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CASE REPORT Open Access

Recurrent advanced colonic cancer occurring 11 years after initial endoscopic piecemeal resection: a case report

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Abstract

Background: The high frequency of local recurrence occurring after endoscopic piecemeal resection (EPMR) for large colorectal tumors is a serious problem. However, almost all of these cases of local recurrence can be detected within 1 year and cured by additional endoscopic resection. We report a rare case of recurrent advanced colonic cancer diagnosed 11 years after initial EPMR treatment.

Case presentation: A 65-year-old male was diagnosed with a sigmoid colon lesion following a routine health check-up. Total colonoscopy revealed a 12 mm type 0-Is lesion in the sigmoid colon, which was diagnosed as an adenoma or intramucosal cancer and treated by EPMR in 1996. The post-resection defect was closed completely using metallic endoclips to avoid delayed bleeding. In 2007, at the third follow up, colonoscopy revealed a 20 mm submucosal tumor (SMT) like recurrence at the site of the previous EPMR. The recurrent lesion was treated by laparoscopic assisted sigmoidectomy with lymph node dissection.

Conclusion: When it is difficult to evaluate the depth and margins of resected tumors following EPMR, it is important that the defect is not closed in order to avoid tumor implantation, missing residual lesions and to enable earlier detection of recurrence. It is crucial that the optimal follow-up protocol for EPMR cases is clarified, particularly how often and for how long they should be followed.

Background

Endoscopic mucosal resection (EMR) is indicated for the treatment of adenoma and intramucosal or submucosal superficial (SM1: less than 1000 μm from the muscularis mucosa) colorectal cancers because of its minimal invasiveness, negligible risk of lymph-node metastasis[1] and excellent results in term of clinical outcome[2-4]. However, the high frequency of local recurrence after endoscopic piecemeal resection (EPMR) for large colorectal tumors is a serious problem. Previous studies have reported the rate of local recurrence following piecemeal resection to be 25-50%[5,6]. However, almost all cases of local recurrence can be detected within 1 year and cured by additional endoscopic resection, making EPMR an acceptable treatment option. Herein, we report a rare case of recurrent advanced colonic cancer occurring 11 years after initial EPMR treatment.

Case presentation

The patient was a 65-year-old male with a history of radical prostatectomy for prostate cancer. Following a positive faecal occult blood test, a total colonoscopy was performed at a previous hospital in 1996 and a sigmoid colon lesion was identified. He was referred to our hospital for more precise examination and treatment. Colonoscopy revealed a 12 mm type 0-Is lesion in the sigmoid colon. We diagnosed the lesion as an adenoma or an intramucosal cancer and tried to remove this lesion by *en bloc* EMR. However, as a result the lesion was removed by piecemeal resection (2-pieces). The post-resection defect was closed using metallic endoclips.

Histopathological examination revealed a well differentiated adenocarcinoma with low grade atypia, and the depth of invasion was intramucosa without lymphovascular

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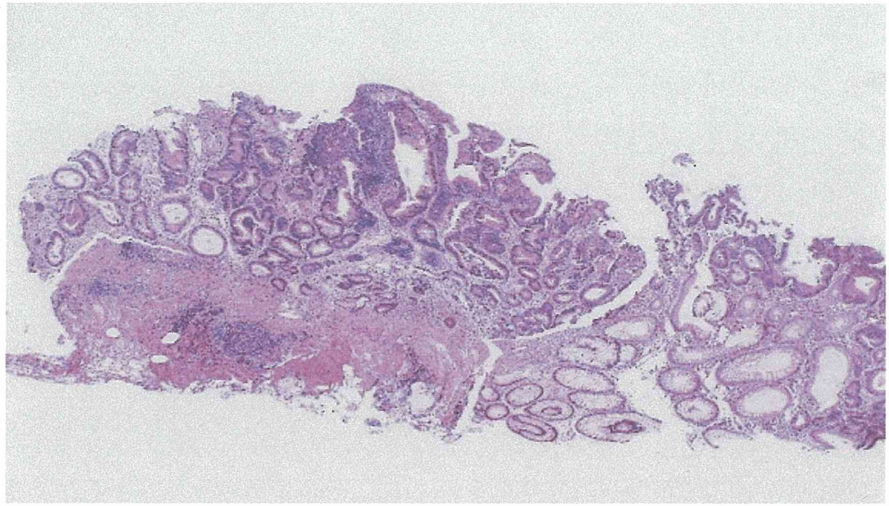

Figure 1 Histopathological findings of the initial EPMR treatment in 1996 revealing a well differentiated adenocarcinoma with low grade atypia.

invasion, cut end margin negative (Figure 1). We considered the treatment to be a curative resection. Follow up colonoscopy was performed 1 and 3 years after endoscopic resection. The EPMR scar was recognized without any residual or recurrent lesion in the follow up (Figure 2). Follow up colonoscopy was scheduled at 5 years after treatment, but cancelled for personal reasons.

In 2007, the third follow up colonoscopy revealed a protruding submucosal tumor (SMT), 20 mm in size at the site of the 1996 EPMR (Figure 3 and 4). The biopsy specimen from the colonic mucosa did not demonstrate any malignancy. Therefore, we planned a follow up colonoscopy 6 months later. The follow up colonoscopy revealed that the SMT-like lesion had grown to a large size, with a reddish surface pitted with crater-like irregularities (Figure 5 and 6). Histopathological diagnosis confirmed an adenocarcinoma, and a laparoscopic-assisted sigmoidectomy with D3 lymph node resection was performed in 2007. Histopathological analysis of the resected lesion revealed a moderately differentiated adenocarcinoma, and the depth of invasion was subserosa

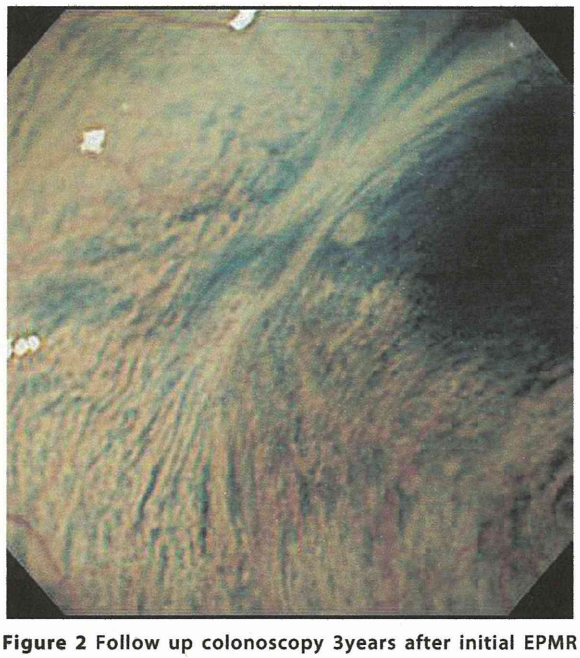

Figure 2 Follow up colonoscopy 3years after initial EPMR treatment. The scar was observed at the site of EPMR.

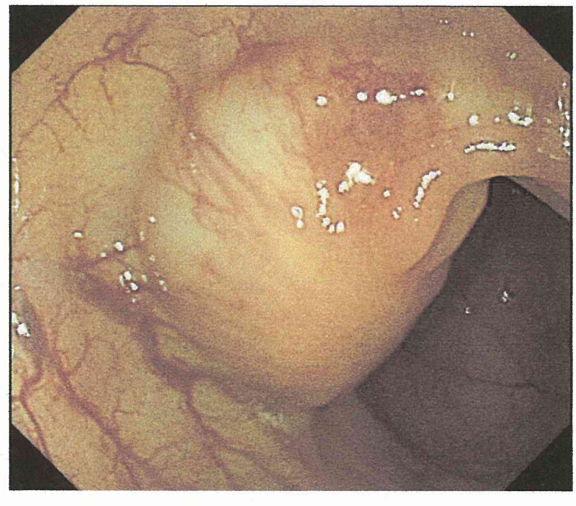

Figure 3 Follow up colonoscopy in 2007 revealed a protruding subumucosal tumor (SMT) at the initial resection site (a), after indigo carmine dye (b).

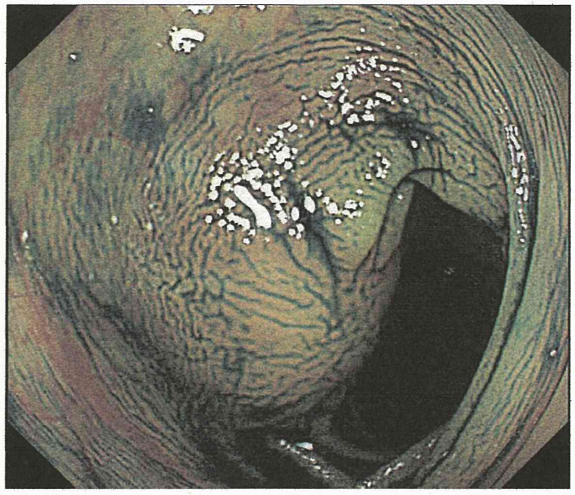

Figure 4 Follow up colonoscopy in 2007 revealed a protruding subumucosal tumor (SMT) at the initial resection site (a), after indigo carmine dye (b).

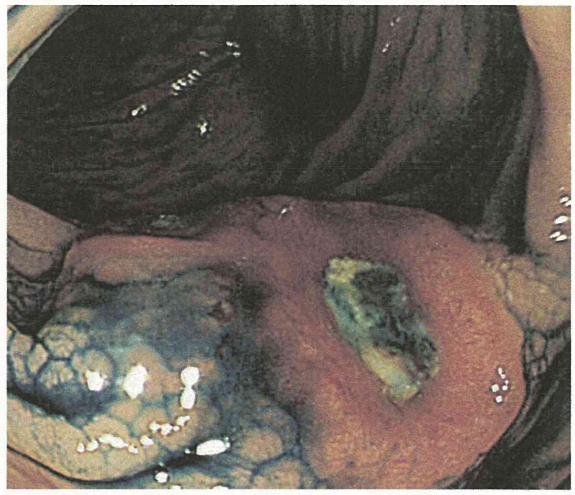

Figure 6 Colonoscopy revealed that the SMT lesion had grown in size, with a reddish surface pitted with crater-like irregularities (a), after indigo carmine dye (b).

with lymph node metastasis, lymphovascular invasion, venous invasion and perineural invasion (Figure 7).

Conclusion

In this case, preoperative examination and histopathological findings revealed no evidence of prostate cancer recurrence. The gross configuration of the SMT-like lesion did not support the diagnosis of a primary colonic cancer, and the lesion was diagnosed as a recurrence of the sigmoid colon cancer previously removed by EPMR, with the biopsy specimen very similar to the initial EPMR specimen.

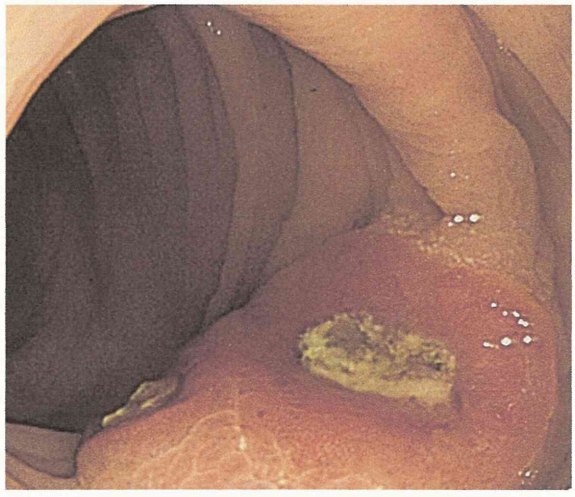

Figure 5 Colonoscopy revealed that the SMT lesion had grown in size, with a reddish surface pitted with crater-like irregularities (a), after indigo carmine dye (b).

Endoscopic resection for early colorectal cancers has been used throughout the world since the 1970 s and EMR with a submucosal injection technique allows the removal of large colorectal lesions. However, local recurrence frequently occurs after EPMR, which is a serious problem[5,6]. Previous research has indicated that most recurrent tumors after EPMR are found within 7 months and treated with additional endoscopic resection[7]. This present case is very rare due to the following reasons; [1] it is a recurrent advanced cancer following initial treatment of an intramucosal cancer, [2] morphologically SMT-like lesion, [3] late recurrence occurring more than 10 years after EPMR treatment. We speculate that micro-residual lesions were made by the EPMR along the edge of the defect and these were then buried into the submucosa by the endoscopic closure using endoclips. Routine follow up was unable to detect these lesions allowing them to develop into SMT. In addition, the micro-residual lesions developed very slowly because the primary lesion was low grade atypia. According to the Guidelines for Colonoscopy Surveillance after EMR: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society, patients with sessile adenomas that are removed piecemeal should be considered for follow up evaluation at shorter intervals (2-6 months) to verify complete removal. Once complete removal has been achieved, subsequent surveillance needs to be individualized based on the judgement of the endoscopist[8]. However, in this case, local recurrence occurred after 11 years, although no residual and no recurrent lesions were identified by the follow up colonoscopy at 1 and 3 years.

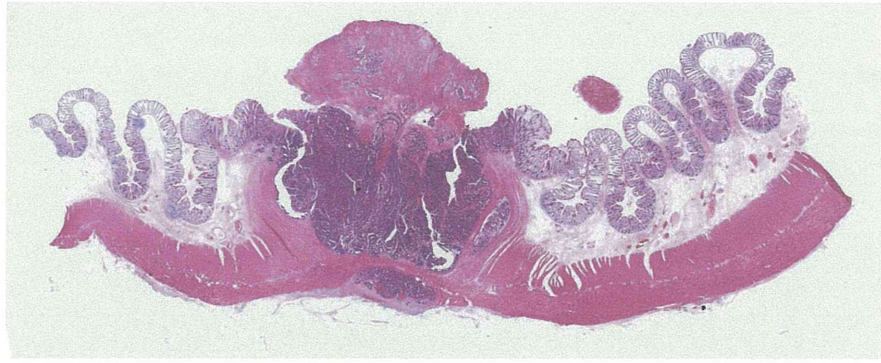

Figure 7 Histopathological finding of the surgically resected specimen.

Results from this case do not support the need for routine long-term follow up colonoscopy. However in cases where it is difficult to evaluate truly the surgical margin and depth of invasion after EPMR, it is important in order to avoid missing residual lesions and to detect recurrent lesions earlier, that where suitable the defect is not closed and follow up colonoscopy should be performed at appropriate intervals.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Abbreviations

EPMR: endoscopic piecemeal mucosal resection; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; SMT: submucosal tumor.

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Authors' contributions

TK collected the data and wrote the report, and was involved in drafting the manuscript. TS was involved in drafting the manuscript. TM revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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PREVALENCE AND CLINICOPATHOLOGICAL FEATURES OF NONPOLYPOID COLORECTAL NEOPLASMS: SHOULD WE PAY MORE ATTENTION TO IDENTIFYING FLAT AND DEPRESSED LESIONS?

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Flat and depressed (nonpolypoid) colorectal lesions have been described for over two decades by Japanese investigators. These neoplastic lesions are typically smaller than polypoid ones and can be more difficult to identify during screening colonoscopy. In particular, depressed type colorectal lesions are usually small in size, with a number of studies showing them to be at greater risk for developing high-grade dysplasia or submucosal invasive cancer. It has also been suggested that they may follow a different carcinogenic pathway to flat elevated or protruding adenomas. This paper summarizes recent data of nonpolypoid colorectal neoplasms from Western and Asian countries.

Key words: Japan Polyp Study, nonpolypoid colorectal neoplasm, screening colonoscopy.

INTRODUCTION

Colorectal neoplasms have traditionally been classified in Western countries as sessile or pedunculated. However, in 1983 the Japanese Research Society for Cancer of the Colon and Rectum also recognized the existence of flat adenomas.[1] In 1985 Muto *et al.* described small 'flat adenomas' as lesions <10 mm in size, flat-elevated, sometimes showing a central redness, and with a significant rate of high-grade dysplasia.[2] In regard to depressed lesions, the first reports of depressed (IIc) type colorectal neoplasms were published in 1977 by Kariya *et al.*[3] Following this, IIc type cancers were thought to be a unique 'Japanese phenomenon' until 1993 when Kudo *et al.*[4] reported their depressed type cancer series and classification. Several studies suggested that flat and depressed lesions may behave differently to sessile or protruding lesions, leading more frequently to high-grade dysplasia or submucosal invasive cancer. Since then, many studies have focused on the clinicopathological characteristics of flat and depressed lesions, so-called 'nonpolypoid' colorectal neoplasms.

In 1998, Fujii and Rembacken *et al.* demonstrated depressed lesions in an English population.[5] In this study, 68 adenomas were identified in 47 of 208 patients undergoing colonoscopy: 40% of these adenomas were nonpolypoid. In 2001, Saitoh *et al.* reported the prevalence of nonpolypoid colorectal lesions in North America while Tsuda *et al.* also reported these lesions in Sweden.[6,7] Although initial reports from the Western world suggested a lower frequency of nonpolypoid lesions than in the Japanese series[8] the implementation of chromoendoscopy performed by specialists trained by Japanese experts has improved the detection of such lesions in Western countries.

For screening colonoscopy to become more effective in reducing the incidence and mortality of colorectal cancer, it is important for endoscopists to recognize both polypoid and nonpolypoid colorectal cancer precursors. Left undetected, nonpolypoid colorectal neoplasms may evolve into invasive cancer within a few years following an assumedly normal colonoscopy.[9] This report is intended to provide an overview of the current understanding of the prevalence and clinicopathological features of nonpolypoid colorectal neoplasms.

PREVALENCE AND CLINICOPATHOLOGICAL FEATURES OF NONPOLYPOID COLORECTAL NEOPLASMS

Recent data from Western and Asian countries

In 2000, Rembacken *et al.* reported data from the UK (Table 1).[10] In this prospective study, 1000 consecutive patients attending routine colonoscopy were examined for flat or depressed lesions. Three hundred and twenty-one adenomas and six Dukes' A adenocarcinomas were identified: 204 (62.4%) were polypoid and 37.6% (123) were nonpolypoid lesions. Among all nonpolypoid lesions, the incidence of cancer was 3.3%. However, it was markedly higher in the depressed lesions (50%; 2/4). The authors

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	All polypoid lesions		All nonpolypoid lesions (0-IIa, IIb, IIc)		Depressed lesions (all IIc)	
	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)
Rembacken *et al.*, UK [10] (n = 327/1000 pts)	204 (62.4)	2 (1.0)	123 (37.6)	4 (3.3)	4 (1.2)	2 (50.0)
Parra *et al.*, Spain [11] (n = 490/1300 pts)	376 (76.7)	10 (2.7)	114 (23.3)	8 (7.0)	3 (0.6)	2 (66.6)
Soetikno *et al.*, USA [13] (n = 1535/1819 pts)	1308 (85.2)	13 (1.0)	227 (14.8)	15 (6.6)	18 (1.2)	6 (33.3)
Chiu *et al.*, Taiwan [14] (n = 5682/12 731 pts)	4653 (81.9)	79 (1.7)	1029 (18.1)	60 (5.8)	39 (0.7)	20 (51.3)

Ca, cancer; M, mucosal invasive cancers; SM, submucosal invasive cancers.

a 2006 Spanish study by Parra *et al.* who reported a review of 00 consecutive colonoscopic examinations.[11] A total of 490 polyps were adenomas and 150 were hyperplastic; 114 (23.3%) adenomas were flat (three were flat-depressed) whereas 376 (76.7%) were protruding. The diameter of flat and protruding adenomas was 9.2 ± 7.9 mm and 7.0 ± 5.9 mm, respectively ($P < 0.001$). This paper concluded that flat adenomas represent nearly one-quarter of all colorectal neoplastic polyps, their most frequent location being the right colon, and that they bear a higher risk of malignancy than protruding adenomas, especially for the flat-depressed type. From the USA, one study analyzed and reclassified 933 surgically removed sessile adenomas described in the National Polyp Study (NPS) and found no difference between polypoid and flat adenomas with respect to high-grade dysplasia or invasive cancer.[12] However, Soetikno *et al.* recently reported the prevalence and clinicopathological features of nonpolypoid colorectal neoplasms.[13] This was a cross-sectional study at a Veteran's Hospital in California with 1819 patients undergoing elective colonoscopy. Among all neoplasms (n = 1535) detected, 14.8% were classified as nonpolypoid lesions (n = 227, flat: 209, depressed: 18). Overall, nonpolypoid colorectal neoplasms were more likely to contain malignant cells (odds ratio, 9.78; 95% confidence interval, 3.93–24.4) than polypoid lesions, irrespective of the size. The depressed type had the highest risk (33.3%) of cancer. Moreover, Chiu *et al.* recently reported on the prevalence and characteristics of nonpolypoid colorectal neoplasms from Taiwan.[14] This study included 12 731 asymptomatic Chinese subjects (8372 of whom were average-risk subjects) who underwent screening colonoscopy. Nonpolypoid colorectal neoplasm was detected in 4.3% of asymptomatic and 4.2% of average-risk subjects. The prevalence of depressed lesions was 0.18% in both asymptomatic and average-risk subjects. This paper concluded that these findings may lead to modification of screening and prevention strategies for colorectal cancer. Meanwhile, Goto and Oda

Data from National Cancer Center Hospital, Tokyo

Subjects and methods

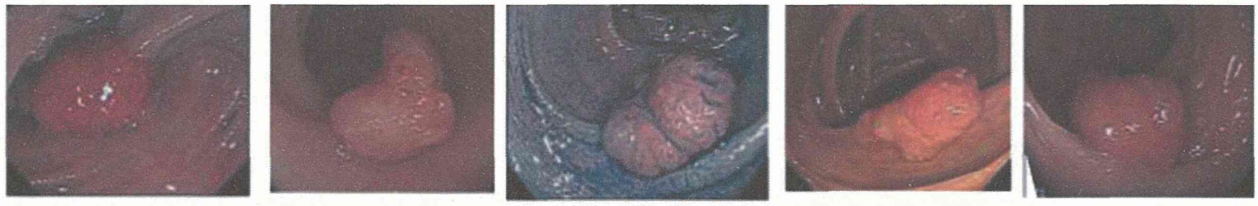
Between January 1998 and April 2003, a total of 6638 colorectal neoplasms in 3952 patients (men: 2800, women: 1152, mean age [standard deviation]: 63.4 years [9.9]) were treated endoscopically or surgically at the National Cancer Center Hospital, Tokyo. To clarify the importance of nonpolypoid colorectal neoplasms, we classified all lesions into three groups (group A: polypoid [Ip, Isp, Is]; group B: flat [IIa, laterally spreading tumor]; group C: depressed [IIc, IIa+IIc]) based on macroscopic identification during colonoscopy (Fig. 1). In addition, to clarify the clinical importance of flat lesions we further divided these lesions into three groups based on lesion size (Fig. 2).

Results

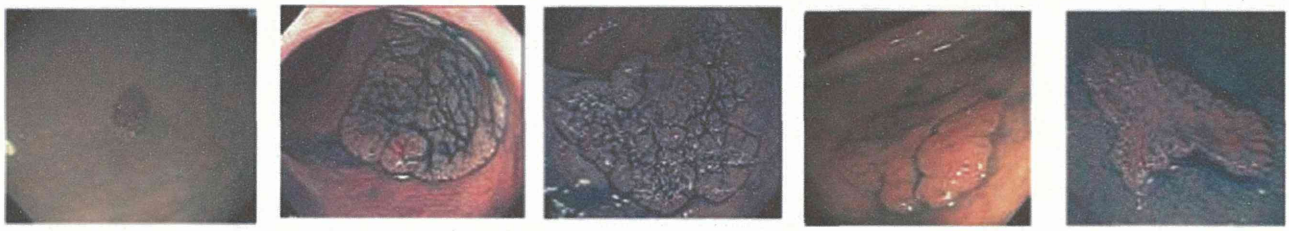
There were 4471 (67.4%) and 2167 (32.6%) polypoid and nonpolypoid colorectal neoplasms, respectively (Table 2). Among all nonpolypoid lesions, there were 178 (2.7%) depressed lesions, of which 109 (61.2%) were diagnosed as high-grade dysplasia (intramucosal cancer) or submucosal invasive cancer. On the other hand, the incidence of intramucosal cancer or submucosal invasive cancer was 15.4% and 18.9% in polypoid and nonpolypoid lesions, respectively.

Histopathological assessment of all lesions identified 5538 (83.4%) lesions as adenoma (low-grade dysplasia), 851 (12.8%) intramucosal cancer (high-grade dysplasia), and 249 (3.8%) submucosal invasive cancers (Table 3). The prevalence of cancers in our data was extremely high (16.6%) compared to other reports. We considered that this imbalance was related to the specific characteristics of our cancer center being a national referring hospital.

Among the lesions diagnosed as adenoma or intramucosal



Group B : Flat [IIa, LST]



Group C : Depressed [IIc, IIa+IIc]

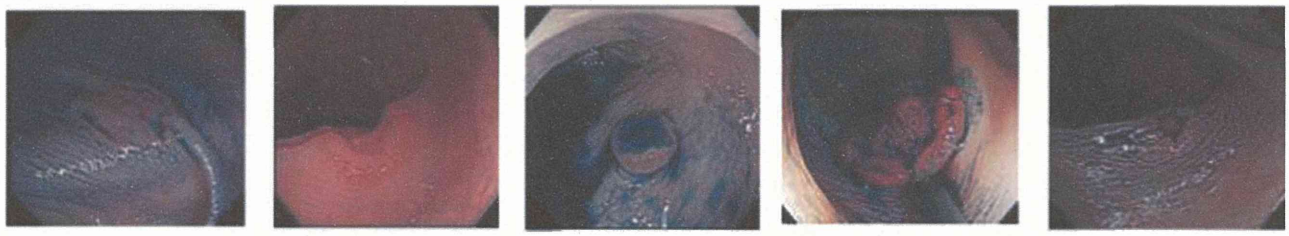


Fig. 1. Prevalence and malignant potential of flat and depressed lesions. LST, laterally spreading tumor (a flat elevated lesion ≥10 mm); LST-G, LST granular; LST-NG, LST non-granular.

Flat lesion [IIa, LST]

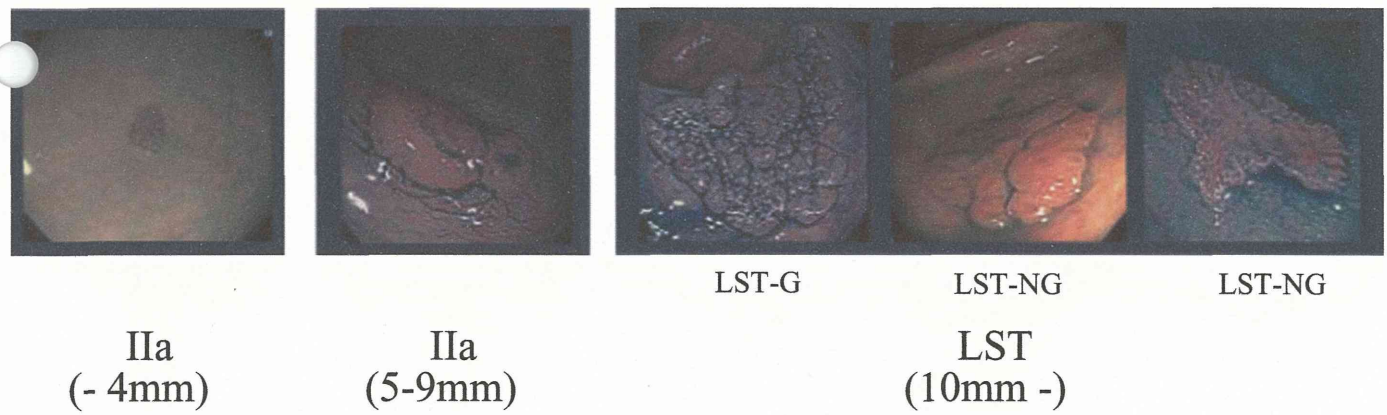


Fig. 2. Flat lesion (IIa, laterally spreading tumor [LST]). LST-G, LST granular; LST-NG, LST non-granular.

	All polypoid lesions		All nonpolypoid lesions (0-IIa, IIb, IIc)		Depressed lesions (all IIc)	
	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)
NCCH (n = 6638/3952 pts)	4471 (67.4)	690 (15.4)	2167 (32.6)	410 (18.9)	178 (2.7)	109 (61.2)

Ca, cancer; M, mucosal invasive cancers; SM, submucosal invasive cancers.

Table 3. Relationship between macroscopic type and histopathological findings (National Cancer Center Hospital [NCCH], Tokyo, 1998–2003)

	Macroscopic type	Adenoma (LGD)	Intramucosal cancer (HGD)	Submucosal invasive cancer
Polypoid	Ip	360	224	25
4471 (67.4%)	Isp	1053	232	40
	Is	2368	122	47
Flat	IIa	1550	96	11
1989 (29.9%)	LST	138	164	30
Depressed	IIc	26	5	13
178 (2.7%)	IIa + IIc	43	8	83
Total: 6638 lesions		5538 (83.4%)	851 (12.8%)	249 (3.8%)

HGD, high-grade dysplasia; LGD, low-grade dysplasia; LST, laterally spreading tumor, (granular and non-granular).

Table 4. Relationship between lesion size and clinicopathological findings (1989 flat lesions, National Cancer Center Hospital, Tokyo, 1998–2003)

Size	Location (C/A/T: D/S: R)*	Adenoma (LGD)	M-SM Ca (HGD-submucosal invasive cancer)
- 4 mm (830)	508:288:34 (61%:35%:4%)	828 (99.8%)	2 (0.2%)
5 - 9 mm (706)	387:276:43 (55%:39%:6%)	657 (93.1%)	49 (6.9%)
10 mm - (453)	260:111:82 (57%:25%:18%)	203 (44.8%)	250 (55.2%)
Total: 1989 lesions	1155:675:159 (58%:34%:8%)	1688 (84.9%)	301 (15.1%)

C, cecum; A, ascending; T, transverse; D, descending; S, sigmoid; R, rectum.

lesions (2.7% *vs* 67.4%, 32.6%), however, the incidence of cancer among depressed lesions was significantly higher than that of the other groups

(34%) in the distal colon and 159 (8%) rectal lesions. Among the lesions diagnosed as small, intermediate and large flat lesions, the incidence of cancers (intramucosal cancer or sub

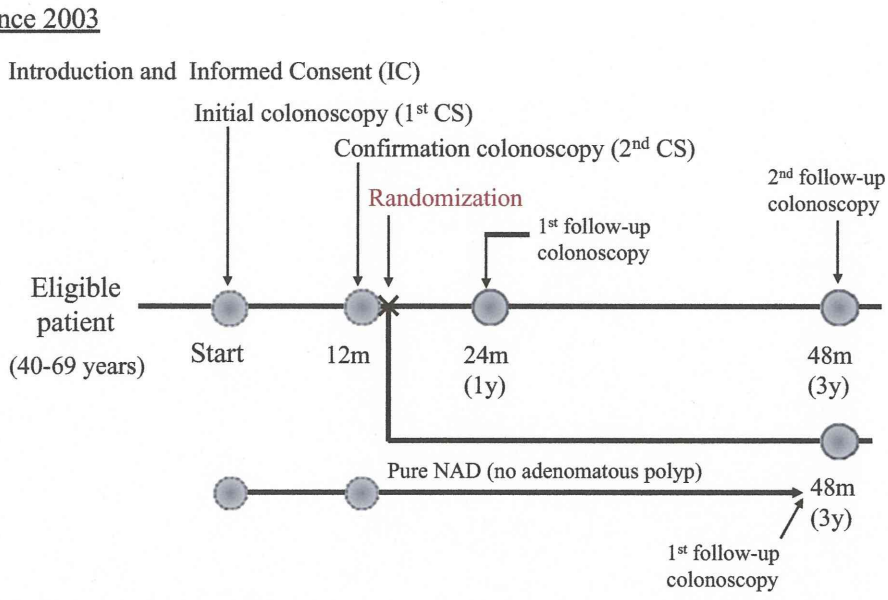


Fig. 3. Schematic overview of the Japan Polyp Study.

CONCLUSION

Although the nonpolypoid (especially depressed type) colorectal neoplasms may be regarded as occurring infrequently, they belong to a distinct subset that demonstrates greater biological aggressiveness, given the high prevalence of intramucosal or submucosal cancers. The detection and diagnosis of the nonpolypoid colorectal neoplasm presents both a challenge and an opportunity. Gastroenterologists need to meet the challenge and become proficient in the endoscopic recognition of these lesions in order to reduce the incidence and mortality from colorectal cancer. Consequently, large-scale prospective data need to be collected to further define the epidemiology and biology of nonpolypoid colorectal neoplasms in all populations. The Japan Polyp Study is a multicenter randomized controlled trial that was initiated in 2003 (Fig. 3).[16] It is prospectively evaluating follow-up surveillance strategies for Japanese populations after complete removal of all polyps, and nonpolypoid colorectal neoplasms, detected by high-resolution chromoendoscopy. The Japan Polyp Study is intended to continue until 2011, and the final step of the randomization process and complete histopathological assessment are ongoing. The clinical significance of nonpolypoid lesions (especially depressed type lesions) in Japan will become clear in this prospective study.

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MINI REVIEW

Our perspective on endoscopic resection for colorectal neoplasms

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Summary Endoscopic mucosal resection (EMR) is a minimally invasive technique for effective treatment of early stage colorectal lesions with no invasive potential. However, the high frequency of local recurrence after piecemeal EMR for large lesions is considered a serious problem. In contrast, endoscopic submucosal dissection (ESD) allows *en-bloc* resection, irrespective of the lesion's size. ESD has been established as a standard method for the endoscopic removal of early cancers in the upper gastrointestinal tract in Japan. Although the use of ESD for colorectal lesions has been studied clinically, ESD is not yet established as a standard therapeutic method. We define the indications for *en-bloc* resection, based on extensive clinicopathological analyses, as a laterally spreading tumor (LST) non-granular type (LST-NG) lesion greater than 20 mm and an LST granular (LST-G) type lesion greater than 40 mm. Both of these lesions had a high submucosal invasion rate. Especially, LST-NG type lesions greater than 20 mm are technically difficult to remove completely even by piecemeal EMR and are considered a "definite indication for *en-bloc* resection". The ESD procedure is undoubtedly an ideal method to achieve *en-bloc* resection, however, the prevalences of suitable lesions among all neoplastic lesions and among all early cancers were not high (1.0% and 5.0%, respectively). Therefore, it is crucial to master more fundamental therapeutic techniques and have knowledge of surveillance strategy after endoscopic treatment.

Introduction

Colorectal cancer is the third most important cause of cancer mortality in Japan [1]. The recognition and removal of early stage colorectal cancer and precancerous lesions are considered to be important for control of colorectal cancer [2]. Endoscopic mucosal resection (EMR) is now a well-established technique worldwide for the treatment of colorectal neoplasms with minimal invasiveness [3–6],

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however, the high frequency of local recurrence after piecemeal EMR for large lesions is considered a serious problem [7,8]. To avoid this problem, Japanese endoscopists developed a new technique that allows *en-bloc* resection of larger colorectal lesions. This technique, known as endoscopic submucosal dissection (ESD), starts with the submucosal injection, followed by dissection beginning at the lateral edges and working through the submucosal layer until the lesion is removed in one piece. Despite its longer procedure time and higher complication rate, ESD resulted in a higher *en-bloc* resection rate compared to that seen with conventional or piecemeal EMR [9–11]. This paper summarizes recent data of colorectal neoplasms, indications for *en-bloc* resection, and prevalence of candidate lesions among all early stage colorectal neoplasms from the database of National Cancer Center Hospital, Tokyo, Japan.

Indication criteria for endoscopic treatment

EMR is indicated to treat intramucosal colorectal cancer because the risk of lymph node metastasis is nil [12,13]. Surgery is indicated to treat submucosal invasive cancers because of the 6–12% risk of lymph node metastasis [14–18]. There is increasing evidence, however, to suggest that lesions with submucosal invasion less than 1000 μm – without lymphovascular invasion and without poor differentiation – also have a minimal risk of lymph node metastasis [19] and can be cured by EMR alone. Though lymphovascular invasion and poorly differentiated adenocarcinoma components are impossible to predict before resection, the vertical depth of invasion of submucosal cancers can be estimated based on the morphologic appearance at the time of endoscopy. It is therefore quite important to be able to distinguish neoplasms that are candidates for EMR from those that will require surgery, because EMR of lesions containing massive submucosal invasive cancer is associated with the risks of bleeding and perforation and is unlikely to be curative.

Current status of colorectal EMR and limitations

EMR is a minimally invasive technique for effective treatment of early stage colorectal lesions with no invasive potential. Several EMR techniques have been described (i.e. strip biopsy [inject, lift, and cut method], cap-assisted EMR [EMR-C], EMR with ligation [EMR-L]). The "inject and cut" method is simple and safe and is used widely for colorectal neoplasms. Lesions that do not lift during submucosal injection are generally not candidates for resections using the standard EMR technique. Due to the size of the snare, cap, and ligation device, these EMR techniques cannot be used to remove larger than 2 cm in one piece. This limitation prevents precise histopathological assessment and increases the risk of local recurrence. For such large colorectal lesions endoscopically diagnosed as intramucosal or submucosal superficial (< 1000 μm) invasion, piecemeal removal is possible, however, studies have shown that the risk of local recurrence is 2.7–23.5% [9–11]. Varying frequencies have been reported across institutions, probably related to the resection technique and varying abilities to judge for a diminutive residual tumor after piecemeal EMR. However, it has been proved that almost all local residual recurrences are not serious problems, because they are adenomatous lesions that have developed from the edge of primary lesions and can be managed by additional endoscopic treatment if vigilant follow-up is carried out [9,10,20]. The length of a suitable interval of surveillance colonoscopy after piecemeal EMR is still controversial (2–6 months) [21].

Endoscopic depth diagnosis and definite indication for "*en-bloc*" resection

Estimation of the depth of cancer invasion before treatment is crucial to decide the therapeutic plan. New diagnostic modalities such as endoscopic ultrasonography using mini-probe and magnifying chromoendoscopy are reported to be useful for the depth diagnosis of early colorectal cancers. However, these modalities are relatively expensive and time consuming. Therefore, if invasion depth could be diagnosed with only conventional colonoscopy, it would be more cost effective and convenient. Saitoh et al. reported that characteristic colonoscopic findings obtained by a combination of videocolonoscopy and chromoendoscopy are clinically useful for determination of the invasion depth of depressed type colorectal cancers [22]. In this report, characteristic colonoscopic findings (i.e. [1] expansion appearance, [2] deep depression surface, [3] irregular bottom of depression surface, and [4] folds converging toward the tumor) suggested the need for surgical treatment.

Magnifying chromoendoscopy is a standardized, validated method that facilitates detailed analysis of the morphological architecture of colonic mucosal crypt orifices (pit pattern) in a simple and efficient manner. The clinical classification of the colonic pit pattern (invasive and noninvasive) by using magnifying chromoendoscopy was originally described by Fujii et al. with the aim to discriminate between intramucosal-submucosal superficial invasion and submucosal deep invasion [23]. The existence of a non-invasive pattern as determined by magnifying chromoendoscopy is the minimum requirement for all lesions that are candidates for endoscopic treatment [24]. An invasive pattern is characterized by irregular and distorted pits observed in a demarcated area suggesting submucosal deep invasion (> 1000 μm).

We define the indications for *en-bloc* resection, based on extensive clinicopathological analyses [25], as a laterally spreading tumor (LST) non-granular type (LST-NG) lesion greater than 20 mm and an LST granular (LST-G) type lesion greater than 40 mm. Both of these lesions had a high submucosal invasion rate (Table 1). Especially, the LST-NG type lesion greater than 20 mm is technically difficult to remove completely even by piecemeal EMR; we define these lesions as a "definite indication for *en-bloc* resection". In contrast, LST-G type lesions greater than 40 mm are considered a "relative indication for *en-bloc* resection". Moreover, large villous tumors, recurrent lesions, and residual intramucosal lesions showing non-

Table 1 Relationship between size of LSTs and rate of submucosal invasion National Cancer Center Hospital, Tokyo, 1998–2006.

	10 mm (%)	20 mm (%)	30 mm (%)	40 mm (%)	Total (%)
IIa (LST-G)	0/115 (0)	0/70 (0)	1/31 (3.2)	0/13 (0)	1/229 (0.4)
Is + IIa (LST-G)	4/72 (5.6)	6/70 (8.6)	9/65 (13.8)	25/114 (21.9)	44/321 (13.7)
IIa (LST-NG)	12/246 (4.9)	24/106 (22.6)	11/33 (33.3)	8/17 (47.0)	55/402 (13.7)

LST-G: laterally spreading tumor, granular type; LST-NG: laterally spreading tumor, non-granular type.

Table 2 Prevalence of LSTs and indicated lesions for ESD National Cancer Center Hospital, Tokyo, 2000–2006.

	All neoplastic lesions % (n = 11,488)	Early colorectal cancers % (n = 1691)
LSTs[a]	5.9 (674)	22.6 (382)
Indication for ESD	2.3 (267)	12.1 (205)
Definite indication for ESD[b]	1.0 (115)	5.0 (85)
Relative indication for ESD[c]	1.3 (152)	7.1 (120)

[a] LSTs: LST-G and LST-NG.
[b] Definite indication: LST-NG lesion ≥ 20 mm.
[c] Relative indication: LST-G mixed type (Is + IIa [LST-G]) ≥ 40 mm.

lifting sign after EMR were also potential candidates for ESD.

ESD procedures

The ESD procedure is undoubtedly one of the ideal methods to achieve *en-bloc* resection. In our center, ESD procedures are primarily performed using a bipolar knife (B-knife) [26] or an IT knife with carbon dioxide (CO_2) insufflations instead of air insufflations to reduce patient discomfort [10,27,28]. Lesion margins are delineated before ESD by using 0.4% indigo-carmine dye spraying. After injection of Glyceol® (10% glycerol and 5% fructose in normal saline solution) [29] and sodium hyaluronate acid into the submucosal layer [30], a circumferential incision is made using the B-knife and ESD is then carried out using both the B-knife and IT-knife.

Prevalence of "definite indication" for ESD-data from National Cancer Center Hospital, Tokyo

Between January 2000 and December 2006, a total of 11,488 colorectal neoplasms (except advanced cancers) in 6369 patients were treated endoscopically or surgically at the National Cancer Center Hospital, Tokyo. To clarify the prevalence of "definite indication for colorectal ESD", we reviewed and analyzed records from our database. There were 9797 adenomas and 1691 early colorectal cancers (intramucosal cancer: 1294, submucosal cancer: 397). Among all neoplastic lesions, the prevalence of LSTs (LST-G and LST-NG) and the proportion for which ESD would have been indicated were 5.9% and 2.3%, respectively (Table 2). In contrast, among all early cancers, the prevalence of LSTs was 22.6% and proportion for which ESD would have been indicated was 12.1%. Moreover, the prevalences of "definite indication for ESD" among all neoplastic lesions and all early cancers were 1.0% (115/11,488) and 5.0% (85/1691), respectively.

Conclusion

The ESD procedure is an ideal method to provide "*en-bloc* resection" even for large colorectal lesions, however, the prevalence of lesions with a "definite indication for ESD" among all colorectal neoplasms is limited. In addition, although the use of ESD for colorectal lesions has been studied clinically, ESD is not yet established as a standard therapeutic method. Therefore, it is crucial to master more fundamental techniques (e.g. hot biopsy, snare polypectomy, conventional EMR, piecemeal EMR) and have knowledge of surveillance strategy after endoscopic treatment.

Furthermore, characteristic colonoscopic findings obtained by a combination of conventional colonoscopy and magnifying chromoendoscopy are useful and clinically important for determination of the invasion depth of early stage colorectal cancers, an essential factor in selecting a treatment modality (i.e. endoscopic treatment or surgical operation). As the therapeutic techniques are developed, preoperative endoscopic diagnosis will become more and more important.

Conflict of interest

The authors have not declared any conflict of interest.

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INDICATIONS FOR ENDOSCOPIC RESECTION OF COLORECTAL POLYPS AND SURVEILLANCE GUIDELINES

LOCAL RECURRENCE AND SURVEILLANCE AFTER ENDOSCOPIC RESECTION OF LARGE COLORECTAL TUMORS

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Local recurrence rates after endoscopic piecemeal mucosal resection (EPMR) typically range from 10 to 23%. In our previous study, the local recurrence rate after a piecemeal resection was significantly higher than that after an en bloc resection, irrespective of tumor size or macroscopic features. To reduce local recurrence after an EPMR, it is important to carefully note the circumferences of the edge and base of the ulcer. Recently, endoscopic submucosal dissection (ESD) was developed and recognized for its effectiveness in large, complete, en bloc resections and precise pathological assessments. ESD also showed lower local recurrence rates, ranging from 0 to 3% in previous, retrospective studies. However, ESD showed a higher perforation rate and longer procedure times; thus, it is necessary to improve ESD. An appropriate surveillance interval after EPMR was still controversial, and recommendations of some guidelines ranged from 2 to 9 months. In order to determine the appropriate interval, a randomized controlled study is necessary.

Key words: colorectal tumor, endoscopic mucosal resection, endoscopic submucosal dissection, local recurrence, surveillance.

INTRODUCTION

Both the incidence and mortality of colorectal tumors have increased recently; currently, colorectal cancers are the first and fourth leading causes of cancer mortality in Japanese women and men, respectively.[1] Large colorectal tumors are typically defined as ≥20 mm in diameter.[2–4] Some large colorectal tumors are adenomas or non-invasive cancers that can be treated successfully with endoscopic resection. Laterally spreading tumor (LST) were described as extending laterally, rather than vertically, and tended to remain in the mucosa.[5,6] Several issues need to be considered in the treatment of large colorectal tumors, including the indication for endoscopic resection, selection of an endoscopic treatment method, the risk of local recurrence, and the surveillance interval. Here, we present a review of the literature and discuss these issues.

INDICATION OF ENDOSCOPIC RESECTIONS

Endoscopic resection is indicated for early colorectal tumors that show negligible risk of lymph node metastases. The conditions for lymph node metastases were studied in a Japanese multicenter survey of colorectal cancers.[7] Based on the report, the pathological conditions that indicated no or low risk of lymph node metastasis included a shallow invasion depth (<1000 μm), no lymphatic invasion, and no sprouting.[7] Of these factors, only the invasion depth can be estimated before treatment. A biopsy is undesirable because it may complicate an endoscopic resection.[8] Furthermore, it is difficult to precisely diagnose the depth of invasion based on a biopsy. In general, a conventional, white light, endoscopic evaluation is used to assess early colorectal cancers; findings of hardness, fold convergence, depression, and irregular shape are considered indicative of submucosal invasion.[9] In pedunculated lesions, a thick stalk and jagged shape are important indications of stalk invasions. However, the accuracy of estimating the invasion depth with conventional endoscopy is insufficient for determining an appropriate therapeutic method that avoids excessive surgery. In our opinion, the most reliable method for predicting invasion depth is magnified chromoendoscopy with crystal violet staining. A pit pattern classification proposed by Kudo and Tsuruta has been adopted by Japanese endoscopists.[10] Type V pit patterns, particularly the VN type pit pattern, are recognized as indications of submucosal invasion.[10] Fujii and colleagues proposed a clinical classification of invasive or non-invasive patterns, taking into account the demarcated area with irregular or distorted pits.[11] We previously reported that the invasive pattern could differentiate between intramucosal or submucosal superficial cancers (<1000 μm) and submucosal deep cancers (≥1000 μm) with sensitivity, specificity, and accuracy of 85.6%, 99.4%, and 98.8%, respectively (Fig. 1).[11] In a multivariable analysis of factors that predicted submucosal deep invasion of non-granular type LST, the invasive pattern was considered a risk factor, together with hardness and large tumor size (≥20 mm).[12] Narrow band

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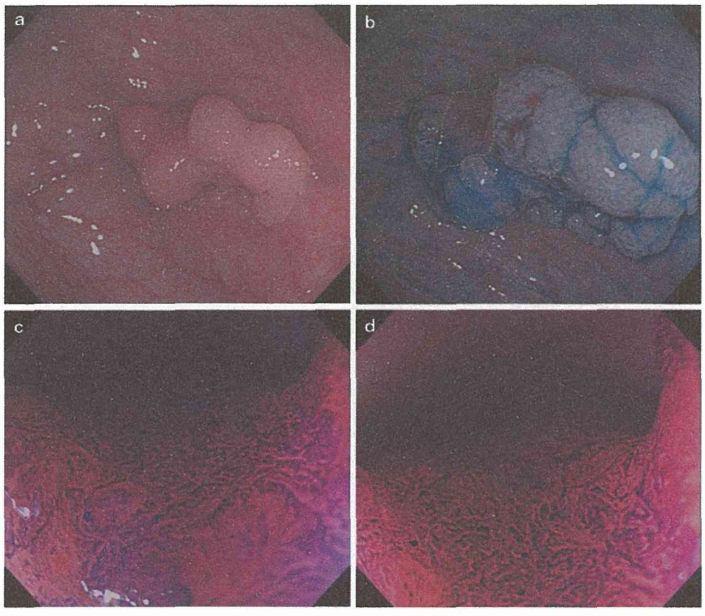

Fig. 1. A case of an invasive pattern. (a) Conventional colonoscopy showed a laterally spreading granular type tumor, with a reddish depressed area, 30 mm in diameter, in the cecum. (b) Chromoendoscopy with indigo-carmine spray dying showed a demarcated area traced by yellow dotted line. (c,d) Magnified chromoendoscopy with crystal violet staining showed invasive pattern in the demarcated area. The lesion was treated with laparoscopic surgery and pathological diagnosis was well-differentiated adenocarcinoma with submucosal invasion (2000 μm).

imaging (NBI) was recently assessed for predicting tumor invasion depth.[13] NBI offers the advantage of a simple, easy method; but currently, its diagnostic accuracy may be inferior to magnified endoscopy with crystal violet staining.[13] Endoscopic ultrasonography was also used for predicting tumor invasion depth, but it requires a higher level of skill and diagnosis is difficult, even in good conditions. Our previous controlled evaluation showed that magnified endoscopy was superior to endoscopic ultrasonography for the estimation of tumor invasion depth.[14]

SELECTION OF ENDOSCOPIC TREATMENT METHODS

The choice of endoscopic treatment methods depends on lesion size and characteristics; they include snare polypectomy, endoscopic mucosal resection (EMR), endoscopic piecemeal mucosal resection (EPMR), or endoscopic submucosal dissection (ESD). We propose that ESD is indicated for non-granular type LST (≥20 mm), due to the relatively high rates of submucosal invasion and the difficultly in predicting the invasion site prior to treatment.[15] Moreover, ESD is indicated for granular type LST, particularly mixed nodular types (≥40 mm), also due to relatively high rates of submucosal invasion.[15] Alternatively, EPMR is indicated for granular type LST (homogeneous type), due to the similarity to adenoma or intramucosal cancer. Recently, a working group for the standardization of colorectal ESD proposed that ESD is indicated for colorectal tumors with the following features: large lesions (≥20 mm in diameter) that are difficult to resect en bloc with a snare EMR, but where an endoscopic treatment is indicated; mucosal lesions with fibrosis caused by prolapse, due to biopsy or peristalsis of the lesion; sporadic localized tumors associated with chronic inflammation, e.g. ulcerative colitis; and local or residual early cancer after an endoscopic resection.[16] For pedunculated lesions, snare polypectomy of an EMR, combined with looping or clipping, is indicated when there is no endoscopic finding of stalk invasion. One controlled trial suggested that a bleeding rate was lower with combination epinephrine injection plus endoloop than epinephrine injection alone.[17]

LOCAL RECURRENCE AFTER ENDOSCOPIC RESECTION

After endoscopic resection local recurrence is an important issue in conventional EMR/EPMR methods (Fig. 2). Local recurrence rates after EPMR typically range from 10 to 23%[2,4,18–20] (Table 1). In our previous study, the local recurrence rate after a piecemeal resection was significantly higher than that after an en bloc resection, irrespective of tumor size or macroscopic features.[20] To reduce local recurrence after an EPMR, it is important to carefully note the circumferences of the edge and base of the ulcer. Magnified observation is ideal for detecting a residual tumor. Tanaka *et al.* reported that magnified observation after an EPMR could effectively reduce the local recurrence rate.[16] Argon plasma coagulation (APC) was also tested for reducing the local recurrence after EPMR. One controlled trial suggested that APC reduced the local recurrence after EPMR of large sessile tumors.[21] However, in a prospective uncontrolled study, similar recurrence rates were found with or without APC after an EPMR.[22] Thus, the usefulness of APC is controversial, but in some high-volume centers, it is routinely

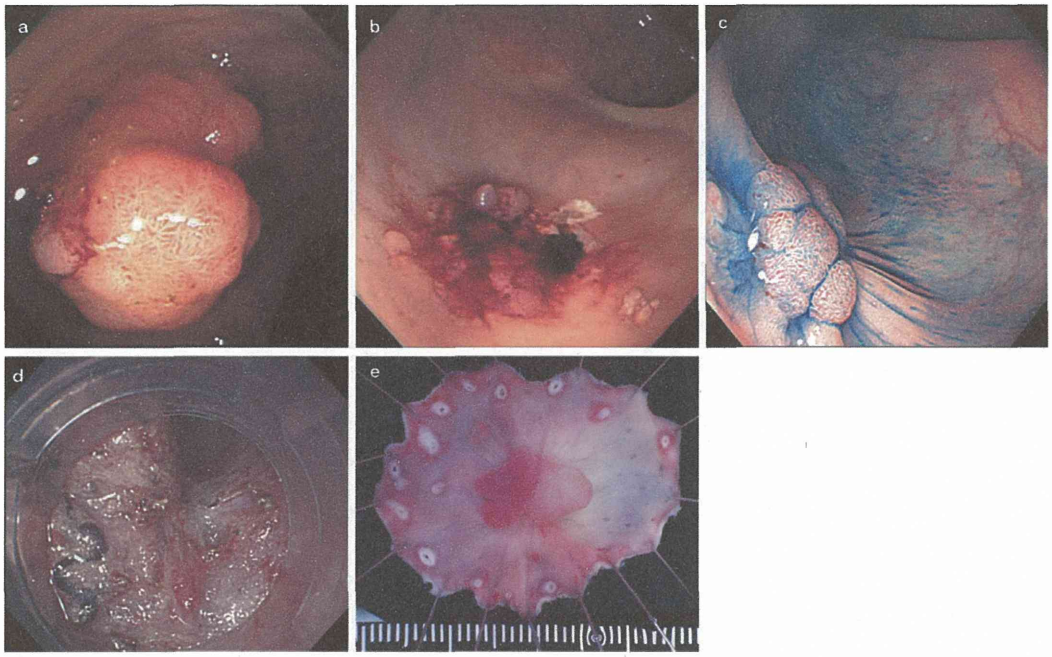

Fig. 2. A case of a local recurrence after endoscopic piecemeal mucosal resection (EPMR). (a) Conventional colonoscopy performed in the previous hospital showed a laterally spreading granular type (mixed nodular type) tumor, 30 mm in diameter, in the rectum. (b) Colonoscopy showed an artificial ulcer after EPMR. Pathological diagnosis was an intramucosal cancer and positive lateral margin. (c) Two months later a local recurrence (a residual lesion) was detected in our hospital as a protruding lesion with fold convergence. (d) The recurrence was treated with endoscopic submucosal dissection. During submucosal dissection severe fibrosis was seen. (e) The en bloc resected specimen revealed that the recurrence was 13 × 8 mm in diameter. Pathological diagnosis was tubulovillous adenoma.

Table 1. Previous reports of local recurrence after endoscopic mucosal resection of colorectal tumors (en bloc versus piecemeal)

Author	Design	Journal	Lesion size	*n*	Local recurrence rates	
					En bloc	Piecemeal
Tanaka S[2]	Retrospective	*Gastrointest Endosc* 2001	≧20 mm	81	4.9% (2/41)	10% (4/40)
Higaki S[17]	Prospective	*Endoscopy* 2003	≧20 mm	24	0% (0/5)	21.1% (4/19)
Hurlstone DP[18]	Prospective	*Gut* 2004	≧10 mm	58	9.1% (2/22)	22.2% (8/36)
Hotta K[19]	Retrospective	*Int J Colorectal Dis* 2009	≧10 mm	572	0.7% (3/440)	23.5% (31/132)
Saito Y[4]	Retrospective	*Surg Endosc* 2009	≧20 mm	228	2.7% (2/74)	20.1% (31/154)

used in clinical settings.[3] Recently, the ESD was developed and recognized for its effectiveness in large, complete, en bloc resections and precise pathological assessments (Fig. 3). ESD also showed lower local recurrence rates, ranging from 0 to 3% in previous, retrospective studies[23–28] (Table 2). Our retrospective controlled study suggested that local recurrence after an ESD (2%) was significantly lower than an EMR/EPMR (14%).[4] However, ESD showed a higher perforation rate and longer procedure times; thus, it is necessary to improve ESD.[4]

APPROPRIATE INTERVAL AFTER ENDOSCOPIC RESECTION

The National polyp study determined the appropriate interval after endoscopic resection for concluding complete removal of small colorectal adenomas.[29] They found that a 3-year interval after the removal of all adenomatous polyps was sufficient to detect newly adenomatous polyps.[29] In Japan, we also conducted a randomized controlled trial (the Japan polyp study) to determine an appropriate interval

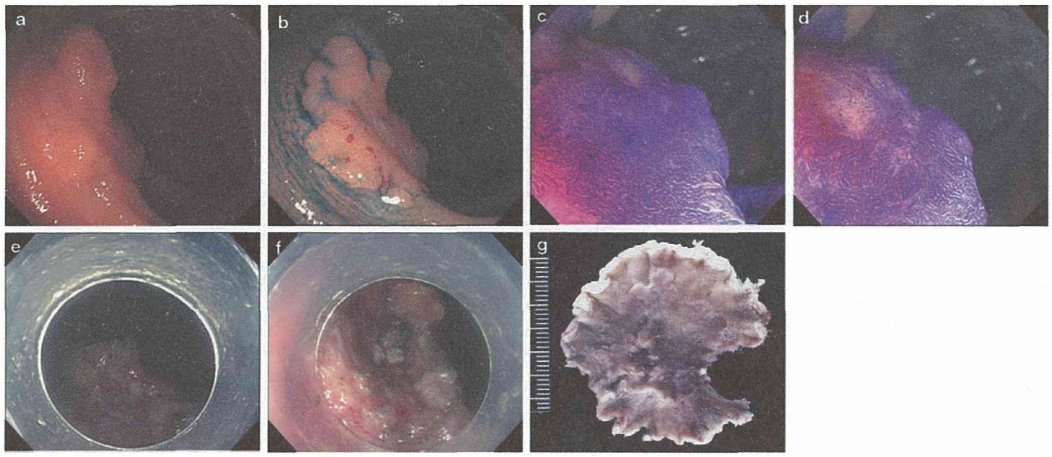

Fig. 3. A case of endoscopic submucosal dissection (ESD). (a) Conventional colonoscopy showed a laterally spreading non-granular type tumor, 30 mm in diameter, on the ileocecal valve. (b) Chromoendoscopy with indigo-carmine spray dying showed a demarcated line of the lesion. (c,d) Magnified chromoendoscopy with crystal violet staining showed a non-invasive pattern. (e,f) The lesion was treated with ESD and lipid deposit and severe fibrosis was seen during submucosal dissection. (g) The en bloc resected specimen revealed that the lesion was 28 × 20 mm in diameter. Pathological diagnosis was submucosal invasive cancer (2000 μm) and additional surgery was carried out later.

Table 2. Previous large-scale reports of colorectal endoscopic submucosal dissection

Author	Journal	*n*	En bloc resection	En bloc and R0 resection	Perforation	Local recurrence
Isomoto H[22]	*Endoscopy* 2009	292	90.1%	79.8%	8.2%	0.3%
Saito Y[23]	*Gastrointest Endosc* 2007	200	84%	83%	5%	0.5%
Fujishiro M[24]	*Clin Gastroenterol Hepatol* 2007	200	91.5%	71%	6%	1%
Zhou PH[25]	*Surg Endosc* 2009	74	93.2%	89.2%	8.1%	0%
Tamegai Y[26]	*Endoscopy* 2007	71	98.6%	95.6%	1.4%	2.8%
Tanaka S[27]	*Gastrointest Endosc* 2007	70	–	80%	10%	0%

after endoscopic resection of not only protruded but also flat and depressed type colorectal tumors.[30] The result of that study will be available in 2012. In the case of large colorectal tumors, the US multi-society task force on colorectal cancer and the American Cancer Society recommended that, after piecemeal removals of sessile adenomas, patients should be considered for follow-up colonoscopy at 2- to 6-month intervals to verify complete removal. Once complete removal has been established, subsequent surveillance should be individualized, based on the endoscopist's judgment. The completeness of removal should be based on endoscopic and pathological assessments.[31] On the other hand, based on the expert panel's opinions, the 2008 European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE II) also recommended that, after piecemeal removals of sessile adenomas, a follow-up colonoscopy was appropriate and necessary within the first 9 months following the index colonoscopy.[32] In our previous study, 572 colorectal tumors were followed up at 3 and 6 months after endoscopic resection. We found that 28 of the 34 lesions with local recurrences were detected at the first follow-up colonoscopy, and the remaining six lesions were detected at the second or a subsequent colonoscopy.[20] Four of the last six local recurrences were missed in the first colonoscopy performed at 3 months, due to the size limits of detection. Thus, we concluded that 6 months was an appropriate interval for assessing complete removal after EPMR to avoid missing local recurrences.[20] When a large colorectal tumor is removed with a complete en bloc resection by ESD, more than 12 months is considered necessary for the follow-up colonoscopy, due to the estimated risk of newly adenomatous polyps.

FUTURE PROSPECTS

No randomized controlled trial has studied surveillance intervals after an EPMR. We are currently conducting a prospective, randomized controlled trial to determine an appropriate interval after EPMR. We are considering follow ups at both 3 and 6 months versus only one at 6 months. Currently, the ESD requires a high level of skill; thus, the indication for

an ESD was proposed as a limited category. Once the problems associated with ESD are overcome, such as complications and procedure times, we will consider expanding the indication for the ESD category. One randomized controlled study revealed that an electrosurgical knife with a water-jet function (the FlushKnife) significantly shortened operation times of ESD for large colorectal tumors compared with a knife without a water-jet function.[33] In our retrospective analysis of a single colonoscopist result, 40 cases were necessary for reducing perforations.[34] Actually after the introduction of ESD, surgical treatments for non-granular type LST, which were adenoma and intramucosal or submucosal superficial cancers, were replaced by ESD.[35] In the near future, as ESD for large colorectal tumors becomes more common, the number of local recurrences after EPMR will be reduced.

CONCLUSION

Local recurrences frequently occur after EPMR of large colorectal tumors. To reduce recurrence, careful observation with magnification may be important. An appropriate interval after EPMR remains controversial, but ranges from 2 to 9 months. A randomized controlled study is necessary to determine the appropriate interval.

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