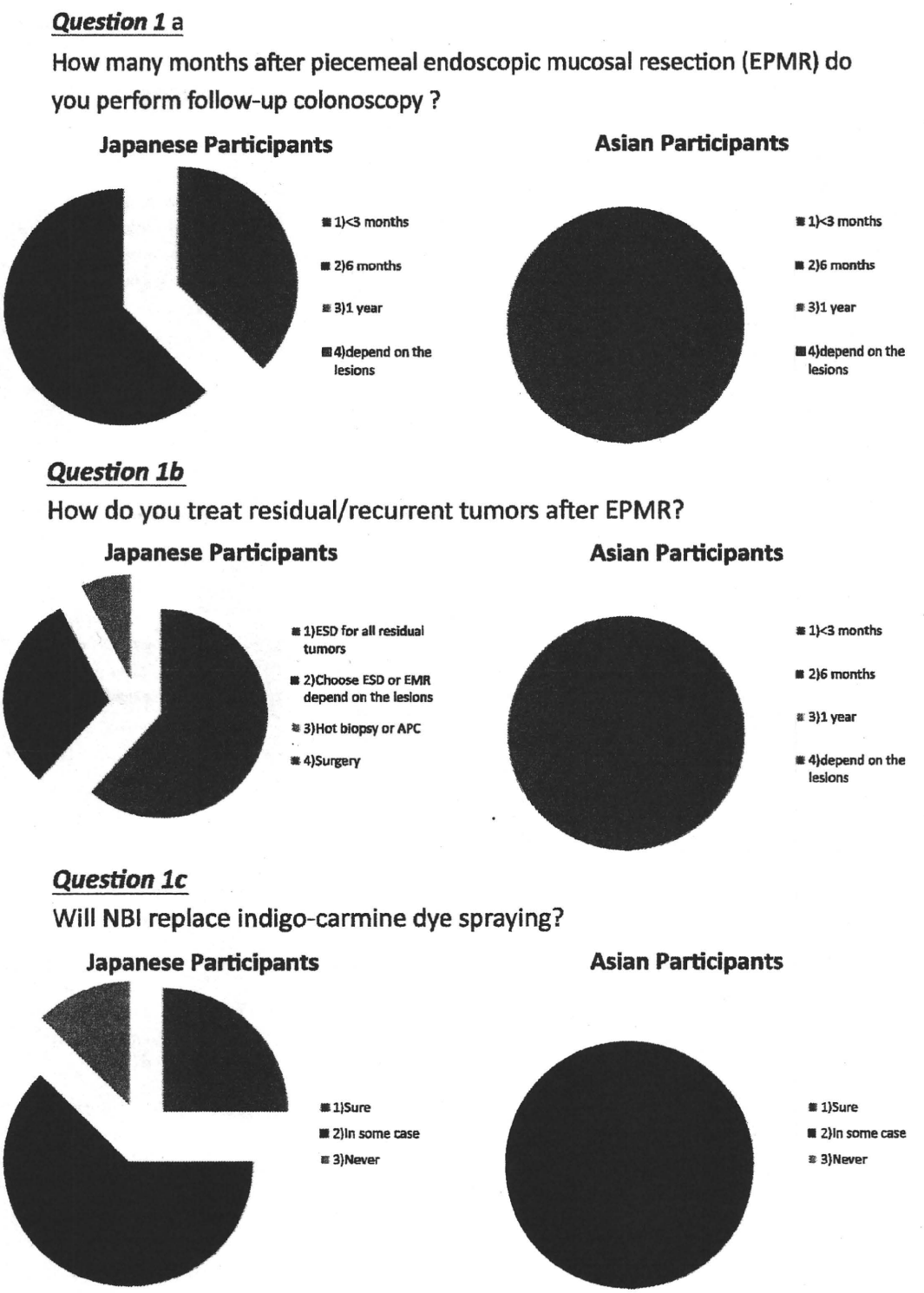

Fig. 1. Results of questionnaire. AFI, autofluorescence imaging; APC, argon plasma coagulation; EMR, endoscopic mucosal resection; EPMR, endoscopic piecemeal mucosal resection; ESD, endoscopic submucosal dissection; NBI, narrow-band imaging.

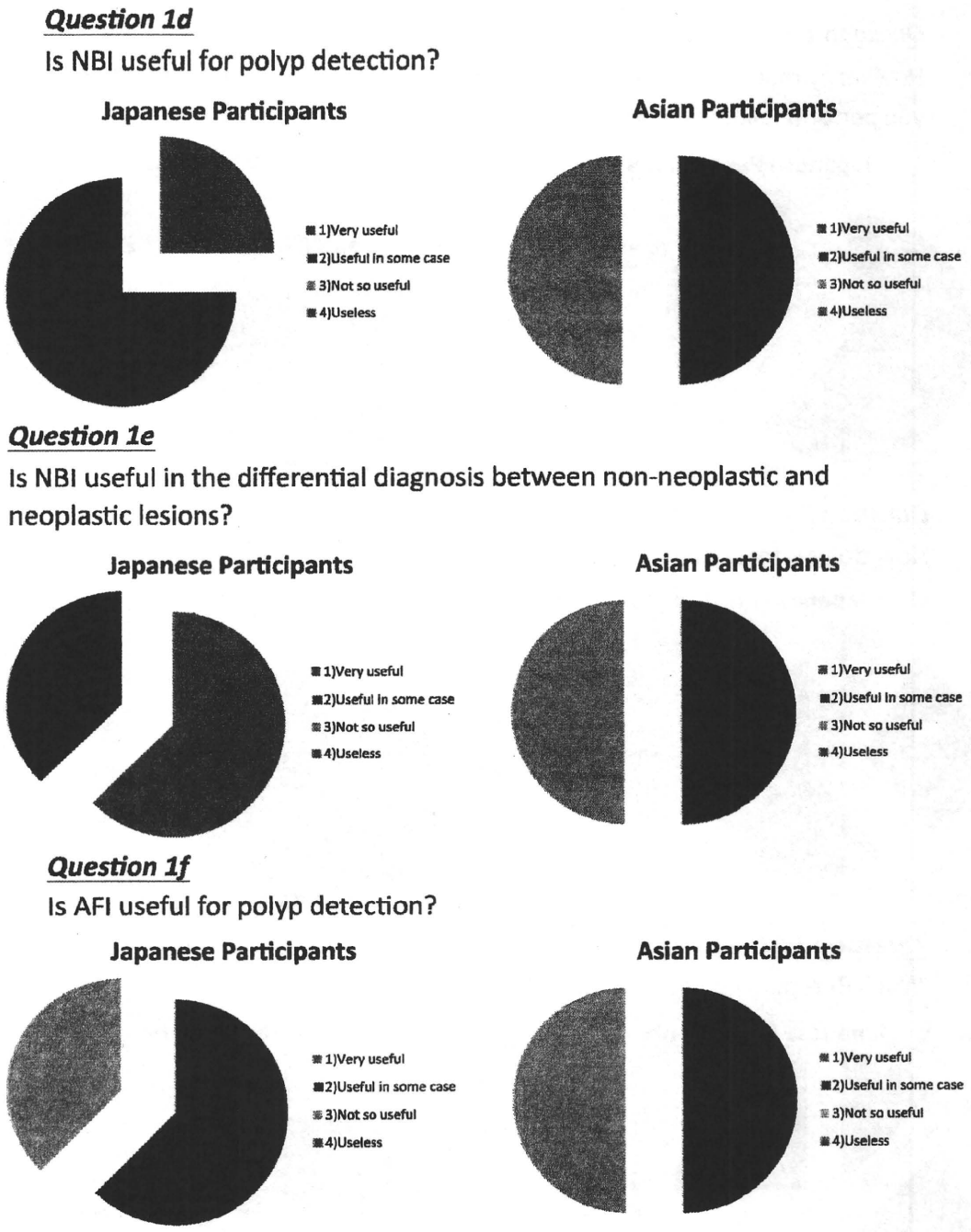

Fig. 1. *Continued*

Japanese participants and the two participants from Singapore and Korea.

Keynote lecturers

Lecture 1 – "How colorectal polyps are treated in Singapore"
Choon Jin Ooi, MD, Singapore General Hospital
Lecture 2 – "How colorectal polyps are treated in Korea"
Dong-Kyung Chang, MD, Samsung Medical Center
Lecture 3 – "Comparison of NPS and JPS"
Takahisa Matsuda, MD, National Cancer Center Hospital

Chairs

Hiro-o Yamano, MD, Gastroenterology Center, Akita Red Cross Hospital
Yutaka Saito, MD, Endoscopy Division, National Cancer Center Hospital

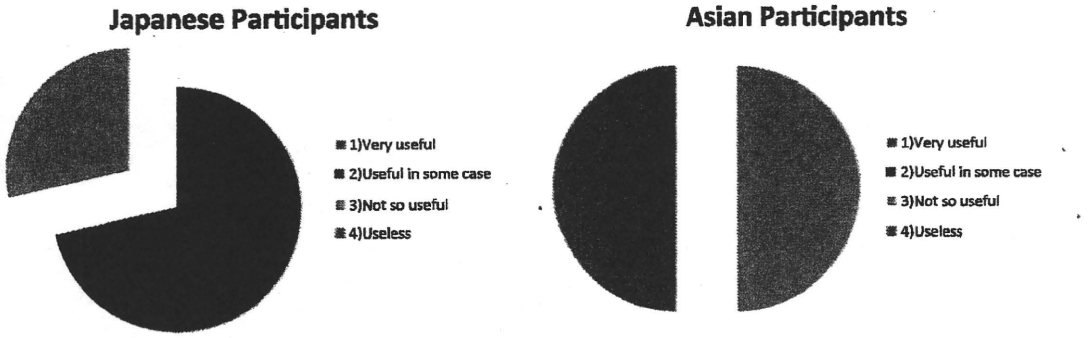

Fig. 1. *Continued*

Additional participants

Toshio Uraoka, MD, Okayama University
Sei Kurokawa, MD, Sapporo-Kosei General Hospital
Youji Takeuchi, MD, Osaka Medical Center for Cancer and Cardiovascular Diseases
Takashi Hisabe, MD, Fukuoka University Chikushi Hospital
Kinichi Hotta, MD, Saku Central Hospital
Takayuki Matsumoto, MD, Kyushu University

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Feasibility of endoscopic mucosal resection for superficial pharyngeal cancer: a minimally invasive treatment

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Background and study aims: New diagnostic techniques have recently been developed so detection of superficial pharyngeal cancer is dramatically increasing and endoscopic mucosal resection (EMR) can now be performed on an experimental basis. The aim of this study was to clarify the effectiveness of EMR for superficial pharyngeal cancer.

Patients and methods: Between 2004 and 2007, 31 patients with 37 pharyngeal lesions underwent EMR at our hospital. EMR using a cap-fitted endoscope (EMR-C) was used on 34 lesions and strip biopsies on the remaining three. We retrospectively assessed the effectiveness of those procedures in treating superficial pharyngeal cancer.

Results: Median procedure time was 45 minutes (range 20–180 minutes) and median hospital stay was 7 days (range 4–12 days). Regarding complications, one patient experienced laryngeal edema, one suffered aspiration pneumonia, and two sustained dermatitis around the mouth caused by Lugol staining. Histologically, 18 lesions were confirmed as carcinoma in situ and the other 19 lesions demonstrated microinvasion of the subepithelial tissue with lymphatic invasion in one case. During the median follow-up period of 40 months (range 21–62 months), two patients received radiotherapy and two patients underwent an additional EMR because of recurrent tumors. Five other patients developed metachronous superficial pharyngeal cancers, but all those lesions were resected primarily by EMR while two of the study's 31 patients died from esophageal cancer. None of the remaining 20 patients experienced any recurrent or metachronous tumors during their follow-up periods.

Conclusions: Our results indicated that EMR was a safe, effective, and minimally invasive treatment for superficial pharyngeal cancer.

Introduction

Although it is possible for gastrointestinal endoscopists to detect pharyngeal cancers, the early detection of superficial pharyngeal cancer by conventional white light endoscopy is extremely difficult because there are so few morphological changes [1,2]. For the detection of esophageal cancers, the widespread use of Lugol staining in high risk populations such as heavy drinkers and heavy smokers is recommended because that technique improves the endoscopic visualization of lesions and often makes it possible to diagnose esophageal cancer at an early stage [3–5].

Unfortunately, there has been no similarly effective diagnostic technique available until quite recently for the detection of pharyngeal cancer at an early stage. Lugol chromoendoscopy cannot be done since it causes severe mucosal irritation leading to significant patient pain and discomfort and can even result in aspiration into the airway [2]. The majority of pharyngeal cancers were previously detected at an advanced stage, therefore, and treated by surgical resection, resulting in both a lower quality of life and a poor prognosis for the patient [6–9]. Two new diagnostic techniques, magnifying endoscopy and narrow band imaging (NBI) [2,10–12], have recently been developed, however, and detection of superficial pharyngeal cancer is now increasing dramatically. Extensive surgical resection for pharyngeal cancer causes loss of swallowing and/or speaking functions and can also lead to cosmetic deformities [6–9]. The development of a new, minimally invasive treatment modality, therefore, was highly desirable for treating pharyngeal cancer. Endoscopic mucosal resection (EMR) is now considered to be one of the possible treatments not only for superficial esophagogastric cancer [13–18], but also for superficial pharyngeal cancer [2,19–22]. Although the feasibility of EMR for superficial esophagogastric cancer has been validated, EMR for

superficial pharyngeal cancer is still an experimental treatment. The aim of this study, therefore, was to determine the short-term outcome of EMR for superficial pharyngeal cancer to help clarify its clinical effectiveness.

Patients and methods

Patients

Between March 2004 and August 2007, EMR was performed by gastrointestinal endoscopists at the National Cancer Center Hospital in Tokyo on 31 men (mean age 64.4 years, range 52–77) with 37 superficial pharyngeal cancers. Of the patients, 30 had either synchronous (n = 14) or prior esophageal carcinomas (n = 16) and only one patient experienced any symptom (throat discomfort) related to pharyngeal cancer. The demographic characteristics of the patients are shown in ● **Table 1**.

In an effort to clarify the clinical effectiveness of EMR for superficial pharyngeal cancer in this study, we retrospectively assessed the clinical characteristics of the EMR procedures, the histological features of the pharyngeal cancers, and the short-term outcomes. The study protocol was approved by the medical ethics committee of our hospital, and the risks and benefits of EMR were explained to every patient and written informed consent was obtained from each of them beforehand.

Table 1 Clinical characteristics of patients.

Age, years	
Mean	64.4
Range	52–77
Sex	
Men	31
Women	0
Esophageal cancer	
Present	30
Synchronous	14
Prior	16
Absent	1

Definition of superficial pharyngeal cancer

According to the Japan Society for Head and Neck Cancer [23], a superficial pharyngeal lesion is defined as one in which invasion depth is comparatively limited and visual changes do not indicate an advanced cancer. The pharynx has no muscularis mucosae so this somewhat vague definition suggests that depth of invasion is limited to the epithelium or just beneath the epithelium, but does not extend to the muscle layer.

Indications for EMR of pharyngeal cancer

The inclusion criteria for EMR of pharyngeal cancer in our hospital were: (i) endoscopic diagnosis of superficial pharyngeal cancer, and (ii) no findings of lymph node or other organ metastasis at computed tomography (CT).

EMR of pharyngeal lesions was excluded in the case of: (i) a large bilateral hypopharyngeal cancer, or (ii) a hypopharyngeal cancer involving the larynx, because of the possible occurrence of laryngeal edema after EMR of such lesions; (iii) advanced stage pharyngeal cancer; or (iv) pharyngeal cancer with lymph node and/or other organ metastasis regardless of invasion depth. Either radiotherapy (chemoradiotherapy) or surgical resection with lymphadenectomy was indicated for such lesions.

EMR procedures

Lesions were removed using conventional EMR techniques, including EMR using a cap-fitted endoscope (EMR-C) and strip biopsy methods. EMR-C was initially attempted with every lesion, but strip biopsy was subsequently used when injection of saline solution did not sufficiently elevate the mucosa for aspiration into the cap. If any residual tumor was observed on the lateral margin of the ulceration after EMR, electrocautery was also done using hot biopsy forceps.

EMR for pharyngeal lesions was done with the patients either under general anesthesia or intravenous deep sedation using diazepam and pentazocine. With relatively small superficial pharyngeal cancer lesions, when the endoscopist who was to perform the procedures and the consulting head and neck surgeon both judged beforehand that endoscopic treatment could be satisfactorily accomplished in a short time without any complications such as laryngeal edema or aspiration, only intravenous deep sedation was used during the procedures. In the remaining cases where endoscopic treatment was considered to be more difficult, EMR was done with general anesthesia to ensure that the procedures were completed safely. All patients also received local injections of lidocaine mixed with epinephrine-saline solution to anesthetize the mucosa [24].

EMR-C. In this procedure a small specialized plastic cap is attached to the tip of a standard endoscope (Olympus Corp., Melville, New York, USA) (● **Fig. 1**). After chromoendoscopy using Lugol staining, diluted epinephrine-saline solution with lidocaine was injected into the base of the lesion with a needle. Prelooping, which involved attaching a crescent-shaped snare (SD-221L-25 or SD-7P-1; Olympus Corp., Tokyo, Japan) to the rim of the cap, was done outside the oral cavity. The endoscope was then inserted into the pharynx, the lesion was suctioned into the cap and the snare was pushed down to the base of the aspirated lesion and closed, thereby strangulating the lesion. The suction was released, correct and complete capture of the lesion was assessed and, finally, the lesion was electrosurgically resected [15, 16].

Strip biopsy. This technique requires a double-channel endoscope (2T240; Olympus). After injection, a snare and grasping forceps were each inserted through a channel. The forceps were then passed through the opened snare and the snare was closed lightly around them. An area near the lesion was grasped with the forceps to elevate the lesion, the snare was opened, the lesion was strangulated, and the tumor was then resected by the application of an electrosurgical current [17, 18].

Histological assessment after EMR

Resected specimens were extended on boards with pins and fixed in 10% formalin for 24 hours. After fixation, all resected specimens were cut into 2-mm width longitudinal slices. These were embedded in paraffin and stained with hematoxylin–eosin. Histological assessments that included tumor size, depth of invasion, and vascular invasion were performed microscopically.

Follow-up care

After EMR, each patient underwent both surveillance laryngoscopy and endoscopy at least every 3 and 6 months, respectively. Surveillance endoscopy was done using conventional white light endoscopy until December 2004, but from January 2005, when an NBI video endoscope system was installed in our hospital, most surveillance examinations were done using NBI. A CT scan