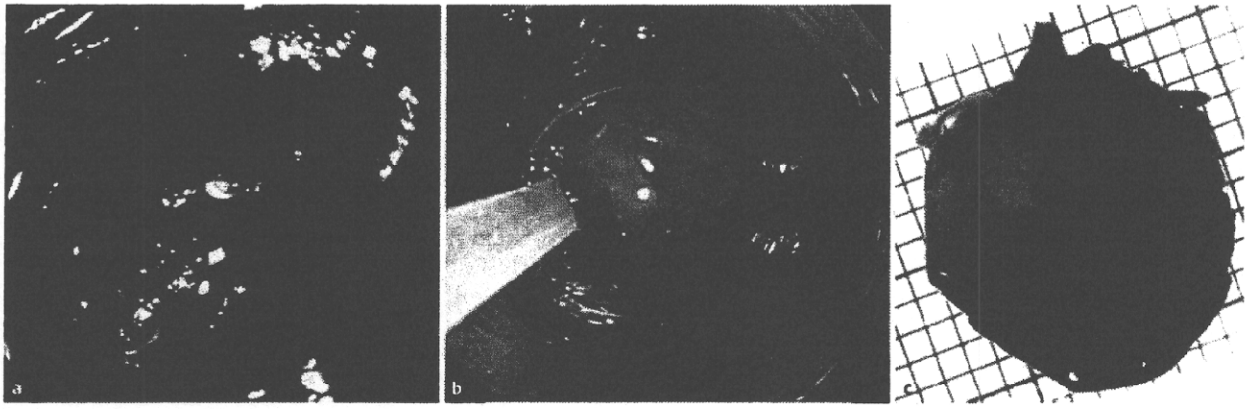

Fig. 1 a Superficial pharyngeal carcinoma in right pyriform sinus. b Endoscopic mucosal resection with cap-fitted device (EMR-C). c Resected specimen.

was also carried out annually to detect any lymph node or other organ metastasis.

A local recurrent tumor was defined as a tumor detected in close proximity to the scar resulting from the EMR, while metachronous tumor was defined as multiple primary tumors detected at other sites away from the location of the EMR scar after more than 6 months.

Results

EMR procedures

EMR-Cs (● **Fig. 1**) were performed on 34 lesions and strip biopsies were done for the other three lesions. In addition, electrocautery with hot biopsy forceps was used with four lesions during EMR to treat marginal residual tumor. En bloc resection was successfully done with 16 lesions (43%), while the remaining 21 lesions (57%) involved piecemeal resection with a median number of three pieces per EMR (range 2–11 pieces). Details of the EMR procedures are shown in ● **Table 2**. The median procedure time was 45 minutes (range 20–180 minutes). With 21 patients (68%) EMR was done with general anesthesia, while 10 patients (32%) had intravenous deep sedation using diazepam and pentazocine.

All 31 patients required hospitalization with a median stay of 7 days (range 4–12 days). Regarding complications, one patient experienced laryngeal edema requiring overnight intubation (● **Fig. 2**), another patient suffered from aspiration pneumonia, and two patients sustained dermatitis around the mouth caused by backflow of Lugol stain from the pharynx. None of the remaining 27 patients had any complications other than throat pain and discomfort which were relieved by nonsteroidal anti-inflammatory drugs. The laryngeal edema and aspiration pneumonia were successfully managed using steroids and antibiotics, respectively, while recovery from the dermatitis was achieved without medication. As a result, all 31 patients were discharged without further complications or any loss of function in terms of swallowing or speaking.

Histological results

Histological findings for the superficial pharyngeal cancers are shown in ● **Table 3**. Of the 37 lesions, 30 (81%) were located in the hypopharynx and seven (19%) in the oropharynx. The pyriform sinus was the most frequent primary site (25, 68%) and the median tumor diameter was 13.5 mm (range 4–40 mm). Histolo-

Table 2 Clinical characteristics of endoscopic mucosal resection (EMR) procedures.

Lesions	
Procedure type, n	
EMR-C	34
Strip biopsy	3
Plus electrocautery with hot biopsy forceps	4
EMR resection type, n	
En bloc resection	16
Piecemeal resection	21
Pieces per EMR piecemeal resection	
Median	3
Range	2–11
Patients	
Procedure time, minutes	
Median	45
Range	20–180
<30	2
≥30 and <60	17
≥60	12
Sedation during EMR, n	
General anesthesia	21
Intravenous deep sedation	10
Hospital stay after EMR, days	
Median	7
Range	4–12
<7	10
≥7 and <10	15
≥10	6
Treatment-related complications	
Present	4
Absent	27

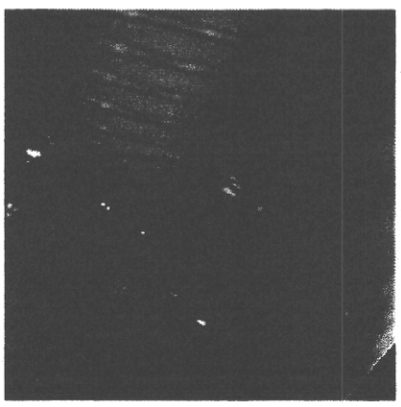

Fig. 2 Complication of laryngeal edema after endoscopic mucosal resection (EMR) required overnight intubation.

Table 3 Lesion characteristics.

	n
Primary site	
Hypopharynx	
Right pyriform sinus	12
Left pyriform sinus	13
Posterior pharyngeal wall	2
Postcricoid area	3
Oropharynx	
Uvula	3
Lateral wall	4
Tumor size, mm	
Median	13.5
Range	4–40
< 10	10
≥ 10 and < 20	14
≥ 20 and < 40	12
≥ 40	1
Histology	
Carcinoma in situ	18
Microinvasion (μm)	19
< 500	9
≥ 500 and < 1000	3
≥ 1000	7
Vascular invasion	
Present	1
Absent	36

gically, all 37 lesions were diagnosed as squamous cell carcinomas (SCCs) with 18 (49%) confirmed as carcinoma in situ and the other 19 (51%) indicating microinvasion of the subepithelial tissue. One of those microinvasive lesions revealed lymphatic invasion, but the remaining 36 lesions had no lymphovascular involvement. Representative endoscopic and histological images of the superficial pharyngeal cancers are shown in **Fig. 3** and **4**.

Follow-up

Follow-up and further treatment outcomes are summarized in **Fig. 5**. Three patients underwent additional radiotherapy either because of recurrent tumors (n = 2) or the presence of lymphatic invasion (n = 1), while two other patients underwent an additional EMR because of recurrent tumors (**Fig. 6**). Five patients developed metachronous superficial pharyngeal cancers, but all those lesions were successfully removed by subsequent EMR (n = 4) or partial surgical resection (n = 1). The two patients who died from esophageal cancer were excluded from the follow-up analysis. Thus, 20/31 patients had no recurrent or metachronous tumors during the median follow-up period of 40 months (range 21–62 months). Likewise, none of the 29 surviving patients had lymph node or other organ metastasis during this median follow-up period.

Discussion

Based on the results of our study, EMR performed by gastrointestinal endoscopists was a safe, effective, and minimally invasive treatment for superficial pharyngeal cancer. Since the median procedure time was only 45 minutes and the median hospitalization period was just 7 days, the physical burden on patients that would have otherwise been associated with their treatment was notably reduced. Although laryngeal edema, aspiration pneumonia, and dermatitis caused by Lugol staining were major complications, all such cases were successfully managed in a short period and every patient was discharged without further complications or the loss of any swallowing or speaking function. In addition, only four of the 31 patients experienced any recurrent tumors during the median follow-up period of 40 months and those patients were treated by either additional EMR (n = 2) or radiotherapy (n = 2). All five cases of subsequent metachronous cancer were detected at an early stage and treated by either local resection with EMR (n = 4) or partial surgical resection (n = 1). These results indicated, therefore, that EMR was both a safe and an effective technique for resection of superficial pharyngeal cancer.

Widespread use of Lugol staining of the esophagus in populations at high risk for esophageal SCC, such as heavy drinkers and heavy smokers, is recommended because it is generally accepted that Lugol chromoendoscopy facilitates the detection of esophageal SCC at an early stage [3–5]. Since a larger number of esophageal cancers can now be detected at an early stage, they are being more widely treated with EMR, resulting in both improved patient prognosis and a better quality of life [15–18].

Early detection of superficial pharyngeal cancers by laryngoscopy or conventional endoscopy is extremely difficult [1, 2] so previously most pharyngeal cancers were detected at an advanced stage and treated by surgical resection with a resultant poor prognosis and poorer quality of life for patients [6–9]. Diagnostic techniques such as magnifying endoscopy and NBI [2, 10–12] have been developed relatively recently, however, so detection of superficial pharyngeal cancers that can be successfully treated by EMR has been increasing dramatically [2, 19–22]. NBI is a novel optical imaging system, using reflected light to visualize superficial tissue structure, that has shown promising results in the diagnosis of both esophageal and pharyngeal cancer. Until recently, we had always sprayed Lugol solution just before performing EMR, but we now believe that NBI will replace Lugol chromoendoscopy as the most effective and noninvasive diagnostic technique for esophageal and pharyngeal cancers, as the availability and use of NBI for diagnosis of these and other cancers becomes more widespread. In such circumstances, the development of a new, minimally invasive modality for the treatment of pharyngeal cancer is also highly desirable. It has previously been reported that superficial pharyngeal cancers have been successfully treated using only EMR, but few reports actually described those procedures in detail [2, 19–22]. This study indicating that EMR was a safe, effective, and minimally invasive technique for such cancers, is therefore particularly significant.

Several authors have reported that SCC of the esophagus was often associated with synchronous or metachronous malignancy of other organs including gastric cancer, head and neck cancers and, especially, pharyngeal cancer [25–28], a phenomenon referred to as field cancerization. In this study, 30 of 31 patients had either synchronous or prior esophageal cancers so our results suggest that in order to make an early diagnosis of pharyngeal cancer, endoscopic examination of the pharyngeal mucosa is important, not only for patients with synchronous esophageal cancer, but also for patients previously treated for esophageal cancer.

In addition, we performed follow-up surveillance laryngoscopy and endoscopy at least every 3 and 6 months, respectively, after EMR. Such regular periodic examinations resulted in the early detection of recurrent or metachronous lesions so that those lesions could also be treated primarily by EMR. There are no reports at the present time, however, that establish an appropriate follow-up period after EMR for diagnosing recurrent or meta-

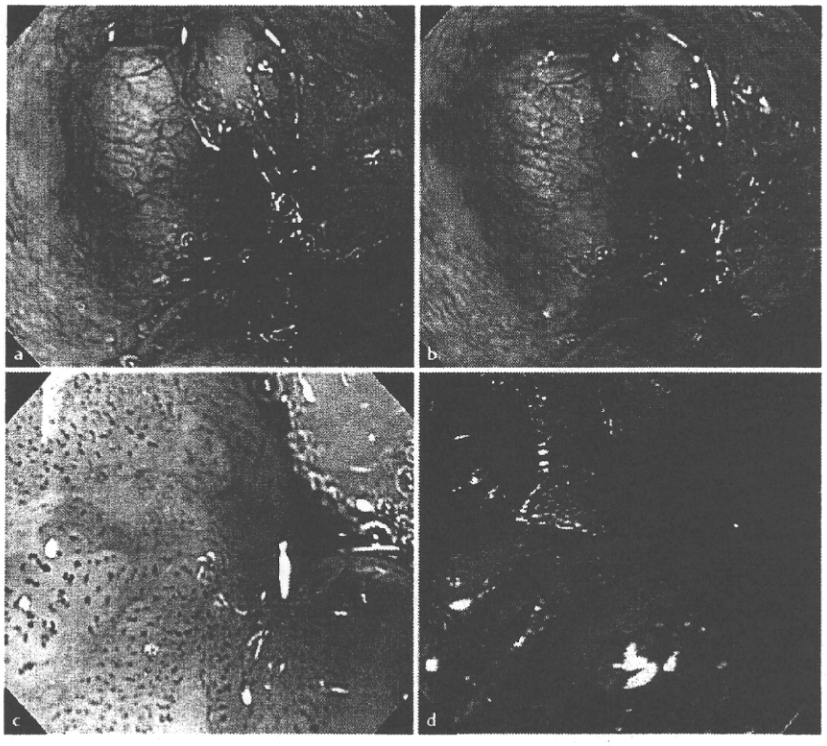

Fig. 3 **a** Conventional endoscopy showed a slightly reddish area in the right pyriform sinus. **b** Narrow band imaging (NBI) endoscopy revealed a clearly demarcated area brownish in color. **c** NBI with magnifying endoscopy highlighted the characteristic changes of intraepithelial papillary capillary loops (IPCLs), including dilatation, tortuosity, and caliber change in a single IPCL, and variation in the shape of multiple IPCLs. **d** Lugol chromoendoscopy with the patient under intubation delineated the lesion margin more clearly.

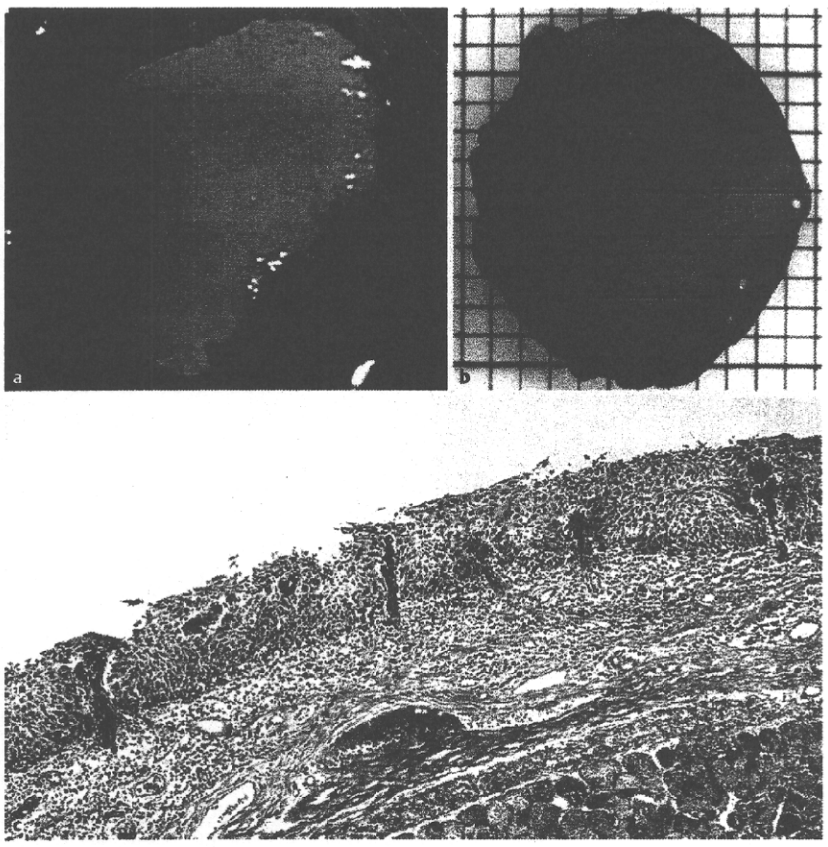

Fig. 4 **a** Another superficial pharyngeal carcinoma in the right pyriform sinus. **b** The resected specimen. **c** Resected specimen revealed squamous cell carcinoma in situ with characteristic intraepithelial papillary capillary loop (IPCL) changes.

chronous lesions at an early stage, so further investigation is needed in this area.

Although using one of the new diagnostic modalities such as NBI enabled us to detect small superficial pharyngeal cancers less than 5 mm in diameter, it has not been determined whether we should treat such lesions immediately, because no reports have been published as yet on how long it takes for superficial pharyngeal cancer to progress to an advanced cancerous stage. It may not be necessary to treat such lesions immediately, but further elucidation as to the nature of pharyngeal cancer is needed to

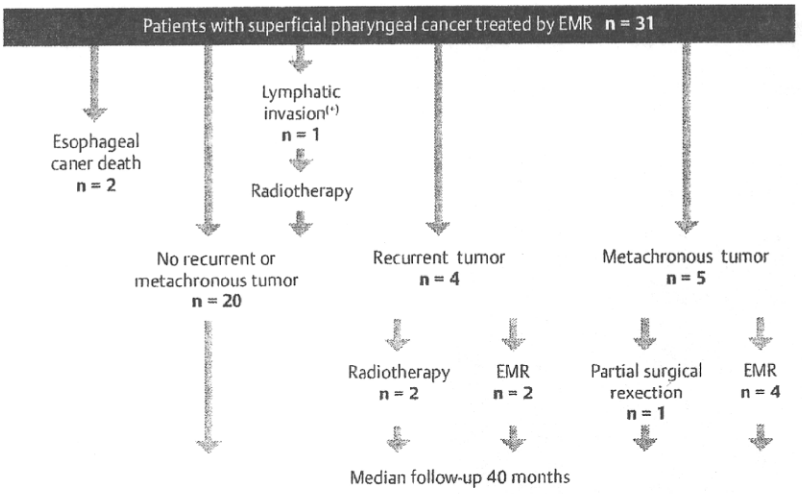

Fig. 5 Follow-up results and further treatments. EMR, endoscopic mucosal resection.

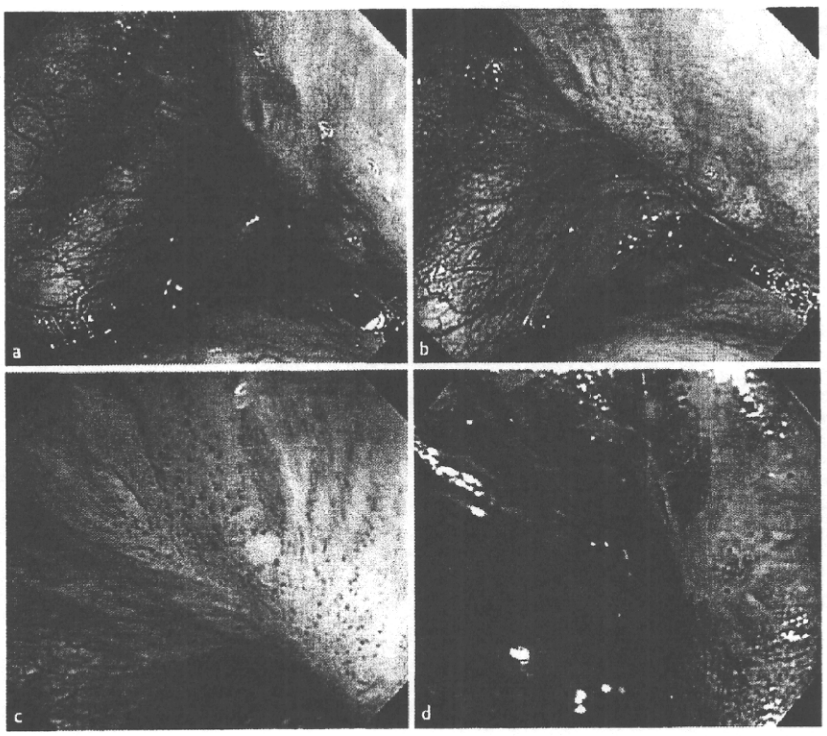

Fig. 6 Local recurrence of pharyngeal carcinoma after endoscopic mucosal resection (EMR) detected near to the EMR scar: a conventional endoscopy view; **b** narrow band imaging (NBI) endoscopy appearance; **c** NBI with magnification endoscopy; **d** Lugol chromoendoscopy appearance.

help clarify both the appropriate form and the timing of treatment.

It seems reasonable to conclude from this study that EMR is a safe, effective, and minimally invasive treatment for superficial pharyngeal cancer, but long-term outcome data, including information concerning recurrent and metachronous tumors as well as lymph node and other organ metastasis, are still lacking. While both carcinoma in situ and slight carcinoma invasion of subepithelial tissue seem to be appropriate indications for EMR, there is little reported evidence supporting these criteria [2, 19–22]. A long-term follow-up study to establish the indications for EMR of pharyngeal cancer, therefore, should be conducted in the future to properly evaluate the suitability of EMR for treating superficial pharyngeal cancer.

Endoscopic submucosal dissection (ESD) also has recently been reported to be effective in the en bloc resection of superficial pharyngeal cancers because endoscopists can confirm an accurate cutting line while performing this procedure [20, 22]. It is difficult to maneuver an endoscope and then perform ESD in the oral cavity which is a narrowly restricted and complex area, however, so such lesions are generally resected in several pieces using EMR at the present time. Although piecemeal resections can result in unsatisfactory histological evaluations and increase the risk of local recurrence, all four of the recurrent tumors in our study were detected at an early stage and could be treated by either additional EMR or radiotherapy. Further investigation should also be conducted, therefore, to evaluate the effectiveness of EMR compared with ESD for the treatment of pharyngeal cancers and to determine the most appropriate treatment for such cancers.

The complications encountered in this study were successfully managed within a short period, but EMR for superficial pharyn-

geal cancer must be performed carefully because of the associated risk of laryngeal edema or aspiration into the airway leading to severe respiratory disorders such as pneumonia and suffocation. With every pharyngeal cancer patient who underwent EMR under intravenous deep sedation without intubation, just before EMR we cautiously dripped a small amount of diluted Lugol solution directly onto the pharyngeal lesion itself, using an endoscopic catheter to avoid aspiration into the airway. When EMR was done with the patient was under general anesthesia with intubation, 3% Lugol solution was sprayed on the pharyngeal lesion utilizing the same procedure used during esophageal cancer examinations. We also sprayed thiosulfate solution and saline on the mucosal site after EMR to rinse away the Lugol stain and prevent laryngeal edema. In order to prevent laryngeal edema and aspiration immediately following EMR, we usually provided steroid treatment (intravenous drip infusion and/or inhalant) and administered antibiotics (intravenous drip infusion) for at least 2 days as well. As a further precaution, we normally covered the patient's face, particularly around the mouth, with adhesive tape to prevent dermatitis caused by any backflow of Lugol stain from the pharynx. In order to avoid complications, properly resolve those that do occur, and otherwise minimize the physical burden on patients, it is recommended that endoscopists routinely collaborate with head and neck surgeons when treating such patients in the future.

Finally, it was difficult to maneuver the endoscope in the oral cavity which is a narrowly restricted and complex area. The current EMR procedures need to be refined and/or new techniques developed that provide improved maneuverability before this treatment modality can become accepted for general clinical use.

In conclusion, the results of this study indicated that EMR performed by gastrointestinal endoscopists was a safe, effective, and minimally invasive treatment for superficial pharyngeal cancer, but long-term outcome data are still lacking at the present time.

Acknowledgment

We wish to express our appreciation to Christopher Dix for his assistance in editing this manuscript.

Competing interests: None

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Digestive Endoscopy (2010) **22** (Suppl. 1), S57–S62 doi:10.1111/j.1443-1661.2010.00967.x

INDICATIONS FOR ENDOSCOPIC RESECTION OF COLORECTAL POLYPS AND SURVEILLANCE GUIDELINES

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 concluded that the polyp-carcinoma hypothesis prompts colonoscopists to search only for polypoid lesions when screening for cancer, and many early colorectal neoplasms may therefore be missed. Adding to this data are results from

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Conflicts of interest: The authors declare no potential conflicts of interest.

Received 18 December 2009; accepted 24 December 2009.

Digestive Endoscopy
Journal for Gastroenterologists and Endoscopic Surgeons

Table 1. Prevalence of non-polypoid colorectal neoplasms (data from Western and Asian countries)

	No. neoplastic lesions and incidence of Ca (M/SM)					
	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 1300 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 *et al.*[15] estimated that depressed (IIc), so-called de novo cancer might comprise up to 22.9% of early colorectal cancers (18.6% in men and 27.4% in women) in a cohort of 14 817 Japanese subjects.

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 cancer, the prevalence of depressed lesions was 1.2–1.5%. In contrast, depressed type submucosal cancers were identified in 38.6% (96/249) of subjects. The prevalence of depressed lesions was relatively low compared to polypoid or flat

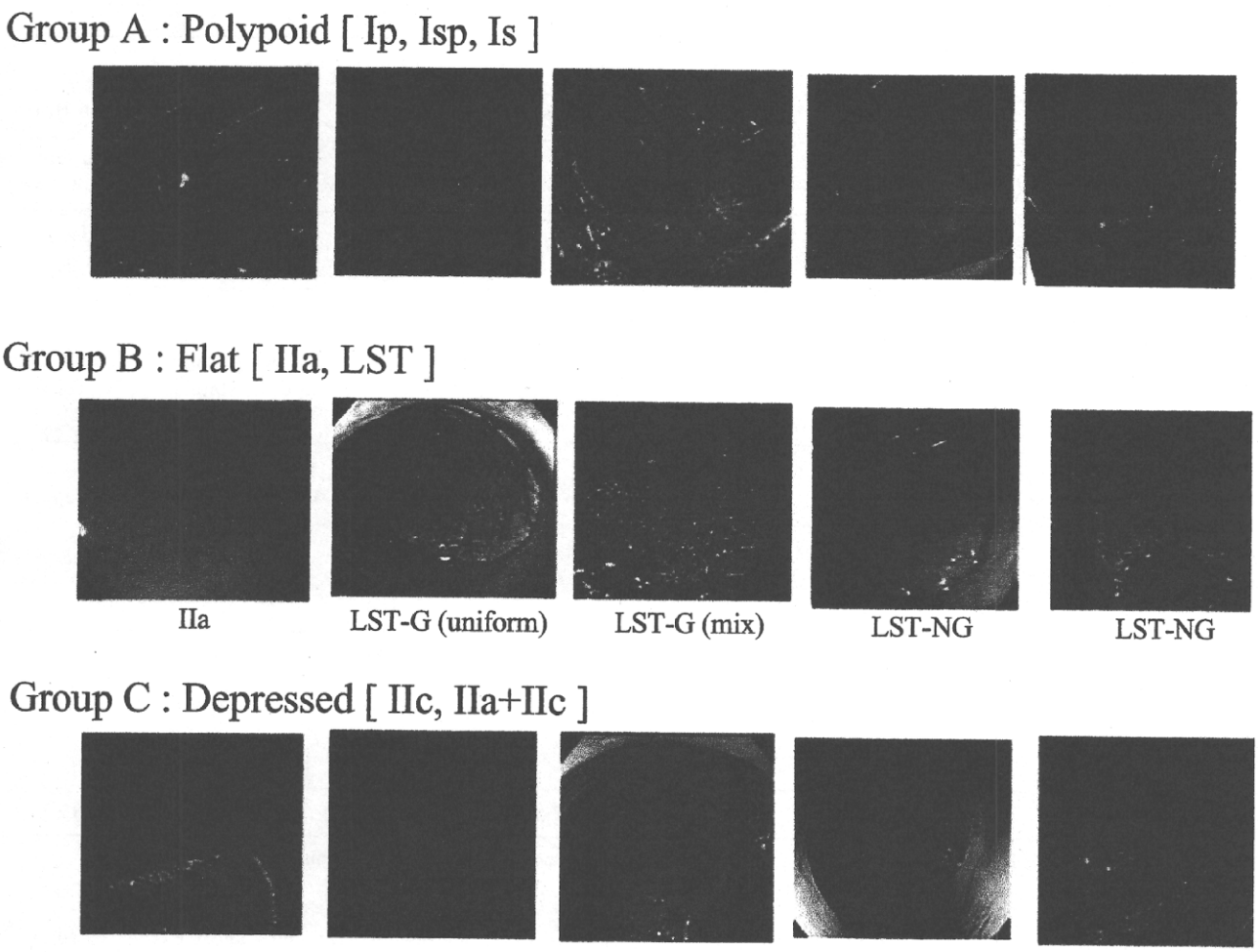

Fig. 1. Prevalence and malignant potential of flat and depressed lesions. LST, laterally spreading tumor (a flat elevated lesion ≥10 mm); LST-G, LST granular; LST-NG, LST non-granular.

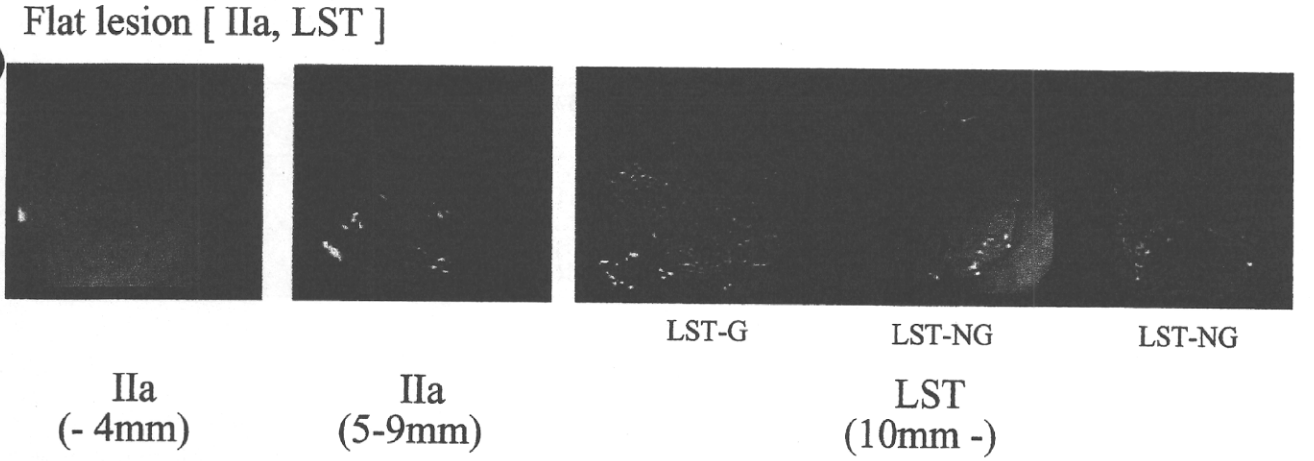

Fig. 2. Flat lesion (IIa, laterally spreading tumor [LST]). LST-G, LST granular; LST-NG, LST non-granular.

Table 2. Prevalence of non-polypoid colorectal neoplasms (National Cancer Center Hospital [NCCH], Tokyo, 1998–2003)

	No. neoplastic lesions and incidence of Ca (M/SM)					
	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.

Regarding flat lesions, there were 830 small (<5 mm), 706 intermediate (5–9 mm) and 453 large (≥10 mm; laterally spreading tumor) lesions (Table 4). As for tumor location, there were 1155 lesions (58%) in the proximal colon, 675 (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 submucosal invasive cancer) was 0.2% (2/830), 6.9% (49/706) and 55.2% (250/453), respectively. Therefore, laterally spreading tumor lesions are undoubtedly clinically more important than small ones.

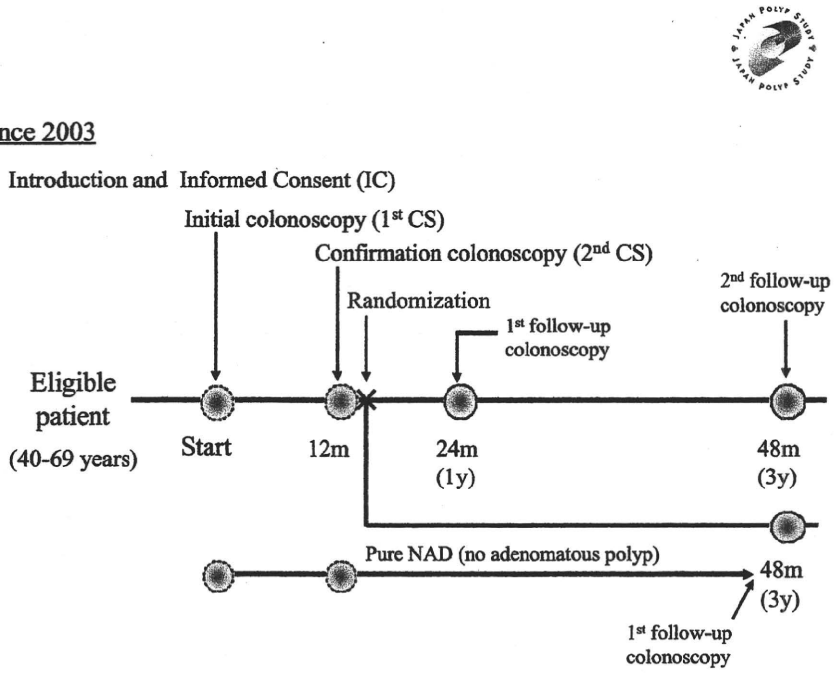

Fig. 3. Schematic overview of the Japan Polyp Study.

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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Digestive Endoscopy (2010) **22** (Suppl. 1), S63–S68 doi:10.1111/j.1443-1661.2010.00965.x

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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Conflicts of interest: The authors declare no potential conflicts of interest.

Received 14 December 2009; accepted 8 January 2010.

Digestive Endoscopy
Journal for Gastroenterologists and Endoscopic Surgeons

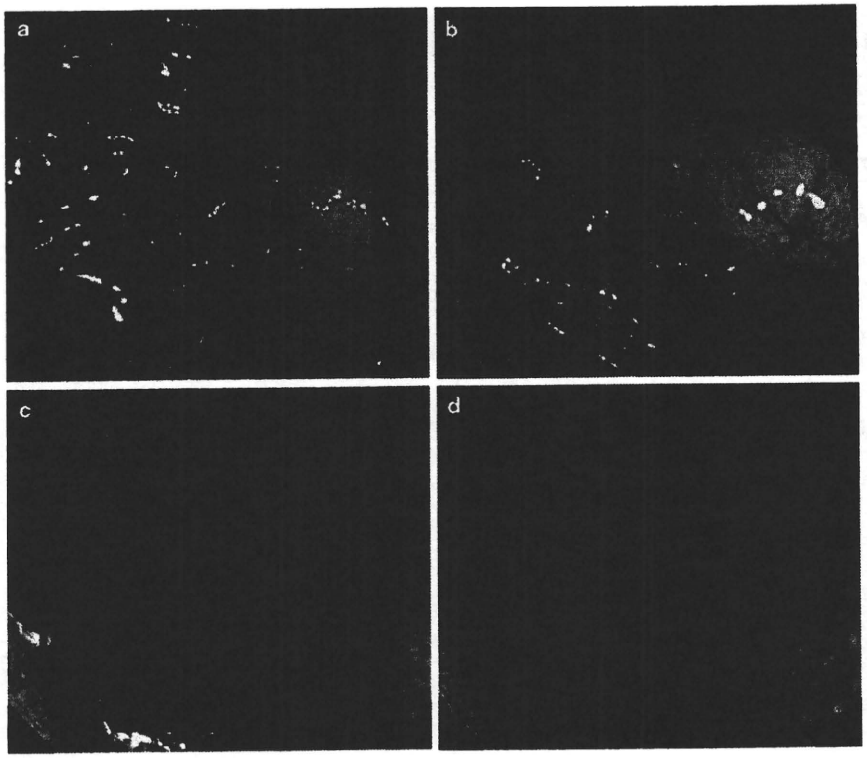

Fig. 1. A case of an invasive pattern. (a) Conventional colonoscopy showed a laterally spreading granular type tumor, with a reddish depressed area, 30 mm in diameter, in the cecum. (b) Chromoendoscopy with indigo-carmine spray dying showed a demarcated area traced by yellow dotted line. (c,d) Magnified 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

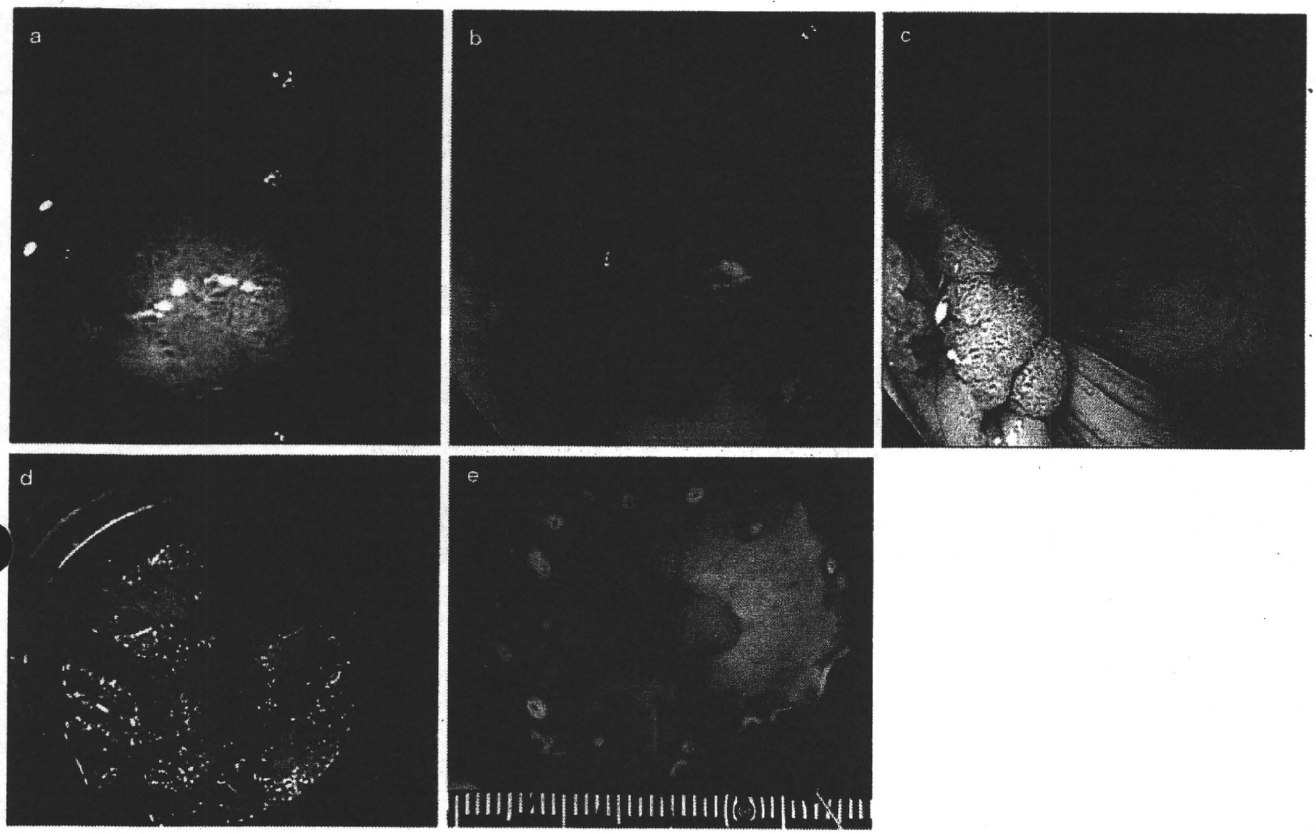

Fig. 2. A case of a local recurrence after endoscopic piecemeal mucosal resection (EPMR). (a) Conventional colonoscopy performed in the previous hospital showed a laterally spreading granular type (mixed nodular type) tumor, 30 mm in diameter, in the rectum. (b) Colonoscopy showed an artificial ulcer 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

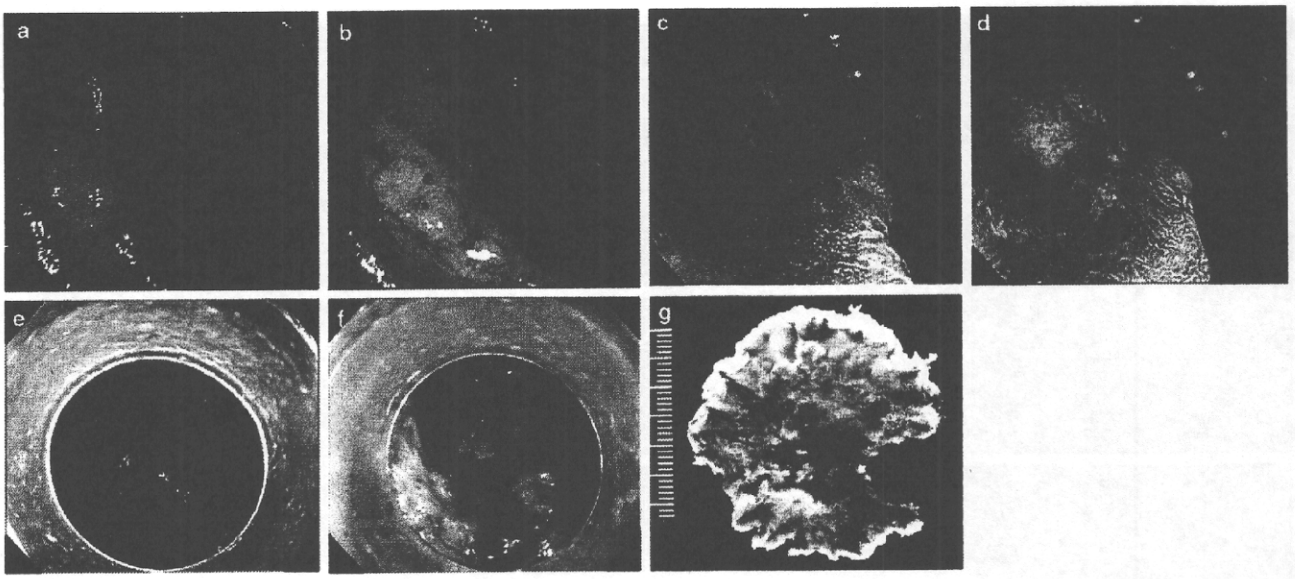

Fig. 3. A case of endoscopic submucosal dissection (ESD). (a) Conventional colonoscopy showed a laterally spreading non-granular type tumor, 30 mm in diameter, on the ileocecal valve. (b) Chromoendoscopy with indigo-carmine spray dying showed a demarcated line of the lesion. (c,d) Magnified chromoendoscopy 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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World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i14.1727

World J Gastroenterol 2010 April 14; 16(14): 1727-1734
ISSN 1007-9327 (print)

ORIGINAL ARTICLE

Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer

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Received: November 30, 2009 Revised: January 20, 2010
Accepted: January 27, 2010
Published online: April 14, 2010

Abstract

AIM: To evaluate the surface microvascular patterns of early colorectal cancer (ECC) using narrow-band imaging (NBI) with magnification and its effectiveness for invasion depth diagnosis.

METHODS: We studied 112 ECC lesions [mucosal/submucosal superficial (m/sm-s), 69; sm-deep (sm-d), 43] ≥ 10 mm that subsequently underwent endoscopic or surgical treatment at our hospital. We compared microvascular architecture revealed by NBI with magnification to histological findings and then to magnification colonoscopy pit pattern diagnosis.

RESULTS: Univariate analysis indicated vessel density: non-dense ($P < 0.0001$); vessel regularity: negative ($P < 0.0001$); caliber regularity: negative ($P < 0.0001$); vessel length: short ($P < 0.0001$); and vessel meandering: positive ($P = 0.002$) occurred significantly more often with sm-d invasion than m/sm-s invasion. Multivariate analysis showed sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13133.1] and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1). Both of these findings when combined were an indicator of sm-d invasion with sensitivity, specificity and accuracy of 81.4%, 100% and 92.9%, respectively. Pit pattern diagnosis sensitivity, specificity and accuracy, meanwhile, were 86.0%, 98.6% and 93.8%, respectively, thus, the NBI with magnification findings of non-dense vessel density and negative vessel regularity when combined together were comparable to pit pattern diagnosis.

CONCLUSION: Non-dense vessel density and/or negative vessel regularity observed by NBI with magnification could be indicators of ECC sm-d invasion.

Key words: Colorectal neoplasms; Narrow-band imaging; Microvasculature

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Fukuzawa M, Saito Y, Matsuda T, Uraoka T, Itoi T, Moriyasu F. Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer. *World J Gastroenterol* 2010; 16(14): 1727-1734 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i14/1727.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i14.1727

INTRODUCTION

Magnified colonoscopy and the development of pit pattern diagnosis[1] not only permits us to distinguish neoplastic from non-neoplastic colorectal lesions[2-5], but also helps to assess the invasion depth of early colorectal cancers (ECC)[6-9]. Similarly, vascular findings on the surface of gastric lesions have also been observed by

magnification endoscopy, and the usefulness in predicting the histological nature of such lesions and assessing their invasion depth has also been reported in the upper gastrointestinal (GI) tract[10-12].

The recently developed narrow-band imaging (NBI) system is a noninvasive optical technique that uses reflected light that provides clearer images of surface microvascular architecture than the conventional observation modality[13]. To date, the use of magnification endoscopy with the NBI system has been studied in the upper GI tract[14-20] and the suitability of this new modality for differentiating neoplastic from non-neoplastic lesions and its potential for pit pattern diagnosis have also been reported for the lower GI tract[21-30].

As previously indicated, colorectal lesions with mucosal (m) or submucosal (sm) superficial invasion < 1000 μm (sm-s) have an extremely low risk of lymph-node metastasis and are good candidates for endoscopic treatment[31]. It is helpful therefore, to differentiate endoscopically between m/sm-s and deeper sm invasion (sm-d ≥ 1000 μm) lesions. There have been only a few reports concerning invasion depth diagnosis using NBI with magnification in a large series of cases, however, a number of questions remain regarding the comparative effectiveness of a diagnosis based on NBI observation and one using pit pattern analysis by dye chromoendoscopy for determining invasion depth.

Using magnification colonoscopy with the NBI system, we evaluated the characteristics of the surface microvascular architecture of ECC and investigated the effectiveness of this new optical modality for the diagnosis of invasion depth. In addition, we evaluated the comparative relationship between NBI with magnification and pit pattern diagnoses.

MATERIALS AND METHODS

NBI system

NBI is a novel technique that uses spectral narrow-band optical filters instead of the full spectrum of white light. It is based on the phenomenon that the depth of light penetration depends on its wavelength, with a short wavelength penetrating only superficially and a longer wavelength penetrating into deeper layers. In the NBI mode, optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are mechanically inserted between a xenon arc lamp and a red/green/blue rotation filter. Thin blood vessels such as capillaries on the mucosal surface can be seen most clearly at 415 nm, which is the wavelength that corresponds to the hemoglobin absorption band, while thick vessels located in the deep layer of the mucosa can be observed at 540 nm. Current NBI technology limits mucosal surface light penetration, thereby enhancing visualization of the fine capillary vessel structure on the surface layer.

Patients and evaluation methods

We studied a total of 112 ECC lesions ≥ 10 mm analyzed with NBI with magnification colonoscopy examination, which then underwent endoscopic or surgical treatment at the National Cancer Center Hospital between January 2006 and February 2007. All colonoscopies were performed with a PCF-Q240ZI or CF-H260AZI endoscope (Olympus Optical Co. Ltd., Tokyo, Japan) by three experienced endoscopists (MF, YS, TM) each of whom had annually performed more than 1000 magnifying chromoendoscopy examinations and at least 500 NBI examinations per year. Endoscopic images of each lesion were taken in the following order: conventional colonoscopy, NBI with magnification, chromoendoscopy and magnification chromoendoscopy. When a lesion was detected by conventional colonoscopy, its surface was washed with proteinase to remove excess mucus. Magnification NBI views of the microvascular architecture concentrated on those portions of the lesion where invasion seemed to have permeated the deepest regions, such as depressed areas and large nodules[32,33].

After completion of NBI with magnification, the pit pattern of each lesion was assessed with magnification chromoendoscopy performed using 0.4% indigo-carmine (IC) dye spraying. When high magnification observation with IC dye did not permit us to determine adequately the surface structure for pit pattern analysis, 0.05% crystal violet was applied for staining[7]. The visible pit pattern was then assessed during the course of the examination by the endoscopist conducting the procedure. All lesions were resected subsequently endoscopically or surgically and histological diagnosis was performed by three experienced pathologists based on the Vienna classification[34,35]. The depth of sm invasion was determined as being either sm-s < 1000 μm or sm-d ≥ 1000 μm[31]. After pathological diagnosis was completed on all resected lesions, three endoscopists (Fukuzawa M, Saito Y and Matsuda T) who performed the examination individually reviewed the endoscopic images of the NBI findings that were taken prior to treatment. All endoscopic images were chosen by one of these endoscopists. Their evaluation of the NBI images of the m/sm-s and sm-d lesions focused on the suspected areas, respectively, of higher grade dysplasia and deepest suspected invasion. Each characteristic of microvascular architecture was finally determined based on the agreement of at least two of the three reviewing endoscopists. Microvascular findings with a high frequency of sm-d were assessed as to whether those were significant sm-d indicators by univariate and multivariate analysis. In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated for each microvascular architectural feature observed during NBI, as well as every pit pattern diagnosis determined by magnification chromoendoscopy. We then compared the various types of microvascular architecture characteristics revealed by NBI with magnification to the chromoendoscopy pit pattern diagnoses.

The protocol for this study was approved by our institutional review board and all patients gave written informed consent.

Chromoendoscopy with magnification

Our pit pattern evaluation method relied on the clinical classification system proposed by Fujii *et al*[7] and Matsuda *et al*[8], with reference to the Kudo Classification System. Lesions were categorized into noninvasive and invasive

patterns. The noninvasive pattern included regular crypts with or without a demarcated area (e.g. depression, large nodule, or reddened area) and irregular pits without a demarcated area, and are usually observed in Kudo's types IIIs, IIIL, IV and VI without demarcated areas (e.g. adenomatous polyps, m and sm-s cancers), with endoscopic resection being the appropriate treatment. The invasive pattern was characterized by irregular and distorted crypts in a demarcated area, as observed in Kudo's type VN and VI with a demarcated area (e.g. sm-d), and should be treated by surgical resection. As indicated, Kudo's type VI can be observed in either noninvasive or invasive patterns. Those differences are dependent on the presence or absence of a demarcated area.

Microvascular architecture of ECC

Microvascular architectural images taken during magnification colonoscopy with NBI were reviewed retrospectively by three endoscopists who referenced the microvascular architectural features of superficial esophageal carcinoma[15], and included the following characteristics: (1) caliber, narrow or wide; (2) caliber regularity, positive or negative; (3) meandering, positive or negative; (4) vessel regularity, positive or negative; (5) vessel length, short or long; and (6) vessel density, non-dense or dense. These characteristics were evaluated by comparing the NBI with magnification images to representative photographs of model examples (Figure 1).

Statistical analysis

We compared microvascular architecture as revealed by NBI with magnification to histological findings using the χ^2 test of independence or Fisher's exact test for univariate analysis. Variables with a P value of < 0.05 in our univariate analysis were subsequently included in a logistic regression multivariate analysis. The StatView program, version 5.0 (SAS Institute, Cary, NC, USA), was used for data analysis and $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathological features of patients and lesions

The clinicopathological details of the patients and colorectal lesions involved in this study are shown in Table 1.

Univariate analysis

Univariate analysis indicated characteristics involving vessel density: non-dense ($P < 0.0001$); vessel regularity: negative ($P < 0.0001$); caliber regularity: negative ($P < 0.0001$); vessel length: short ($P < 0.0001$); and vessel meandering: positive ($P = 0.002$) occurred significantly more often with sm-d invasion than m/sm-s invasion (Table 2).

Multivariate analysis

Multivariate analysis demonstrated that sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13 133.1]; and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1) (Table 2). The sensitivity, specificity, PPV, NPV and diagnostic accuracy rate for each characteristic are shown in Table 3. The two vascular findings that were confirmed by multivariate analysis had the highest values for specificity, PPV and accuracy (non-dense vessel density: specificity 0.99, PPV 0.95, accuracy 90.2%; negative vessel regularity: specificity 0.99, PPV 0.95, accuracy 90.2%).

Table 1 Clinicopathological features of evaluated colorectal lesions

	m/sm-s	sm-d
Lesions (n = 112)	69	43
Gender (male/female)	42/27	24/19
Age (range, yr)	63.2 (37-79)	62.5 (32-80)
Location		
Right colon	29	15
Left colon	18	12
Rectum	22	16
Morphology[1]		
Ip/Is/Isp	21	18
IIa/IIa + IIc/IIc	10	16
LST-G	20	5
LST-NG	18	4
Mean size (range, mm)	32.3 (10-100)	24.4 (10-90)

[1]Update on the Paris classification of superficial neoplastic lesion in the digestive tract[36]. LST-G: Laterally spreading tumor-granuler type; LST-NG: Laterally spreading tumour-non granular type; m/sm-s: Mucosal/submucosal superficial; sm-d: Submucosal-deep.

Pit pattern diagnosis

The pit patterns of 21 m/sm-s lesions were evaluated following IC dye spraying, whereas the pit patterns of the other 48 m/sm-s lesions and all 43 sm-d lesions were assessed after crystal violet staining. We subsequently calculated the sensitivity, specificity, PPV, NPV and accuracy in differentiating m/sm-s from sm-d for: (1) the pit patterns that were diagnosed as being invasive; and (2) the NBI with magnification characteristic findings of (a) non-dense vessel density and/or negative vessel regularity and (b) non-dense vessel density and negative vessel regularity, which were both considered to be indicators for sm-d invasion. Pit pattern analysis sensitivity, specificity, PPV, NPV and diagnostic accuracy were 0.86 (95% CI: 0.72-0.95), 0.99 (0.92-0.99), 0.97 (0.86-0.99), 0.92 (0.83-0.97) and 93.8%, respectively. The NBI with magnification characteristic findings of non-dense vessel density and negative vessel regularity were comparable to pit pattern diagnosis results [0.81 (0.67-0.92), 1.00 (0.95-1.00), 1.00 (0.90-1.00), 0.90 (0.81-0.95), 92.9%] (Table 4). Seven of the lesions in this study were incorrectly diagnosed using pit pattern analysis including six sm-d lesions mistakenly diagnosed as m/sm-s invasion depth. In two of these cases, however, both non-dense vessel density and negative vessel regularity had also been observed by magnification NBI, which suggests its potential use as a supplementary diagnostic tool to pit pattern diagnosis (Figures 2 and 3).

DISCUSSION

It has been reported previously that observation of intra-