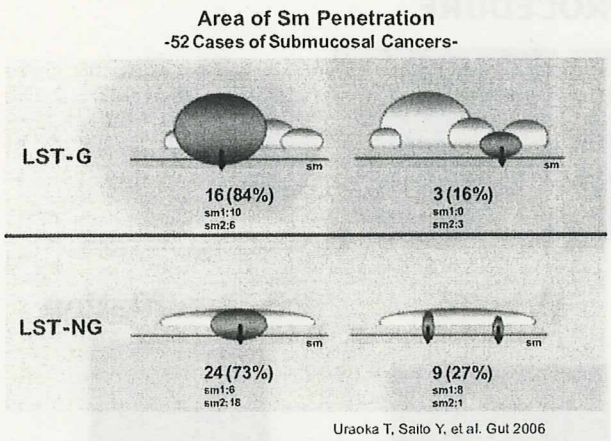

Fig. 1. Histologically, 27% of submucosal (sm) invasions are multi-focal in laterally spreading tumors (LST)-non granular (NG) and such invasions are difficult to predict before treatment. In contrast, LST-granular (G) have a lower rate of submucosal invasion and most such invasions are found under the largest nodule.

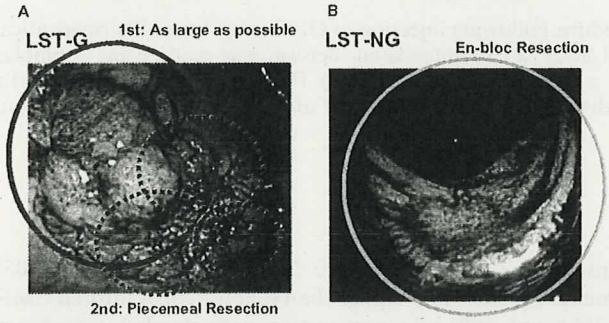

Fig. 2. (A, B) Endoscopic mucosal resection (EMR) Strategy for laterally spreading tumors (LST). An LST-granular (G) >20 mm can be treated by planning endoscopic piecemeal resection (EPMR) rather than endoscopic submucosal dissection (ESD) with the area including the largest nodule resected first followed by the remaining tumor (A). In contrast, LST-non granular (NG) >20 mm should be treated by en-bloc resection using ESD technique or laparoscopic surgery (B).

Yamamoto *et al.*[14] have reported the usefulness of sodium hyaluronate solution as a sm injecting solution in combination with a small-caliber-tip transparent hood (ST Hood) to provide a counter traction for colonic ESD. Sodium hyaluronate solution is a hypertonic solution which produces a longer lasting and higher sm elevation compared to normal saline or glycerol.[15] The ST Hood enables us to expand the narrow sm layer to visualize the cutting line.

Other traction systems that facilitate ESD procedures have been reported recently such as the percutaneous traction-assisted (PTA)-EMR[16] and the magnetic anchor system.[17] The PTA-EMR is not appropriate for colorectal ESD because of it's use of a laparoscopic device which is not suitable in the colon; and the magnetic anchor system requires a large magnetic control system that is not yet available for clinical use.

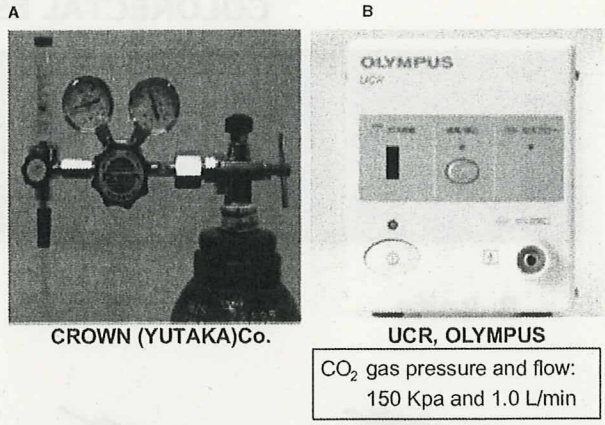

Fig. 3. (A, B) CO_2 gas regulator. (A) CO_2 was administered by using a commercially available CO_2 regulator (Gas Regulator, Crown, Model FR-IIS-P; Yutaka Engineering, Tokyo, Japan), which was connected to a CO_2 bottle. (B) A new type CO_2 regulator (Olympus UCR, Olympus, Tokyo, Japan). CO_2 was administered by using a CO_2 regulator (Olympus UCR, Olympus), which was connected to the endoscope supply tube by means of a 'quick lock' connector, and a flow indicator provides visual confirmation that CO_2 is being delivered. CO_2 was constantly set at 1.5 liters per minutes during the procedures.

A non-invasive and simple tool that facilitates the direct visualization of the sm layer, therefore, is needed to reduce the risk of complications in colorectal ESD. As a result, we have developed a sinker system for traction-assisted ESD of colonic LST-NGs > 20 mm in size[18] and more recently a thin endoscope-assisted ESD.[19]

A. Estimation of the depth of invasion

In each lesion, a non-invasive pattern[20-22] was observed indicating that it was suitable for endoscopic resection because of an estimated depth less than sm1. No biopsies were performed before any procedure.

B. ESD procedures at NCCH

The procedures were primarily performed using a bipolar needle knife (B-knife) (XEMEX Co., Tokyo, Japan)[23] or IT knife with CO_2 insufflation instead of air insufflation to reduce patient discomfort (Fig. 3A,B).[24-26] Following injection of Glycerol (Chugai Pharmaceutical Co, Tokyo, Japan)[15] and sodium hyaluronate acid solution into the sm layer,[14] a circumferential incision was made using a B-knife and an ESD was then carried out using both a B-knife and IT knife (Fig. 4).

CLINICAL OUTCOME OF ESD AT NCCH (Table 3)

The en-bloc resection rate was 87% and the curative resection rate was 86% among the 405 ESDs: 101 involved tubular adenomas, 255 intramucosal cancers or minute sm cancers (sm1), 46 sm2 cancers and 3 others (MALT and carcinoid tumors). The median operation time was 90 minutes and the

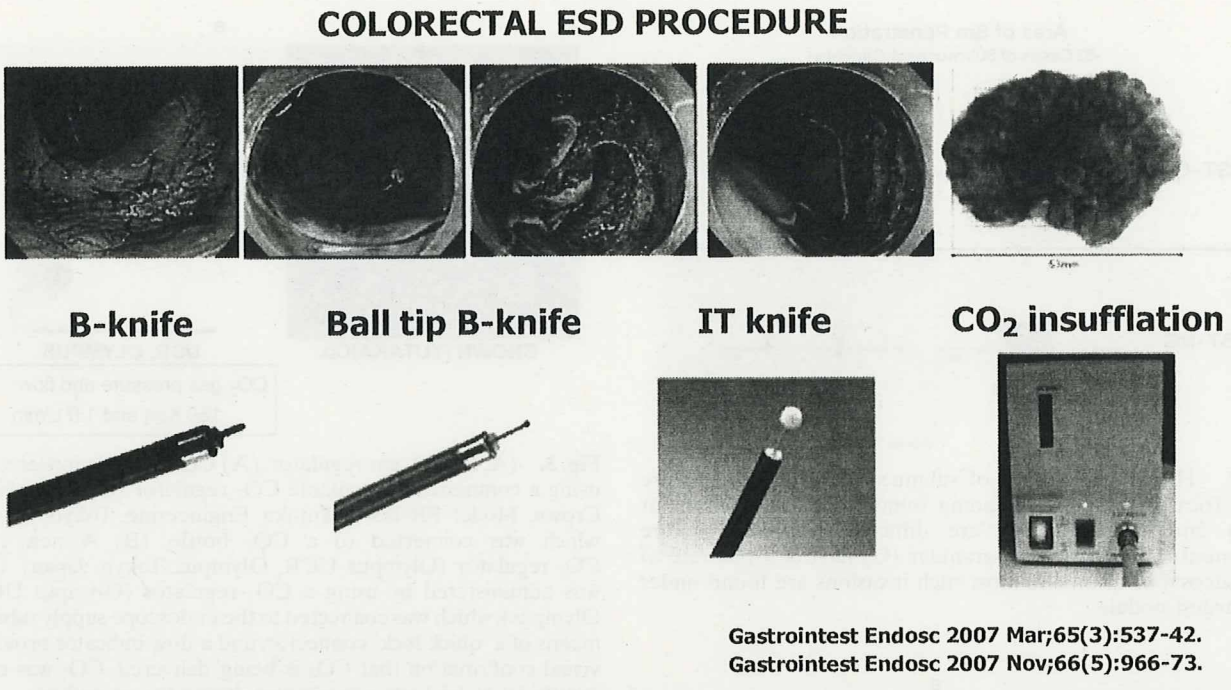

Fig. 4. (A) Colorectal endoscopic submucosal dissection (ESD) procedure. Following injection of Glycerol (Chugai Pharmaceutical Co, Tokyo, Japan) and sodium hyaluronate acid into the submucosal layer, a circumferential incision was made using a bipolar needle knife (B-knife) and an ESD was then carried out using both a B-knife and IT knife. (B) The procedures were primarily performed using a B-knife (XEMEX Co., Tokyo, Japan) or IT knife with CO_2 insufflation instead of air insufflation to reduce patient discomfort.

Table 3. Results of 405 colorectal endoscopic submucosal dissections (ESDs)

Macroscopic types	
LST-G/LST-NG	173/168
Depressed/Protruded	15/21
Recurrence	25
SMT	3
Location	C:39, Rt:153, Lt:102, R:111
Size of resected specimens Mean ± SD (range)	40 ± 20 (15–150) mm
Pathology	Adenoma:101, M-SM1:255, SM2~:46 Others:3
Procedure time	90 ± 73 (15–390) min.
En-bloc resection	352/405 (87%)
Non-curative resection	57/405 (14%)
Complications	
Perforation	14* (3.5%)
Delayed bleeding	4 (1%)

*All cases except one treated without surgery.
LST-G, laterally spreading tumor-granular; LST-NG, laterally spreading tumor-non granular; SM1, submucosal tumor.

mean size of resected specimens was 40 mm (range: 15–150 mm).

COMPLICATIONS OF ESD (Table 3)

The post-operative bleeding rate for ESD was 1.0% (4/405) which is almost the same as that for conventional EMR. In contrast, the perforation rate for ESD was 3.5% (14/405) which is considerably higher than that for conventional EMR (1.3%), but only one perforation case needed emergency surgery because endoscopic clipping was ineffective. There have been no delayed perforations observed as of now.

DISCUSSION

Until recently, colorectal ESDs have been performed mainly in Japan[25-29] because of the technical difficulty and the most frequent indication for ESD is early gastric cancer, which is a common finding in Japan but rare in Western countries. But, some trained endoscopists have started to do colorectal ESD even in Europe[30] and the USA.[31]

Complications resulting from ESD occasionally occur mainly due to inaccurate identification of the cutting line because the ablated mucosa cannot be stabilized and pulled away.[32] The resultant cutting of sm vessels causes bleeding and underestimation of the depth of the sm layer results in perforations. To reduce the perforation rate in colorectal ESD, therefore, the use of specialized knives,[9,23] distal attachment[14] and hypertonic solution which produces a longer lasting and higher sm elevation (glycerol[15] and sodium hyaluronate solution)[14] are necessary for safer ESD given the thinner colonic wall.

At NCCH, the perforation rate of 3.5% in the ESD group was considerably higher than the 1.3% perforation rate in the EMR group, however, most perforation cases were successfully treated conservatively without surgery by endoscopic

clipping and the perforation rate has been decreasing based on the increase of the endoscopists skill and recent ESD device developments.

As a result, the perforation rate of 3.5% in the ESD group was considered to be acceptable although further instrument improvements and technique refinements will both be necessary to reduce the perforation rate.

The primary advantage of ESD compared to EMR is higher en-bloc resection rate for large colonic tumors which had been treated by surgery. Consequently, ESD has a lower recurrence rate compared to EPMR and also a better quality of life for patients compared with surgery. We should compare, therefore, the clinical outcome between ESD and surgery not with EMR because the indications for ESD and EMR were different as were the tumor characteristics.

A total of 145 lesions treated with ESD and 228 lesions with conventional EMR for which follow-up colonoscopy examinations could be carried out more than six months after treatment were further analyzed for recurrence rate. There were only three cases (2%) of local recurrence in the ESD group (mean endoscopic follow-up period, 20 ± 13 months). In comparison, local recurrence occurred in 14% (33/228) of the lesions in the EMR group (mean endoscopic follow-up period, 26 ± 17 months). Two EPMRs required surgery because of invasive recurrence while a third piecemeal resection also required surgery because of technical difficulty in performing another EMR despite the intramucosal nature of that particular recurrence. Curative EMR resections were achieved for all other recurrences.

FUTURE PROSPECTS

Currently, most sm2 cancers have been treated surgically because of the risk of LN metastasis, however, few cases of those surgical patients proved to have LN metastasis. As a result, most of those surgical patients received unnecessary surgeries without any evidence of LN or distant metastasis.

Lesions without risk of LN metastasis will be elucidated by further analysis including molecular biology in the near future. ESD for invasive cancer without risk of LN metastasis will then be appropriate.

CONCLUSIONS

The ESD technique with CO_2 insufflation is a feasible method for treating large superficial colorectal tumors safely. It offers the advantage of obtaining an en-bloc resection which, in turn, results in more accurate histological analysis and less frequent recurrence.

CONFLICT OF INTEREST

No conflict of interest has been declared by Y Saito, T Sakamoto, S Fukunaga, T Nakajima, S Kiriyama or T Matsuda.

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Case Report

Application of Endoscopic Submucosal Dissection for Removal of Deep Invasive Submucosal Colon Carcinoma

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Endoscopic submucosal (sm) dissection (ESD) is a recently used technique that enables *en-bloc* resection of large colorectal tumors allowing a more precise histopathological analysis of the resected specimen. However, it has not been widely adopted even in Japan mainly due to its technical difficulty and increased risk of perforation. Herein, we present an ESD-treated lesion with deep sm invasion removed without complications, such as bleeding or perforation, from a patient at high-risk for surgical intervention. A successful ESD was achieved although the sm invasion was greater than 1000 μm from the muscularis mucosae, and the nonlifting sign was positive. It is our belief that this procedure should be performed at least in patients at high-risk for surgical intervention. At present, we have removed 16 lesions with deep sm invasion by ESD without complications, demonstrating that deep sm cancer can be successfully resected by this technique as a local resection. Herein, we report on one of these cases

1. Introduction

In Japan, as shown in [1–3], EMR is the treatment of choice for superficial early colorectal cancer due to the minimal invasiveness and efficacy of the procedure. However, when dealing with flat lesions greater than 20 mm in diameter, the rate of piecemeal resection, incomplete removal, and local recurrence after EMR increases, as discussed in [4–6]. Endoscopic submucosal (sm) dissection (ESD) is a recently used technique that enables *en-bloc* resection of large colorectal tumors allowing a more precise histopathological analysis of the resected specimen, as shown in [7, 8]. However, as cited in [9, 10], colorectal ESD has not been widely adopted even in Japan mainly due to its technical difficulty and increased risk of perforation.

Herein, we report on an ESD-treated lesion with deep sm invasion removed from a patient at highrisk for surgical intervention. The role of ESD for lesions with sm invasion greater than 1000 μm from the muscularis mucosae is discussed.

2. Case Presentation

A 79-year-old male was diagnosed to have a lesion of 28 mm in diameter located in the rectosigmoid colon, with a 0-IIa + IIc macroscopic type (**Figure 1**). Pathological findings of biopsy specimens revealed a well-differentiated adenocarcinoma. The nonlifting sign was positive. As discussed by Matsuda [11], high magnifying observation with crystal violet staining showed an invasive pattern with irregular and distorted epithelial crypts in the demarcated area suggesting sm invasion greater than 1000 μm from the muscularis mucosae. Open surgery was the first choice offered to the patient. However, as he was considered to be at high risk for surgical intervention due to his history of two acute myocardial infarction episodes and an abdominal aorta bypass procedure, endoscopic resection of the lesion was recommended to avoid open surgery.

As decribed in [12–15], under conscious sedation, with CO_2 insufflation, after indigocarmine dye spraying and injection of glycerol and sodium hyaluronate acid into

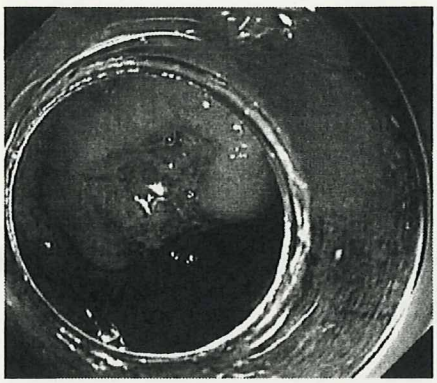

FIGURE 1: Conventional view of a 0-IIa + IIc lesion located in the rectosigmoid colon. A definite depressed margin and irregular reddened surface of depression suggested submucosal deep invasion.

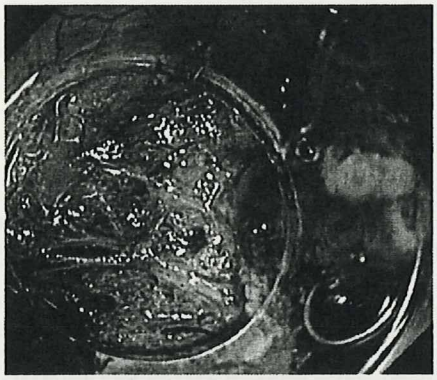

FIGURE 2: Direct observation of the submucosal and muscle layers is possible due to the utility of distal attachment.

the sm layer, a circumferential mucosal incision was made using a bipolar current needle knife (B-knife) (XEMEX Co., Tokyo, Japan). The sm dissection was performed using a B-knife and an insulation-tipped diathermic knife (IT-knife) (Olympus Medical Systems Corp., Tokyo, Japan) providing a direct observation of the sm and muscle layers (Figure 2). The resection left an ulcer bed without muscle damage or bleeding (Figure 3). The *en-bloc* resection and removal of the specimen was completed in approximately 80 minutes without any complication (Figure 4). Histopathological analysis of the resected specimen showed a well-differentiated adenocarcinoma, and the depth of invasion was sm 2500 μm with negative lateral and vertical margins (Figure 5).

3. Discussion

According to the Paris classification of superficial neoplastic lesions [16], lesions with sm invasion of less than 1000 μm from the muscularis mucosae should be removed by ESD. In contrast, lesions with sm invasion exceeding 1000 μm are currently considered for surgical resection, as shown in [17, 18]. In this particular case, due to the patient's

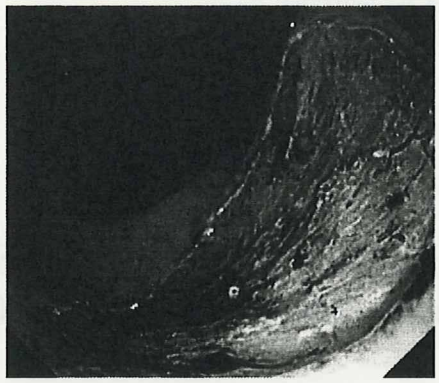

FIGURE 3: Ulcer bed after *en-bloc* resection of the lesion. There is no muscle damage or bleeding.

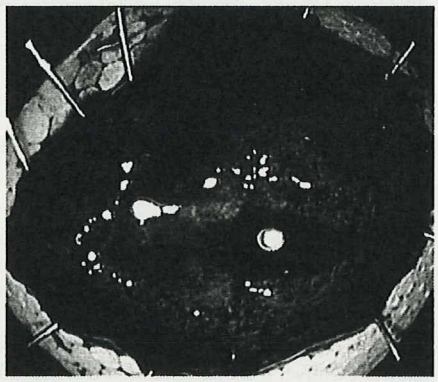

FIGURE 4: A view on the *en-bloc* resected specimen. The surgical margin is visible.

FIGURE 5: Histopathological analysis of the resected specimen showed a well-differentiated adenocarcinoma, and the depth of invasion was sm 2500 μm with negative lateral and vertical margins.

critical heart condition, ESD was performed although the sm invasion exceeded 1000 μm in depth, and the nonlifting sign was positive.

At the National Cancer Center Hospital a total of 16 cases with deep invasive sm lesions have been successfully removed by ESD, with negative lateral and vertical margins observed during histopathological analysis of the resected specimen.

During ESD for sm cancer, a direct observation of the sm and muscle layers possibilitates a total sm resection. If the lesion has invaded the muscularis propria though, ESD should not be performed because of the risk of colonic perforation. However, as discussed by Saito [7], the use of the B-knife in ESD has decreased the perforation rate. By using this device, a safer procedure is achieved probably because

the electric current is centered to the tip of the needle, as shown in [19].

This case has demonstrated that the removal of lesions with sm invasion greater than 1000 μm from the muscularis mucosae can be successfully resected by ESD as a local resection. It is our belief that this procedure should become the treatment of choice for deep invasive sm cancer at least in patients at high risk for surgical intervention, which would avoid the risk of a surgical procedure and would improve the patient's quality of life.

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ORIGINAL ARTICLES

Size does not determine the grade of malignancy of early invasive colorectal cancer

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Abstract

AIM: To clarify the clinicopathological characteristics of small and large early invasive colorectal cancers (EI-CRCs), and to determine whether malignancy grade depends on size.

METHODS: A total of 583 consecutive EI-CRCs treated by endoscopic mucosal resection or surgery at the National Cancer Center Hospital between 1980 and 2004 were enrolled in this study. Lesions were classified into two groups based on size: small (≤ 10 mm) and large (> 10 mm). Clinicopathological features, incidence of lymph node metastasis (LNM) and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

RESULTS: There were 120 (21%) small and 463 (79%) large lesions. Histopathological analysis of the small lesion group revealed submucosal deep cancer (sm: ≥ 1000 μm) in 90 (75%) cases, LVI in 26 (22%) cases, and PDA in 12 (10%) cases. Similarly, the large lesion group exhibited submucosal deep cancer in 380 (82%) cases, LVI in 125 (27%) cases, and PDA in 79 (17%) cases. The rate of LNM was 11.2% and 12.1% in the small and large lesion groups, respectively.

CONCLUSION: Small EI-CRC demonstrated the same aggressiveness and malignant potential as large cancer.

Key words: Colorectal cancer; Submucosal invasion; Lymph node metastasis; Endoscopic mucosal resection

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INTRODUCTION

Colorectal cancer (CRC) is the third most important cause of cancer mortality in Japan, and its incidence is gradually increasing. To reduce CRC mortality, early detection and appropriate treatment are required. In general, small lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size[1-3]. Therefore, lesion size is considered to be indicative of the depth of invasion and presence of lymph node metastasis (LNM). In contrast, flat, and in particular depressed lesions, are considered to have a tendency to invade rapidly the submucosal layer, even when small[4-6]. However, clinicopathological features of small EI-CRCs have still

not been studied extensively.

The aim of this retrospective study was to clarify the clinicopathological characteristics of small and large EI-CRCs and their implications for endoscopic treatment.

MATERIALS AND METHODS

Subjects

Five hundred and eighty-three patients (374 male and 209 female) with EI-CRC that had been resected surgically or endoscopically at the National Cancer Center Hospital, between January 1980 and January 2004, were examined retrospectively. In all of these patients, cancer cells invaded through the muscularis mucosa into the submucosal layer but did not extend deeply into the muscularis propria. Eligibility also required the lesions to be macroscopically non-pedunculated (sessile, flat and depressed). Patients with synchronous advanced CRC, multiple EI-CRCs, inflammatory bowel disease, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis were excluded from the study.

Methods

All lesions were classified into two groups according to their endoscopic image size: small ($\leq$ 10 mm) and large (> 10 mm). Furthermore, lesions were classified into three categories (sessile, 0- I s, I s+ II a; flat, 0- II a; and depressed, 0- II c, II a+ II c, I s+ II c) according to the Paris classification[7]. Clinicopathological features, incidence of LNM and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

Histopathology

Resected specimens were fixed in 10% formalin and examined histopathologically following hematoxylin and eosin staining. Histopathological diagnosis was based on the World Health Organization (WHO) criteria[8]. Submucosal invasion was measured from the muscularis mucosa to the deepest portion. When the muscularis mucosa could not be identified because of cancer invasion, the vertical length was measured from the surface of the lesion to the deepest portion according to Kitajima's classification[9]. Tumors with a vertical length of < 1000 μm in the submucosal layer were classified as submucosal superficial invasive cancers (sm-superficial), and lesions with a length $\geq$ 1000 μm were classified as submucosal deep invasive cancers (sm-deep). The tumor growth patterns were histopathologically divided into polypoid growth (PG) and non-polypoid growth (NPG) types. Shimoda *et al*[10] have reported polyp cancers with protrusions caused by intramucosal proliferation of the carcinoma or coexistent adenoma that behaved as PG type carcinoma, while flat/depressed type carcinoma without polypoid proliferation of intramucosal tumor behaved as NPG type carcinoma.

Statistical analysis

The significance of differences in proportions was assessed by the χ^2 test, Fisher's exact test and the Wilcoxon matched-pairs signed-ranks test using SPSS statistical software (SPSS for Windows , version 16.0J, Tokyo, Japan). Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 583 EI-CRCs were retrospectively evaluated, with 120 (21%) small and 463 (79%) large lesions identified (Table 1). The gender ratio (male/female) was 2.4 and 1.7, and the mean age was 61.5 and 62.4 years in the small and large lesion groups, respectively. Mean size of the small and large lesions was 8.3 and 22.1 mm, respectively.

Macroscopic type, growth type and location

Macroscopic assessment of small lesions identified 51 cases as sessile (42%), 14 as flat (12%), and 55 as depressed (46%). Similarly, large lesion groups comprised 233 sessile (50%), 64 flat (14%), and 166 depressed (36%) type. PG types were identified in 32% (38/120) and 54% (250/463) of small and large lesions, respectively. In contrast, the prevalence of NPG type in the small lesion group was significantly higher than in the large lesion group (68% *vs* 46%, $P < 0.0001$). Regarding tumor location, there were 33 (27%) rectal, 56 (47%) distal colon and 31 (26%) proximal colon cancers in the small lesion group. In contrast, there were 213 (46%) rectal, 139 (30%) distal colon and 111 (24%) proximal cancers in the large lesion group. The incidence of rectal cancer in the large lesion group was significantly higher than in the small lesion group ($P = 0.02$).

LNM

Among the lesions treated surgically, the incidence of LNM was 11.2% (10/89) and 12.1% (46/381) in small and large lesion groups, respectively ($P = 0.85$) (Table 2).

Depth of invasion/LVI/PDA

Histopathological analysis of the small lesion group revealed sm-deep cancer in 90 (75%) cases, LVI in 26 (22%) and PDA in 12 (10%). Similarly, the large lesion group exhibited sm-deep cancer in 380 (82%) cases, LVI in 125 (27%), and PDA in 79 (17%). Therefore, in relation to depth of invasion, LVI and PDA, there were no significant differences between the groups.

Treatment strategy

Among the small lesion group, 62 (52%) cases were initially treated with endoscopic mucosal resection (EMR), while 58 (48%) cases were surgically resected. In contrast, among the large lesion group, 133 (29%) cases were initially treated with EMR, while 330 (71%) cases were surgically resected. Among all lesions treated by EMR, there were no differences in the rate of positive and unknown vertical and/or lateral cut margins in the small (18%, 11/62) and large lesion groups (20%, 26/133). Furthermore, among all positive cut margin cases in the small and large lesion groups, there were 11 (100%) and 18 (69%) positive vertical margin cases (Table 3, Figures 1 and 2).

Table 1 Comparison of clinicopathological and endoscopic characteristics for 583 study cases

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
No. of lesions, *n* (%)	120 (21)	463 (79)	
Gender (M/F)	85/35	289/174	0.09
Age (yr), mean (range)	61.5 (39-84)	62.4 (30-90)	0.86
Macroscopic type, *n* (%)			
Sessile (0-Is, Is+IIa)	51 (42)	233 (50)	0.13
Flat (0-IIa)	14 (12)	64 (14)	
Depressed (0-IIc, IIa+IIc, Is+IIc)	55 (46)	166 (36)	
Size (mm), mean ± SD	8.3 ± 1.6	22.1 ± 9.6	
Growth pattern (PG/NPG)	38/82	250/213	< 0.0001
Location, *n* (%)			
Rectum	33 (27)	213 (46)	0.02
Distal colon[1]	56 (47)	139 (30)	
Proximal colon[2]	31 (26)	111 (24)	

[1]Descending-sigmoid colon; [2]Cecum-transverse colon.

Table 3 Comparison of treatment, surgery and positive rate between small and large EI-CRC

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
Initial treatment			
EMR	62 (52)	133 (29)	< 0.0001
Surgery	58 (48)	330 (71)	
Positive rate of cut margin[1]	11 (18)	26 (20)	0.81
In EMR cases			
Lateral	0 (0)	8 (31)	0.08
Vertical	11 (100)	18 (69)	

[1]Positive and unknown cut margin. EMR: Endoscopic mucosal resection.

According to the initial treatment, there were 134 (69%) and 336 (87%) sm-deep cancers in the EMR and surgery groups, respectively. Furthermore, there were 33 (17%) and 118 (30%) LVI-positive, and 18 (9%) and 73 (19%) PDA-positive cases in the EMR and surgery groups, respectively. There were 37 (19%) positive cut margin cases, including 29 (78%) positive vertical margins in the EMR group. In contrast, there were no positive cut margin cases in the surgery group. In the EMR group, 82 (42%) patients underwent additional surgery with LN dissection after EMR within 6 mo. The incidence of LNM was 11.0% (9/82) and 12.1% (47/388) in the EMR and surgery groups, respectively ($P = 0.79$) (Table 4).

DISCUSSION

Several authors have reported a strong association between lesion size and submucosal invasion or risk of LNM when referring to the grade of malignancy of early CRC. Large lesion size has been considered an indicator of deep submucosal invasion and presence of LNM. However, in this large retrospective study, small EI-CRC demonstrated a similar aggressive behavior and malignant potential to those of large lesions, with a similar risk of LNM , LVI and PDA among both groups.

Intramucosal CRC is thought generally to have no potential for LNM. In contrast, it has been reported that

Table 2 Incidence of LNM and clinicopathological characteristics based on tumor size *n* (%)

	Small (≤ 10 mm)	Large (> 10 mm)	*P* value
LNM	10/89 (11.2)	46/381 (12.1)	0.85
Depth of invasion			
sm-superficial (< 1000 μm)	30 (25)	83 (18)	0.08
sm-deep (≥ 1000 μm)	90 (75)	380 (82)	
LVI	26 (22)	125 (27)	0.23
PDA	12 (10)	79 (17)	0.06

LVI: Lymphovascular invasion; PDA: Poorly differentiated adenocarcinoma; LNM: Lymph node metastasis.

Table 4 Comparison of clinicopathological characteristics and incidence of LNM based on the treatment strategy *n* (%)

	EMR (*n* = 195)	Surgery (*n* = 388)	*P* value
Depth of invasion			
sm-superficial (< 1000 μm)	61 (32)	52 (13)	< 0.0001
sm-deep (≥ 1000 μm)	134 (69)	336 (87)	
LVI	33 (17)	118 (30)	0.0006
PDA	18 (9)	73 (19)	0.0006
Positive rate of cut margin[1]	37 (19)	0 (0)	< 0.0001
Lateral	8 (22)	0 (0)	
Vertical	29 (78)	0 (0)	
Additional surgical operation	82 (42)	-	
LNM	9/82 (11.0)	47/388 (12.1)	0.79

[1]Positive and unknown cut margin.

LNM occurs in 6%-13% of patients with submucosal invasive CRC[11-15]. Therefore, radical surgery with LN dissection is recommended strongly in these cases. At present, EMR provides an endoscopic cure of early stage CRC when there is no risk of LNM. Advances in endoscopic instruments and techniques have increased the detection rates of early stage CRC and have expanded the indications for EMR[16].

In the past 20 years, many investigators have proposed the following histopathological criteria when considering additional surgery after EMR of submucosal cancers: massive submucosal invasion (≥ 1000 μm), and/or LVI, and/or PDA[17-22]. Among these factors, LVI and PDA are impossible to predict before resection. At this point, it is crucial to predict the vertical depth of invasion of submucosal cancers prior to EMR. In our center, we use routinely a magnifying colonoscope to decide on the adequate treatment of early stage CRC. Magnifying chromoendoscopy (MCE) is a standardized validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern), in a simple and rapid manner. We have reported previously the efficacy of MCE to diagnose an invasive pattern as a typical finding of sm-deep cancers, and have demonstrated that it provides a good correlation between pit pattern and tumor depth in flat and depressed CRC[23-27].

Many authors have reported that depressed and/or NPG type lesions are considered to have a high malignant potential, compared to the polypoid type lesions of similar

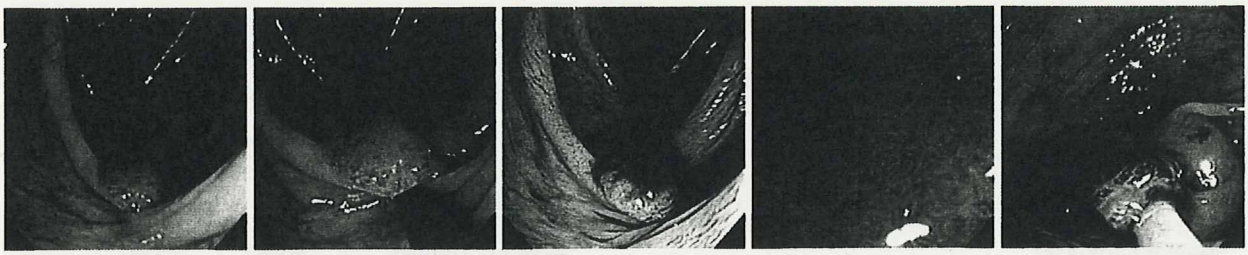

Figure 1 The lesion was located in the transverse colon. Endoscopic examination revealed a flat, elevated lesion with a central depression, which was macroscopically diagnosed as 0- II a+ II c. The high-magnification view revealed a typical type VI pit (invasive) pattern on the depressed margin. The final endoscopic diagnosis was a 0- II a+ II c type early colon cancer with submucosal deep invasion. However, patient strongly hoped EMR as an initial treatment. We performed EMR after injecting normal saline into the submucosa.

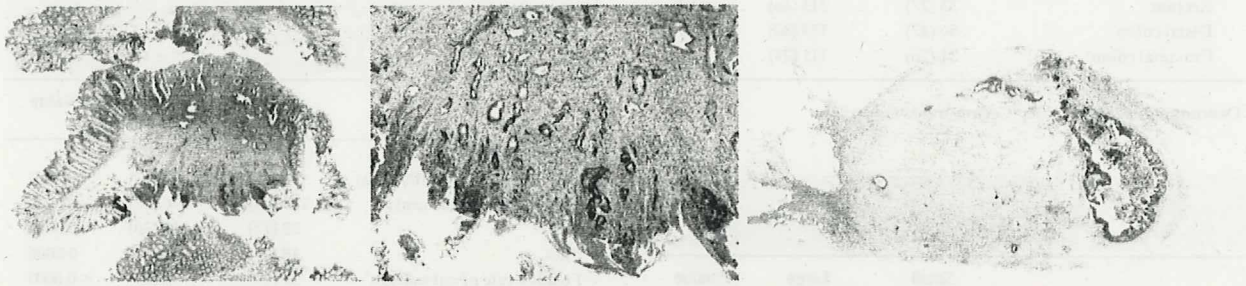

Figure 2 The final histopathological diagnosis was early invasive colon cancer, well-differentiated adenocarcinoma, sm-deep, NPG type, ly (-), v (-), cut end (+) (vertical margin positive). Since cancer was exposed in the vertical cut margin, additional surgical resection was performed and LNM was detected.

size[4,28-31]. Kurisu *et al*[20] have investigated the development and progression of EI-CRC. In that study, NPG lesions were significantly smaller in size (14.2 mm *vs* 24.2 mm) but showed deeper infiltration than PG types. They concluded that tumor development and the degree of invasion differed significantly between the two types of carcinoma. On the other hand, non-polypoid colorectal neoplasms (NP-CRNs) have been reported recently in the United States. Soetikno *et al*[31] have reported the prevalence of NP-CRNs in a veterans' hospital population. The overall prevalence of NP-CRNs and NP-CRNs with in situ or submucosal invasive carcinoma was 9.35% and 0.82%, respectively. They also concluded that NP-CRNs were more likely to contain carcinoma (OR: 9.78) than polypoid lesions, regardless of size. In the present study, small EI-CRCs $\leqslant$ 10 mm in diameter showed a significantly higher incidence of NPG type lesions than in the large lesion group ($P < 0.0001$). However, there was no significant difference in proportion of the macroscopic type between the groups ($P = 0.13$). Among the lesions diagnosed as Is type (sessile) in the small lesions group, 47% (14/30) were classified as NPG type histopathologically. From these results, we conclude that further investigation is required to confirm the growth pattern, especially for small sessile lesions diagnosed during colonoscopy.

In contrast, the rate of EMR as an initial treatment was 33% (195/583) in our study. In particular, it was significantly higher in the small lesion than the large lesion group (52% *vs* 29%, $P < 0.0001$). Among the 195 lesions removed by EMR as an initial treatment in both groups, 61 cases (32%) were sm-superficial cancers. On the other hand, there was no significant difference in the positive rate of cut margins between the small and large lesion groups (18% *vs* 20%). This result implies that EMR should not be performed readily for EI-CRC, from the viewpoint of no-touch isolation[32] and EMR complications. Intramucosal lesions (adenoma or intramucosal cancer) are usually well lifted by submucosal injection. In contrast, invasive cancer, especially sm-deep cancer, cannot be lifted because of the presence of submucosal fibrosis or desmoplastic reaction. Uno *et al*[33] have reported this phenomenon as the "non-lifting sign". Kobayashi *et al*[34] have reported, among 271 colorectal neoplastic lesions, that the non-lifting sign of deeper infiltration had a sensitivity of 61.5%, specificity of 98.4%, and accuracy of 94.8%. In contrast, endoscopic diagnosis had a sensitivity of 84.6%, specificity of 98.8%, and accuracy of 97.4%, with statistically significant differences in terms of sensitivity and accuracy. Furthermore, since submucosal injection varies depending on the expertise of the endoscopist, we consider that an endoscopic diagnosis is much more important and accurate when endoscopic resection is considered as the therapeutic option.

There are some limitations to this study. Firstly, this was a single-center study, and although the number of examined EI-CRCs was adequate, a multicenter analysis should be performed to clarify the clinical importance of small EI-CRCs. In addition, this study was carried out retrospectively between 1980 and 2004. In relation to endoscopic treatment for early CRC, endoscopic submucosal dissection (ESD) technique and Glycerol/Sodium hyaluronate as an injected solution during EMR has made progress recently[35,36]. In particular, ESD provides not only an *en bloc* large specimen but also

negative lateral and vertical cut margins.

In conclusion, with regard to the risk of LNM, small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions. Moreover, from the perspective of the concept of no-touch isolation, therapeutic cost, and complications during EMR, special attention must be paid when treating even small early stage lesions, especially NPG type lesions.

COMMENTS

Background

In general, small colorectal lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size.

Research frontiers

The aim of this retrospective study was to clarify the clinicopathological characteristics of small (≤ 10 mm) and large (> 10 mm) EI-CRCs.

Innovations and breakthroughs

A total of 583 EI-CRCs were evaluated retrospectively, with 120 (21%) small and 463 (79%) large lesions identified. With regard to the risk of lymph-node metastasis (LNM), small EI-CRCs demonstrate the same aggressiveness and malignant potential as large lesions.

Peer review

The authors examined retrospectively a large group of patients with EI-CRCs gathered over 20 years in a national cancer hospital, and demonstrated that small EI-CRCs (≤ 10 mm) had the same aggressiveness and malignant potential as large cancers. Special attention must be paid when treating even small lesions.

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Treatment strategy for laterally spreading tumors in Japan: Before and after the introduction of endoscopic submucosal dissection

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colonoscopy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), laterally spreading tumor.

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Abstract

Background and Aims: Laterally spreading tumors (LST) in the colorectum are considered good candidates for endoscopic resection (ER). Because LST-non-granular (NG) tumors show multifocal invasion into the submucosal layer, en bloc resection is necessary for adequate histopathological evaluation. Therefore, surgical resection has been recommended when a lesion is suspected to be an invasive cancer and too large to resect en bloc. The aim of the present study was to evaluate whether the introduction of colorectal ESD, which was developed for en bloc resection of early gastric cancers, could improve the en bloc resection rate of large LST-NG-type tumors and reduce the surgical resection rate.

Methods: Between January 1999 and December 2005, a total of 166 LST-NG-type tumors measuring ≥ 20 mm in 161 patients were included in this study. The en bloc resection rate and the surgical resection rate were historically compared between two periods, before and after the introduction of ESD.

Results: The en bloc resection rate for ER lesions was significantly higher in the latter period (35.0% [14/40] *vs* 76.5% [75/98]; $P < 0.001$), and the rate of surgery for adenomas and intramucosal or sm minute cancers was significantly lower in the latter period (20.0% [10/50] *vs* 1.1% [1/89]; $P < 0.001$).

Conclusions: The introduction of colonic ESD was able to change our treatment strategy for LST, improving the en bloc resection rate and reducing the surgical resection rate.

Introduction

Flat and depressed colorectal lesions have been well described in both Eastern and Western countries, and the importance of early detection and definitive endoscopic resection (ER) has been emphasized.[1–7] Laterally spreading tumors (LST) are typical flat lesions that extend laterally and circumferentially rather than vertically along the colonic wall, and are considered to be good candidates for ER.[8–10] LST have been subdivided into the granular type (LST-G type) and the non-granular type (LST-NG type).[5] It has been reported that the LST-G-type tumors show a low incidence of submucosal invasion and, when present, that submucosal invasion occurs under the largest nodule in the majority of such tumors. Therefore, piecemeal resection is acceptable for accurate histological assessment if the largest nodule can be included in one piece. However, LST-NG-type tumors have a higher incidence of submucosal invasion, which is often multifocal and, therefore, it is difficult to estimate the deepest point of invasion endoscopically. This means that piecemeal resection has a possibility to miss the deepest point of invasion or lymphovascular involvement if the lesion is divided at these significant points. Hence, en bloc resection is necessary for LST-NG-type tumors to evaluate the resected specimen adequately.[11,12] However, because of their larger size, en bloc resection of LST-NG-type tumors is sometimes difficult by conventional endoscopic mucosal resection (EMR), especially for lesions ≥ 20 mm in size, and such lesions are resected surgically even if they are adenoma or intramucosal cancer. Therefore, we have introduced the endoscopic submucosal dissection (ESD) technique to overcome such size limitations and to allow resection of large LST-NG-type tumors en bloc. ESD was originally developed to achieve en bloc resection of large early gastric cancers in 1995,[13] and its use as a standard therapy for gastric cancer is becoming widespread in Japan.[14–17] Although ESD has made it possible to achieve a high en bloc resection rate and has reduced the rate of recurrence of gastric cancer, it can only be used for colorectal or esophageal cancer in the hands of experienced endoscopists because of its technical difficulty and high complication rate.[14,18–21]

The aim of the present study was to evaluate whether the introduction of colorectal ESD could improve the en bloc resection rate of LST-NG-type tumors and increase LST-NG-type tumors cured by ER.

Methods

Patients

Between January 1999 and December 2005, a total of 526 colorectal LST measuring ≥ 20 mm in 507 patients were resected endoscopically or surgically at the National Cancer Center Hospital. The study period was divided into two periods, before and after the introduction of ESD in October 2003. The medical charts were collected and analyzed retrospectively. We defined LST as lesions with a low vertical axis extending laterally along the interior luminal wall, and subdivided them into two subtypes based on endoscopic findings. The granular type (LST-G type) was defined as a lesion with even or uneven nodules on the surface, and the non-granular type (LST-NG type) as a lesion with a smooth surface (Fig. 1).

Patients who had advanced colorectal cancer, familial adenomatous polyposis or inflammatory bowel disease were excluded from this study. Finally, 166 LST-NG-type tumors measuring ≥ 20 mm in 161 patients were included, and the rate of LST-NG-type tumors which were resected en bloc or cured by ER were historically compared between the two periods before and after the introduction of ESD.

Endoscopic assessment for diagnosis of invasion depth

When a LST lesion was identified, its surface was washed with water, and 0.4% indigo carmine was sprayed directly through the accessory channel of the scope. Lesions with fold convergence, an expansive appearance, an irregular surface contour, a demarcated depressed area or a large nodule (≥ 1 cm) were regarded as deeply infiltrated submucosal cancer.[12,22] Pit pattern analysis using high-magnification colonoscopy (CF-200Z, CF-240ZI, PCF-240ZI and CF-H260AZI; Olympus Optical Co., Tokyo, Japan) was added to determine the invasion depth in all cases.[23–25]

Therapeutic strategy for LST-NG-type tumors

Colorectal ESD was officially introduced to the National Cancer Center Hospital in October 2003, and it changed our therapeutic strategy for LST-NG-type tumors ≥ 20 mm in diameter.

In the period before the introduction of colorectal ESD, EMR using a snare with submucosal injection was the first choice. Because LST-NG-type tumors sometimes invade the submucosal layer multifocally, we tried to resect the lesions en bloc for accurate histological assessment.[11,12] Therefore, we recommended surgical resection when a lesion was considered a possible invasive cancer and was too large, especially exceeding 30 mm in size, or showing non-lifting sign positivity, defined as a case in which the surrounding mucosa, but not the lesion, was elevated by submucosal injection.[22]

In the latter period, we started to carried out ESD for lesions ≥ 20 mm in size or lesions not lifted by submucosal injection to obtain specimens suitable for histological assessment. However, we also carried out conventional EMR and endoscopic piecemeal mucosal resection (EPMR) for selected lesions which were relatively small and well lifted by submucosal injection.

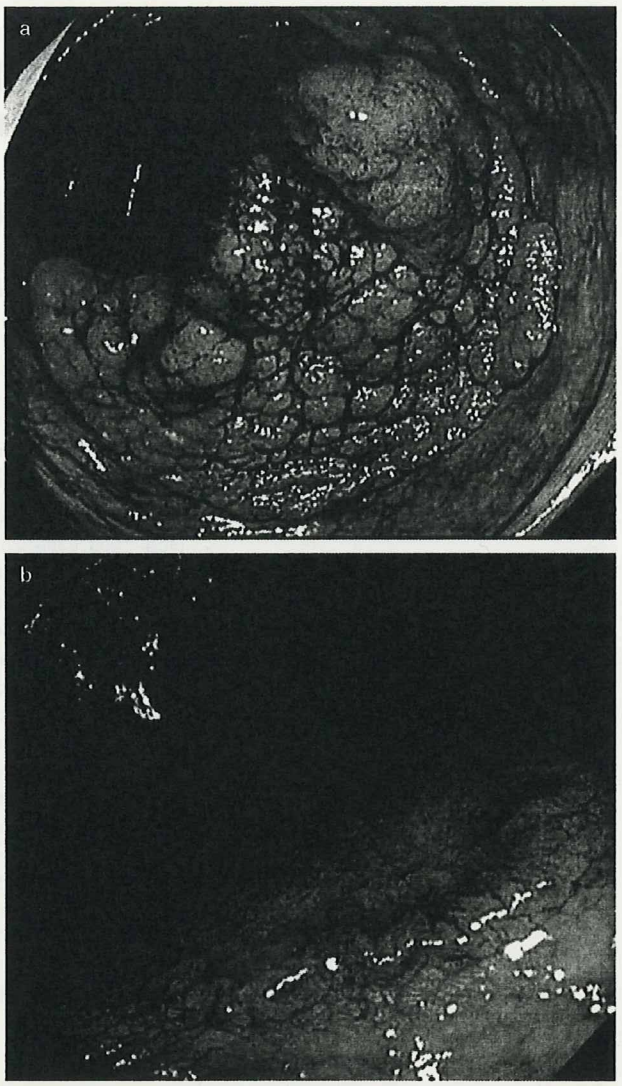

Figure 1 (a) Laterally spreading tumors granular type (LST-G): a lesion with even or uneven nodules on the surface. (b) LST-non-granular type (LST-NG): a lesion with a smooth surface.

Adenomas, intramucosal cancers and submucosal minute invasion cancers (submucosal invasion but less than 1 mm below the muscularis mucosae[26,27]) without lymphovascular involvement or a poorly differentiated component are considered to rarely have lymph node metastasis, and therefore we judged such cases to have been curatively resected and did not recommend additional therapy.[28] Lateral cut-end-positive status was not considered to assess the curability; therefore, some cases were judged as curative even in the EPMR cases.

EMR and ESD procedures

Endoscopic mucosal resection was carried out using the inject and cut technique. Normal saline or glycerol (Glyceol [10% glycerol and 5% fructose in normal saline solution]; Chugai Pharmaceutical Co., Tokyo, Japan) was injected into the submucosa of the lesion with a 23-gauge needle,[29] and then the lifted lesion was resected using an oval snare (SD-210L-25; Olympus). In this study, we distinguished EMR from EPMR according to the number of resected specimens: single or multiple.

ESD was carried out using a monopolar needle knife, a flex knife (Olympus) and a bipolar needle knife (B-knife) (XEMEX Co, Tokyo, Japan) with submucosal injection of sodium hyaluronate solution.[14] Other devices, such as an insulation-tipped knife (IT knife; Olympus), were used to cut the submucosal layer if necessary.[18] Although several lesions were finally resected using a snare after circumferential incision, they were regarded as ESD. Sedation using midazolam and carbon dioxide insufflation was routinely used during ESD.[30]

Both procedures were basically carried out in the inpatient setting, and length of stay was 3 or 4 days for E(P)MR and 5 days for ESD, if the complication did not occur.

Histopathological analysis

All resected specimens were fixed in 10% buffered formalin solution and stained with hematoxylin and eosin. Histopathological diagnosis was based on the Japanese classification of cancer of the colon and rectum, and submucosal cancers are subclassified into minute and deep (≥ 1 mm from the muscularis mucosae to the deepest point of invasion).[27]

Statistical analysis

All values are reported as mean ± standard deviation when applicable. Comparisons were made with the χ^2, Fisher's exact and *t*-tests. Differences at $P < 0.05$ were considered to be statistically significant. All calculations were conducted using the SPSS statistical software package (SPSS, Chicago, IL, USA).

Results

Clinicopathological characteristics of LST in each period are shown in Table 1. There were no significant differences between the initial and latter periods except for the incidence of LST-NG-type tumors (25.7% [63/245] *vs* 36.7% [103/281]; $P = 0.007$).

Initial treatment for LST-NG-type tumors in the initial period

In the initial period, 63 LST-NG-type tumors measuring ≥ 20 mm were resected endoscopically or surgically in our hospital. Forty of these lesions were carried out ER, and 14 (35.0%) lesions were resected en bloc (Table 2). All of the 40 lesions resected endoscopically were judged curative on the basis of histopathology, and no additional treatment such as surgery or radiation therapy was carried out.

Although 50 of all 63 LST-NG-type tumors were adenomas and intramucosal or sm minute cancers which were regarded as the curable candidates for ER, 10 (20.0%) were resected surgically. The reasons for selecting surgical resection were the presence of non-lifting sign and difficulty with endoscopic resection in three lesions, a size excessive for ER in four lesions, and possible presence of invasive cancer and likely indication for definitive en bloc resection in three lesions.

Initial treatment for LST-NG-type tumors in the latter period in comparison with the initial period

In the latter period, 103 LST-NG-type tumors ≥ 20 mm were resected endoscopically or surgically. Ninety-eight of these lesions were carried out ER, and 75 (76.5%) lesions were resected en bloc (Table 3). Ten of 98 (10.2%) lesions resected endoscopically were

Table 1 Clinicopathological characteristics of the lesions

	Initial period	Latter period
No. LST ≥ 20 mm	245	281
No. LST-NG type ≥ 20 mm	63 (25.7%)	103 (36.7%)
Size of LST-NG type ≥ 20 mm (mean[SD])	25.3 (6.2)	25.4 (7.5)
Location		
Proximal colon	46 (73.0%)	67 (65.0%)
Distal colon	10 (15.9%)	24 (23.3%)
Rectum	7 (11.1%)	12 (11.7%)
Histopathology		
Adenoma or m-Ca	40 (63.5%)	76 (73.8%)
sm-minute-Ca	10 (15.9%)	13 (12.6%)
sm-deep-Ca	13 (20.6%)	14 (13.6%)

m-Ca, intramucosal cancer; sm-deep-Ca, submucosal deep invasion cancer; sm-minute-Ca, cancer with submucosal invasion but less than 1 mm below the muscularis mucosae.

Table 2 Initial treatment for LST-NG type ≥ 20 mm in the initial period

	EMR		ESD		Surgery
	En bloc	Piecemeal	En bloc	Piecemeal	
Group A ($n = 50$)	14 (28%)	26 (52%)	–	–	10 (20%)
Group B ($n = 13$)	0	0	–	–	13 (100%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Group A, adenomas, m-Ca and sm-minute-Ca; Group B, sm-deep-Ca.

Table 3 Initial treatment for LST-NG type ≥ 20 mm in the latter period

	EMR		ESD		Surgery
	En bloc	Piecemeal	En bloc	Piecemeal	
Group A ($n = 89$)	18 (20%)	17 (19%)	47 (53%)	6 (7%)	1 (1%)
Group B ($n = 14$)	1 (7%)	0	9 (64%)	0	4 (29%)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Group A, adenomas, m-Ca and sm-minute-Ca; Group B, sm-deep-Ca.

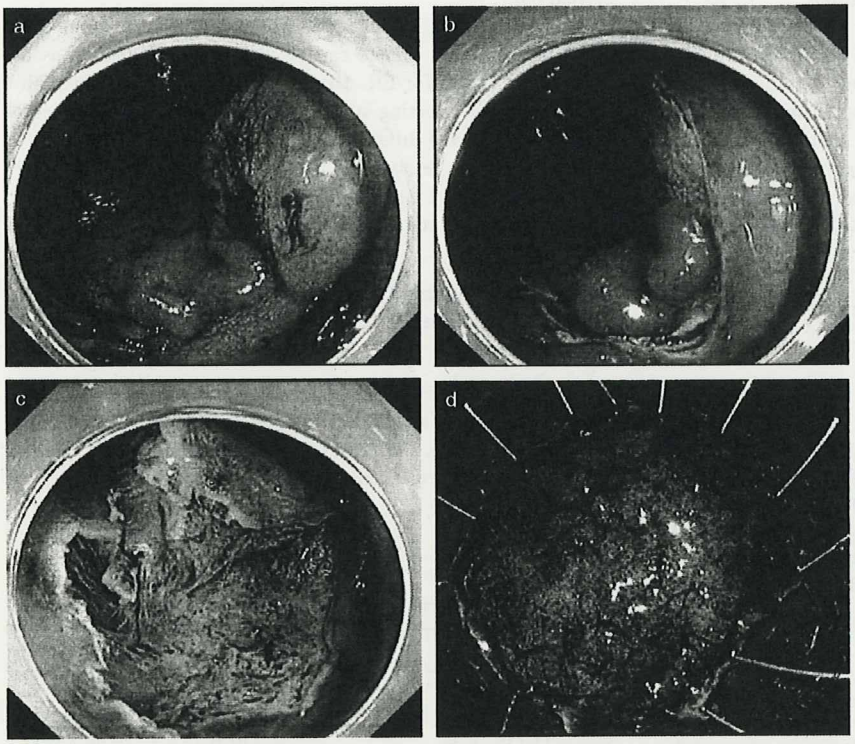

Figure 2 Endoscopic submucosal dissection (ESD) case treated in the latter period: (a) Laterally spreading tumors non-granular type (LST-NG) lesion, approximately 30 mm in size, was located in the transverse colon. Although the lesion showed non-lifting sign positivity, it was diagnosed as intramucosal cancer. (b,c) Circumferential incision in the mucosa was made by a needle knife, and the sm layer was cut by an IT knife. (d) Resected specimen revealed sm1 cancer, and the resected margin was histopathologically free of tumor.

diagnosed pathologically as sm deep invasion, and additional surgery was recommended.

ESD was carried out for 62 lesions, and 56 lesions were resected en bloc (Fig. 2). The en bloc resection rate of ESD was 90.3%.

Only one of 89 (1.1%) curable candidates for ER was resected surgically, because ESD for this large lesion was judged difficult at the time immediately after introduction of this technique.

The en bloc resection rate of the ER lesion in the latter period was significantly higher than that in the initial period (76.5% *vs* 35.0%; $P < 0.001$), and the rate of surgery for the curable candidates for ER (adenoma and intramucosal or sm minute cancers) was significantly lower in the latter period (1.1% *vs* 20.0%; $P < 0.001$) (Table 4). In contrast, the rate of non-curative ER that was detected histopathologically as sm deep invasion was significantly higher in the latter period (10.2% *vs* 0%; $P = 0.036$).

Complications of ER

In the initial period, no perforation and late bleeding occurred during or immediately after ER. However, three cases of perforation during the ER procedure occurred in the latter period. All three of these were ESD cases (4.8% of 62 ESD cases), and were manageable conservatively with antibiotic therapy and fasting after endoscopic closure using endoclips.

Discussion

We have shown that, in our institution, the introduction of colorectal ESD has dramatically improved the en bloc resection rate of LST-NG-type tumors and increased LST-NG-type tumors cured by ER. It has overcome two difficulties with endoscopic therapy for such tumors. One is the size limitation of en bloc resection, and the other is positivity for the non-lifting sign after submucosal injection. Generally, lesions ≥ 20 mm in size are difficult to resect en bloc by conventional EMR, whereas ESD has no size limitation if the operator is sufficiently experienced. In the initial period before the introduction of ESD, 52% of adenomas and intramucosal or sm minute cancers were treated by EPMR, and this could lead to insufficient histological assessment and a high likelihood of local recurrence.[10,23] Since its introduction, ESD has provided specimens that are suitable for accurate histological assessment, and it is also predicted to lead to the reduction of local recurrence.

Table 4 Comparison between the initial and latter periods

	Initial period	Latter period	*P*
En bloc resection for EMR/ESD lesions	35.0% (14/40)	76.5% (75/98)	< 0.001[1]
Surgical resection for Group A	20.0% (10/50)	1.1% (1/89)	< 0.001[1]
Non-curative EMR/ESD for Group B	0% (0/40)	10.2 (10/98)	0.036[2]

[1]χ^2-test.
[2]Fisher's exact test.
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Group A, adenomas, m-Ca and sm-minute-Ca; Group B, sm-deep-Ca.

In contrast, en bloc resection using the ESD technique is sometimes difficult even for the experienced endoscopist. We previously reported that perforation occurred in 10 of 200 patients and median operation time of colorectal ESD was 90 min.[31] In this series, the en bloc resection rate of ESD was 90.3%, in line with other reports by Japanese experts,[19–21] although the range of those reported rates was not narrow (80.0–98.4%). In addition, the perforation rate of ESD was higher than that for conventional EMR. The rate of perforation in our series was 4.8%, and thus compatible with other reports (1.4–14.3%).[19–21,32] Although all patients with perforation were manageable conservatively,[33] the potential for severe complications, such as peritonitis and pneumoscrotum,[32,34] exists. In order to establish colorectal ESD as a standard therapy, a number of negative factors need to be overcome, such as the risk of perforation, the long procedure time and technical difficulty.

Recently, the first series of colorectal ESD from Western countries was published by Repici *et al.*[35] Their ESD method differed from ours in some respects; they did not use sodium hyaluronate solution for submucosal injection and routinely performed snaring, and their en bloc resection rate (55.1%) was considerably lower than that in some series reported from Japan.

The rate of non-curative ER followed by additional surgery in the latter period was significantly higher than that in the initial period. This may have been due to the fact that we tended to underestimate the invasion depth of LST after the introduction of ESD, because we intended to carry out EMR or ESD for all curable candidates for ER. When we were unable to judge the invasion depth of the lesion with confidence, we recommended ESD not only for treatment but to obtain an adequate specimen for histopathological diagnosis. After ESD, we were able to decide whether additional surgery was necessary. An additional explanation is that more accurate histopathological evaluation using en bloc specimens revealed the 'true' invasion depth of the lesions. Histopathological diagnosis using a multi-fragment specimen may result in underestimation of the invasion depth. The introduction of ESD overcame the limitation of lesion size and changed not only our treatment strategy but also the efficiency of our endoscopic and histopathological diagnosis.

Our study had two limitations. One is that the comparison was a historical one between two different periods. Therefore, some factors, such as the development of devices and improvement of the operator's technique, might have influenced our results. For example, when considering lesion characteristics, the incidence of LST-NG-type tumors was significantly higher in the latter period. One possible reason may have been the increase in the number of patients referred from private physicians who knew that ESD had been introduced at our hospital. In Japan, colorectal ESD is not as widespread as gastric ESD, and is available at only a few academic centers.[14,19–21,31] Another limitation of our study is that follow up was not evaluated. Although high en bloc resection rate correlates to low local recurrence rate,[36] long-term outcome date, including not only local recurrence but additional treatment, is necessary to prove the superiority of ESD. Moreover, comparison between ESD and laparoscopic colectomy would help to clarify the effectiveness of ESD in terms of outcome, complication and cost.

In conclusion, we have shown that the introduction of colorectal ESD has changed our treatment strategy for LST, achieving an improvement of the en bloc resection rate and a reduction of the surgical resection rate. In order to establish colorectal ESD as a standard therapy for LST-NG-type tumors $\geq$ 20 mm in size, efforts should be made to overcome its technical difficulty and high complication rate.

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Evaluation of visualization of squamous cell carcinoma of esophagus and pharynx using an autofluorescence imaging videoendoscope system

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Abstract

Background and Aim: An autofluorescence imaging (AFI) videoendoscope system produces pseudo-color images combining autofluorescence and green reflectance, with the utility of this system previously confirmed for the diagnosis of bronchial squamous cell carcinoma (SCC). Our aim was to evaluate visualization of esophageal and pharyngeal SCC comparing AFI with white light endoscopy (WLE).

Methods: Thirty-two patients with superficial esophageal SCC and 11 patients with superficial pharyngeal SCC diagnosed in other hospitals were enrolled in this prospective study. We observed the esophagus and pharynx with WLE followed by AFI and took both WLE and AFI images of the esophageal and pharyngeal SCC. Three experienced endoscopists subsequently evaluated the visualization quality of images from both systems on a three-tier scale: visible, illegible and invisible.

Results: A total of 39 superficial esophageal SCC were diagnosed with 20, 11 and eight lesions classified as visible, illegible and invisible, respectively, by WLE compared to 31, three and five lesions, respectively, using AFI. Using AFI, 79% of superficial esophageal SCC lesions were visible, compared to only 51% with WLE ($P < 0.05$). In addition, 12 superficial pharyngeal SCC were diagnosed with four, five and three lesions considered as visible, illegible and invisible, respectively, using WLE in contrast to nine, three and 0 lesions, respectively, by AFI. Thus, using AFI, 75% of superficial pharyngeal SCC lesions were visible compared with only 33% with WLE ($P = 0.13$).

Conclusion: The AFI system appears to be more useful than WLE for early diagnosis of SCC of the esophagus and pharynx.

Introduction

Esophageal squamous cell carcinoma (SCC) is devastating because of its aggressive clinical course and high mortality rate. However, the prognosis of esophageal SCC has been improving recently because of earlier detection, which increases the possibility of curative treatments such as esophagectomy with three-field lymph-node dissection[1,2] and endoscopic resection (ER).[3,4] In particular, the prognosis of patients treated for carcinomas confined within the intraepithelium or proper mucosal layer has been excellent with reported 5-year survival rates ranging from 85% to 100%.[5,6]

In order to detect esophageal SCC at an early stage, Lugol chromoendoscopy (LC) has been widely used in high-risk populations, resulting in a dramatic increase in the number of superficial SCC detected.[7-9] Adverse effects such as retrosternal pain and discomfort, however, often occur because of the mucosal irritation caused by Lugol staining.[10-14]

It is well known that patients with esophageal SCC often have synchronous and metachronous pharyngeal SCC.[15] The long-term outcome of patients after ER for esophageal SCC has been influenced to a greater extent by the existence of a second malignancy, particularly pharyngeal cancer, in addition to the initial esophageal cancer.[15,16] Few effective screening and follow-up strategies have been developed, however, and pharyngeal cancer is usually diagnosed at an advanced stage with a resultant poor prognosis.[17-22] In addition, we cannot carry out LC for pharyngeal SCC because it causes severe mucosal irritation leading to patient pain and discomfort and can even result in airway aspiration.

Therefore, in order to detect not only esophageal SCC, but also pharyngeal SCC at an earlier stage without Lugol staining, a new effective endoscopic technique needs to be developed. The autofluorescence imaging (AFI) videoendoscope system (Olympus Medical Systems Corp., Tokyo, Japan) is one of the most recently developed, non-invasive, optical techniques.[23-27] It produces real-time, pseudo-color images that combine autofluorescence and