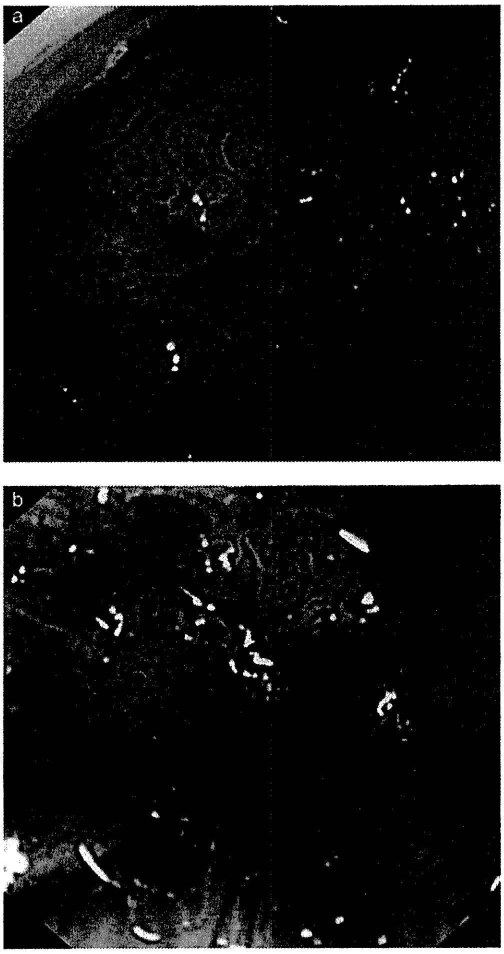

**Figure 3** Representative transanal resection case. (a) Large 0–Is lesion located in the lower rectum; (b) tumor spread to anal canal.

while TAR procedure times were measured from the initial incision to the completion of resection and hemostasis, as determined by the individual surgeons. The lateral and vertical margins of specimens resected by ESD and TAR were examined macroscopically for any tumor involvement by endoscopists or surgeons.

An en-bloc R0 resection was successfully achieved when both the lateral and vertical margins of a specimen were free of neoplasm, with resection in one piece. Specimens with deep submucosal (> 1000 μm from the muscularis mucosae) invasion, lymphatic invasion, vascular involvement, or histologically poorly-differentiated component were diagnosed as non-curative.[9] Histological diagnosis was based on the Japanese classification of cancer of the colon and rectum,[10] and the Vienna classification.[11]

### Endoscopic and other modality follow up

All patients with curative resection were examined endoscopically 6 months after their original treatment. Indigo carmine dye was sprayed on the previously-resected areas, and high-magnification views were obtained to check for the existence of any recurrence for all patients. One or two biopsies were performed as indicated, with recurrent neoplastic disease identified as type-IIIs, -IIIL, -IV, or -V pit patterns (neoplastic pattern) using high-magnification chromocolonoscopy, according to the criteria established by Kudo and Fujii.[12,13] When a type I or II pit pattern (non-neoplastic pattern) was identified using high-magnification chromocolonoscopy, no biopsy was performed, as there was no evidence of recurrence.[13] Patients with intramucosal cancer and adenoma did not require computed tomography (CT) scan on follow up. Curative resection cases with superficial submucosal invasion (T1sm1) were followed up by annual abdominal and pelvic CT scan.

### Statistical analysis

Statistical differences were analyzed using the $\chi^2$-test or *t*-test with a *P*-value less than 0.05, considered as statistically significant. Calculations were made using SPSS version 8.0 for Windows (SPSS Japan, Tokyo, Japan).

## Results

### Patient characteristics and lesion clinical features

A total of 85 patients were recruited into the study. Fifty-two patients were treated by ESD, and 33 patients were treated by TAR (Table 1). The mean lesion size was 40 mm and 39 mm in diameter for the ESD and TAR groups, respectively. Eleven lesions in the ESD group were located in the upper rectum (Ra; oral side from the middle transverse fold of rectum), 37 in the lower rectum (Rb; anal side from the middle transverse fold of the rectum), and four extended from the Rb to the anal canal (Rb–P). In comparison, none (0%) of the lesions in the TAR group was located in the Ra, 22 lesions were in the Rb, and 11 were in the dentate line (Rb–P).

Histological results of adenoma/intramucosal carcinoma (Tis)/T1sm1/deep submucosal carcinoma (T1sm2) were 9/26/6/11 in the ESD group and 2/18/2/11 in the TAR group, respectively.

The mean procedure time of the ESD group was significantly longer than that of the TAR group (131 *vs* 63 min, $P < 0.001$). The mean length of hospital stay in the ESD group was significantly shorter than that of the TAR group (4.9 days *vs* 7 days, $P < 0.001$).

### Histopathological results and local recurrence rates

The macroscopically-clear resection margin rates of ESD and TAR were 100% (Table 2). En-bloc resection with the microscopically-clear resection margin (En-bloc R0 resection) was successfully achieved in 67% of the ESD group, which was significantly higher than the 42% in the TAR group ($P < 0.001$).

### Clinical results in the curative resection subgroup

After histological examination, 11 ESD and 11 TAR were found to have deep submucosal invasion, including one TAR with lymphovascular involvement. These 11 ESD and 11 TAR patients

**Table 1** Patient characteristics and lesion clinical features

| | Endoscopic submucosal dissection | Transanal resection | *P*-value |
|---|---|---|---|
| No. lesions | 52 | 33 | |
| Age (Mean [SD]), years | 61 ± 11 | 64 ± 13 | NS |
| Tumor size, mm | 40 ± 21 | 39 ± 24 | NS |
| Location | | | |
| Ra/Rb/Rb–P | 11/37/4 (21/71/8%) | 0/22/11 (0/67/33%) | < 0.001 |
| Macroscopic type | | | |
| Sessile/flat/recurrent | 4/44/4 (8/84/8%) | 17/16/0 (52/48/0%) | NS |
| Histological depth | | | |
| Adenoma/Tis/T1sm1/T1sm2 | 9/26/6/11 (17/50/12/21%) | 2/18/2/11 (6/55/6/33%) | NS |
| Procedure time, min (mean ± SD) | 131 ± 100 | 63 ± 54 | < 0.001 |
| Hospital stay, days | 4.9 ± 0.8 | 7.0 ± 3.0 | < 0.001 |

NS, not significant; Ra, oral side from the middle transverse fold of rectum; Rb, anal side from the middle transverse fold of the rectum; Rb–P, oral side from the middle transverse fold of rectum to the anal canal; SD, standard deviation; T1sm1, submucosal invasion < 1000 μm; T1sm2, submucosal invasion > 1000 μm; Tis, intramucosal.

**Table 2** Comparison of clinical results

| | Endoscopic submucosal dissection | Transanal resection | *P*-value |
|---|---|---|---|
| Macro clear resection rate† | 100% (52/52) | 100% (33/33) | NS |
| En-bloc resection rate | | | |
| All | 88% (46/52) | 85% (28/33) | NS |
| Sessile | 100% (4/4) | 94% (16/17) | NS |
| Flat | 91% (40/44) | 75% (12/16) | NS |
| Recurrent | 50% (2/4) | — | |
| En-bloc R0 resection rate‡ | | | |
| All | 67% (35/52) | 42% (14/33) | < 0.001 |
| Sessile | 100% (4/4) | 65% (11/17) | NS |
| Flat | 66% (29/44) | 19% (3/16) | < 0.005 |
| Recurrent | 50% (2/4) | — | |

†Macroscopically-clear resection margin; ‡en-bloc and negative resection margin. NA, not applicable; NS, not significant.

received additional surgical procedure or chemoradiotherapy. Sixty-three lesions, including 41 lesions treated by ESD and 22 lesions treated by TAR, were diagnosed as curative resections (Table 3). Among the patients who received curative resection, en-bloc R0 resection was successfully achieved in 78% of the ESD group, which was significantly higher than the 27% in the TAR group ($P < 0.001$). There was no recurrence for all these en-bloc R0 resection cases in the ESD group (26 flat lesions, 4 sessile lesions, and 2 recurrent lesions after other resections) over a median follow-up period of 60 months.

In the remaining nine cases of ESD, seven were resected in one piece, but the lateral margins of the resection specimen were histologically positive for neoplastic components, and two cases were resected in two pieces. These nine ESD resections were all flat lesions, but there was also no local recurrence in any of these cases over a median follow-up period of 35 months.

In comparison, six cases of TAR achieved en-bloc R0 resections. In the other 16 cases of TAR, 11 cases were resected in a single piece, but the lateral margins were histologically positive for neoplastic components. These 11 TAR cases were all flat lesions, and three of them developed local recurrences. The other five cases of TAR were resected as piecemeal, and recurrences were present in two of these five lesions.

The overall local recurrence rate was 23% ($P < 0.01$) in the TAR group cases over a median follow-up period of 55 months. The median time interval of local recurrence was 12 months after TAR. All five local recurrences in the TAR group underwent additional treatment: two proceeded with ESD, two repeated TAR, and one received low anterior resection with lymph node dissection. Curative resections were achieved in all five local recurrent cases.

## Complications

Three kinds of complications occurred in the ESD group, including rectal perforations in two patients, minor delayed bleeding in one patient, and one case of subcutaneous emphysema. All four patients were successfully managed by conservative means, using endoclips without the need of blood transfusion or any additional procedure. In comparison, two kinds of complications occurred in the TAR group, including one case of delayed bleeding after the

**Table 3** Comparison of clinical results for curative resection cases

| | Endoscopic submucosal dissection (41 cases) | Transanal resection (22 cases) | *P*-value |
|---|---|---|---|
| En-bloc R0 resection rate† | | | |
| All | 78% (32/41) | 27% (6/22) | < 0.001 |
| Sessile | 100% (4/4) | 44% (4/9) | NS |
| Flat | 76% (26/34) | 15% (2/13) | < 0.001 |
| Recurrent | 67% (2/3) | — | |
| Local recurrence rate | | | |
| All | 0% (0/41) | 23% (5/22) | < 0.01 |
| Sessile | 0% (0/4) | 22% (2/9) | NS |
| Flat | 0% (0/34) | 23% (3/13) | < 0.05 |
| Recurrent | 0% (0/3) | — | |
| Median recurrence period, months | NA | 12 (7–17) | NA |

†En-bloc and negative resection margin. NA, not applicable; NS, not significant.

**Table 4** Comparison of complications

| | Endoscopic submucosal dissection | Transanal resection |
|---|---|---|
| Perforation | 2 (4%) | 0 |
| Minor delayed bleeding | 1 (2%) | 1 (3%) |
| Subcutaneous emphysema | 1 (2%) | 0 |
| Temporary delirium | 0 | 1 (3%) |
| Dental injury | 0 | 1 (3%) |

procedure and two complication cases related to the use of general anesthesia in which one patient experienced temporary delirium and the other suffered a dental injury (Table 4).

## Discussion

To the best of our knowledge, this is the first study to compare the effectiveness of ESD with TAR in treating non-invasive rectal tumors (adenoma, intramucosal carcinoma, and superficial submucosal carcinoma). In our study, ESD was proven to be a more effective treatment for non-invasive rectal neoplasms than TAR in terms of both curability and shorter hospital stay. ESD achieved a higher en-bloc R0 resection rate and resulted in no local recurrence. It also had no serious complication, despite a longer procedure time.

Various minimally-invasive local excision treatments for early rectal cancer, such as TAR, TEM, and endoscopic resection techniques, including EMR and ESD, are gaining acceptance in many countries.[1–8,14–19] EMR is the least invasive among all these procedures, but it has been technically difficult to perform en-bloc resection for a flat lesion ≥ 20 mm. Therefore, TAR or TEM are usually performed instead of a piecemeal EMR.

In our study, five local recurrences (23%) occurred in the TAR group, in spite of a high macroscopically-clear resection rate. In the subgroup of flat lesions, the en-bloc R0 resection rate was significantly lower, and the recurrence rate was higher in TAR when comparing to ESD. The reason was probably due to poor visualization of the operative field in TAR, thus the margin of flat tumors could not be clearly observed. Technical failure resulted in piecemeal resection in five cases of TAR. Lack of a high-magnification endoscopic view in the TAR procedure was the main reason for the technical failure.

In this study, no TAR was performed for tumors located in Ra, because it is very difficult to perform TAR in upper rectal tumors. However, more TAR than ESD have been performed for tumors in Rb because it is easy for surgeons to reach low rectal tumors in a transanal approach, as is the case with hemorrhoid surgery.

Endoscopic diagnosis and treatment could be performed at the same time using a flexible endoscope, and the tumor margin could be observed clearly using a magnifying colonoscope. The retroflex view was especially useful for the endoscopic diagnosis and treatment of rectal lesions spreading to the dentate line. When TAR was performed, the tumor margins were usually identified directly by the surgeon's eyes, whereas ESD enabled the use of a high-definition magnified view for precise tumor margin determination. In addition, visualization of the operative field during TAR was more difficult in the rectum because air or $CO_2$ insufflation could not be used as in ESD. When ESD was performed, the tumor margins were recognized clearly by high-magnification chromocolonoscopy, which resulted in a lower recurrence rate.

Although the en-bloc R0 resection rate of curative resection by ESD was 78%, the fact that there was no recurrence in the ESD group was probably because any residual tumor at the lateral margins would have been observed by magnifying endoscopy and removed during the ESD. Sessile-type lesions could be treated completely without chromocolonoscopy, but it was sometimes difficult to ascertain the margins of flat, laterally-spreading tumors without indigo carmine dye spray. This could have been the reason for the higher local recurrence rate for the TAR procedure, which was performed without the benefit of high-magnification chromocolonoscopy. If TAR is to be performed for flat rectal lesions when ESD cannot be performed because of technical difficulties, we would recommend TAR after marking around the tumor is done using a needle knife under high-magnification chromocolonoscopy view.

In this study, all ESD procedures were performed under conscious sedation, in which patients received 2–4 mg midazolam intravenously. In contrast, all the patients in the TAR group required general or spinal anesthesia that took a long time to administer. Although the total ESD procedure time was significantly longer than that for TAR, the actual amount of time spent in the operating room did not differ much between the two groups, when considering the extra time needed for sedation and anesthesia. In addition, ESD patients could be discharged from the hospital earlier than those patients who underwent TAR.

With the advent of improving ESD technique, it is now possible to perform en-bloc resection for non-invasive rectal tumors of any size, so the indications for ESD and TAR now overlap to a considerable extent. However, there have been reports regarding recurrence after TAR, with the rate varying between 2.8% and 30% in previously-published series;[20–24] this would be considerably higher when compared to ESD.

TEM is a minimally-invasive surgical procedure for the local excision of rectal tumors that enables resection of the entire depth of the rectal wall. However, TEM requires a high level of technical skill, expensive devices, as well as either general or spinal anesthesia.

The minimal distance of the resected tumor from the anal verge by TEM was 5 cm in a previous study, because of the use of rigid rectoscope.[25] Therefore, it will be difficult to perform TEM if the lesion is near to the dentate line.

In comparison, ESD can be performed even if the lesion is located on the dentate line or in the proximal colon using the flexible endoscope.

The limitations of this study are the retrospective study design; single-center, relatively small sample size; and potential selection bias in treatment options.

ESD needs the specialized technical skills of endoscopists, particularly for the proximal colon lesions, but rectal ESD is relatively easy to perform.

In conclusion, ESD is proven to be more effective than TAR in treating non-invasive rectal tumors, with a much lower local recurrence. ESD is particularly recommended for flat rectal lesions.

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## SPECIAL REPORT

# MID-TERM PROGNOSIS AFTER ENDOSCOPIC RESECTION FOR SUBMUCOSAL COLORECTAL CARCINOMA: SUMMARY OF A MULTICENTER QUESTIONNAIRE SURVEY CONDUCTED BY THE COLORECTAL ENDOSCOPIC RESECTION STANDARDIZATION IMPLEMENTATION WORKING GROUP IN JAPANESE SOCIETY FOR CANCER OF THE COLON AND RECTUM

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We carried out a retrospective questionnaire survey of 792 submucosal colorectal carcinoma (CRC) cases from 15 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in Japanese Society for Cancer of the Colon and Rectum. In these cases, endoscopic resection (ER) and surveillance was carried out without additional surgical resection. Local recurrence or metastasis was observed in 18 cases. Local submucosal recurrence was observed in 11 cases, and metastatic recurrence was observed in 13 cases. Among the 15 cases in which the depth of submucosal invasion was measured, two cases showed depth less than 1000 μm, which has other risk factors for metastasis. Metastatic recurrence was observed in the lung, liver, lymph node, bone, adrenal glands, and the brain; in some cases, metastatic recurrence was observed in multiple organs. Death due to primary disease was observed in six cases. The average interval between ER and recurrence was 19.7 ± 9.2 months. In 16 cases, recurrence was observed within 3 years after ER. Thus, validity of ER without additional surgical resection for cases with the conditions that the depth of submucosal invasion is less than 1000 μm and the histological grade is well or moderately differentiated adenocarcinoma with no lymphatic and venous involvement was proven.

**Key words: endoscopic resection, prognosis, recurrence, submucosal colorectal carcinoma.**

## INTRODUCTION

In the Guidelines for Colorectal Cancer Treatment, 1st Edition, 2005 by Japanese Society for Cancer of the Colon and Rectum (JSCCR),[1] the curative conditions after endoscopic resection (ER) for submucosal colorectal carcinoma (CRC) state that 'if a lesion is completely resected by ER, the depth of submucosal invasion is less than 1000 μm, and the histological grade is well or moderately differentiated adenocarcinoma with no lymphatic and venous involvement, the possibility of lymph node (LN) metastasis will be extremely low so that the surveillance is allowed without additional surgical resection.' This statement has generated a certain consensus. However, these conditions were established on the basis of the analysis of submucosal CRC cases obtained from surgical resection,[2] and there are very few reports of cases in which surveillance after ER for submucosal CRC was carried out extensively.

In the present study, we obtained information on the non-surgical submucosal CRC cases with surveillance after ER; this information was obtained from the institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. Using the information for these cases, we analyzed the risk factors for recurrence, the interval between ER and recurrence, and the recurrence pattern (local or metastatic). In this report, we have introduced data that can be used to verify the validity of the curative conditions after ER for submucosal CRC.

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## QUESTIONNAIRE SURVEY METHOD

The retrospective questionnaire survey was carried out for submucosal CRC cases obtained from the institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. In these

**Table 1.** Facilities that answered the questionnaire

| |
|---|
| Kitasato University East Hospital |
| Hiroshima University Hospital |
| National Cancer Center East Hospital |
| Asahikawa City Hospital |
| Jichi Medical University Hospital |
| National Cancer Center Hospital |
| Osaka Medical Center for Cancer and Cardiovascular Diseases |
| Nagoya City University Hospital |
| Kobe University Hospital |
| Fukuoka University Chikushi Hospital |
| Showa University Northern Yokohama Hospital |
| Cancer Institute Hospital Ariake |
| Tokyo University Hospital |
| Kyusyu University Hospital |
| Juntendo University Hospital |

cases, surveillance had been carried out after ER without additional surgical resection for various reasons.

The following factors were surveyed: age of the patient at the initial ER, gender, tumor size, location, macroscopic type, ER technique (en bloc or piecemeal resection), histological margin (lateral or vertical), histological grade, histological grade at the deepest invasive portion, depth of submucosal invasion (μm), lymphatic/venous involvement, follow-up period after ER, existence of recurrence, recurrence pattern, and vital prognosis. Tumor size, location, macroscopic type, histological margin, histological grade, depth of submucosal invasion and lymphatic/venous involvement were recorded according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus, 7th Edition, Revised Version by JSCCR[3]. Further, we directly used the clinical and histopathological findings stated in the questionnaire.

## QUESTIONNARIE SURVEY RESULTS

Among the 28 institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR, 15 institutions participated in this questionnaire survey (response rate, 53.6%) (Table 1). The information for 792 patients (556 male and 236 female) was collected from these 15 institutions. The average age of the patients was 72.9 ± 12.3 years (range, 19–93 years). The lesions were located in the cecum (25 cases), ascending colon (91 cases), transverse colon (77 cases), descending colon (56 cases), sigmoid colon (339 cases), and rectum (204). The average size of the lesions was 16.2 ± 8.2 mm (3–60 mm). The macroscopic type of the lesions showed that there were 0-Ip (209 cases), 0-Isp (197 cases), 0-Is (142 cases), 0-IIa (141 cases), 0-IIa + IIc (76 cases) and 0-IIc (27 cases). En bloc resection was carried out in 569 cases, and piecemeal resection was carried out in 114 cases; the ER technique was not mentioned in 109 cases. The histological lateral margin-positive was reported in 50 cases and was negative in 504 cases; the lateral margin was not mentioned in 238 cases. The histological vertical margin-positive was reported in 34 cases and was negative in 563 cases; the vertical margin was not mentioned in 195 cases. With regard to the histological grade, 724 lesions were graded as well differentiated adenocarcinoma, 63 were graded as moderately differentiated adenocarcinoma, two were graded as poorly differentiated adenocarcinoma, and the histological grade was not mentioned in three cases. The average depth of submucosal invasion was 1388 ± 1546 μm (5–10 000 μm); submucosal invasion less than 1000 μm was observed in 324 cases; deeper than 1000 μm was observed in 315 cases; and the depth of submucosal invasion was not mentioned in 153 cases. The average follow-up period was 38.7 ± 83.0 months, and recurrence was observed in 18 cases (2.3%). The recurrence rate for the cases that underwent en bloc resection was 2.5% (14/569) and that for the cases that underwent piecemeal resection was 3.5% (4/114); there was no significant difference between these two techniques. In 368 cases, the lesion satisfied the curative conditions after ER for submucosal CRC, whereas the lesion did not satisfy the curative conditions after ER for submucosal CRC in 302 cases; the relationship between the lesion and the curative conditions after ER for submucosal CRC was not mentioned in 122 cases.

## HISTOPATHOLOGICAL RISK FACTORS FOR RECURRENCE

Among the 792 cases with surveillance after ER for submucosal CRC, information on all factors related to the histopathological findings was obtained in 387 cases (48.9%). These cases were re-examined to determine the relationship between the following factors and recurrence: histological grade, histological grade at the deepest invasion portion, existence of budding,[4] submucosal invasive depth of 1000 μm, lymphatic involvement, and venous involvement.

Among these 387 patients, there were 275 males and 112 females. The average age of the patients was 64.4 ± 11.2 years (19–93 years). The average tumor size was 15.7 ± 8.3 mm (4–60 mm). The lesions were located in the cecum (6 cases), ascending colon (47 cases), transverse colon (37 cases), descending colon (40 cases), sigmoid colon (174 cases), and rectum (83 cases). Macroscopic type of the lesions revealed 0-Ip (138 cases), 0-Isp (105 cases), 0-Is (43 cases), 0-IIa (45 cases), 0-IIa+IIc (24 cases), 0-IIc (9 cases), and other type (23 cases). The average follow-up period after ER was 39.5 ± 36.7 months (3–174 months). Further, recurrence was observed in 10 cases. There were no intramucosal recurrent cases.

Using univariate analysis, each of the following factors was confirmed to be significantly related to recurrence: existence of budding,[4] submucosal invasion depth deeper than 1000 μm, and lymphatic/venous involvement (Table 2). Multivariate analysis using logistic-regression analysis was carried out using these four factors. Consequently, submucosal invasion depth deeper than 1000 μm and lymphatic involvement were indicated as the factors with high odds ratios, and only lymphatic involvement was considered as an independent risk factor for recurrence (Table 3).

## CLINICOPATHOLOGICAL CHARACTERISTICS OF THE CASES SHOWING RECURRENCE

The 18 cases (11 male and 7 female) of recurrence are shown in Table 4. The average age of the patients was

**Table 2.** Recurrence rate after ER for submucosal CRC in relation to pathological features ($n = 387$)

| Pathological features | $n$ | Recurrence positive (%) | $P$ value |
|---|---|---|---|
| Histological grade | | | |
| well or mod | 387 | 10 (3) | |
| por or muc | 0 | | – |
| Histological grade at the deepest invasive portion | | | |
| well or mod | 367 | 9 (2) | |
| por or muc | 11 | 1 (9) | 0.2756 |
| Budding | | | |
| Positive | 42 | 4 (10) | |
| Negative | 345 | 6 (2) | 0.0015 |
| Depth of submucosal invasion (µm) | | | |
| <1000 | 220 | 1 (0.5) | |
| ≧1000 | 167 | 9 (5) | 0.0016 |
| Lymphatic involvement | | | |
| Positive | 29 | 5 (17) | |
| Negative | 358 | 5 (1) | 0.0002 |
| Venous involvement | | | |
| Positive | 18 | 3 (17) | |
| Negative | 369 | 7 (2) | 0.0070 |

CRC, colorectal carcinoma; ER, endoscopic resection; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; well, well differentiated adenocarcinoma.

**Table 3.** Multivariate analysis of risk factors for recurrence after ER for submucosal CRC ($n = 387$)

| Risk factors | Odds ratio | ($P$-value) | 95%CI |
|---|---|---|---|
| Depth of submucosal invasion ≧1000 µm | 7.014 | (0.0753) | 0.820–60.01 |
| Lymphatic involvement positive | 6.363 | (0.0139) | 1.457–27.79 |
| Budding positive | 2.258 | (0.3466) | 0.414–12.31 |
| Venous involvement positive | 2.275 | (0.3446) | 0.634–11.64 |

CRC, colorectal carcinoma; ER, endoscopic resection.

69.2 ± 7.2 years. The lesions were located in the cecum (2 cases), ascending colon (2 cases), sigmoid colon (6 cases), and the rectum (8 cases). The average size of the lesions was 19.7 ± 9.2 mm. The macroscopic type of the lesions revealed 0-Ip (6 cases), 0-Isp (4 cases), 0-Is (3 cases), 0-IIa (3 cases), 0-IIa+IIc (1 case), and another type (1 case). En bloc resection was carried out in 14 cases, and piecemeal resection was carried out in four cases. Histological lateral margin-positive was reported in eight cases, and histological vertical margin-positive was reported in eight cases. Among the 15 cases in which the depth of submucosal invasion was reported, the depth was <1000 µm in one case and ≧1000 µm in 14 cases.

Local intramucosal recurrence was observed in four cases with a histological positive lateral margin. Among these four cases, metastatic recurrence was observed in two cases (lung metastasis was observed in one case, and the details were unknown in one case). However, as the details of the vertical margin were unknown, the exact depth of submucosal invasion could not be measured. Among the 18 cases in which the submucosal invasive carcinoma showed recurrence, local recurrence in the form of submucosal carcinoma was observed in 11 cases, and metastatic recurrence was observed in 13 cases. Among the 15 cases in which the depth of submucosal invasion was measured, two cases showed depth <1000 µm; however, these cases had lymphatic involvement and a positive vertical margin. Among the cases in which metastatic recurrence was observed in the organs, recurrence was observed in the lung (5 cases), liver (4 cases), LN (4 cases), bone (2 cases), adrenal gland (1 case), and brain (1 case); in some cases, metastatic recurrence was observed in multiple organs. Among the eight cases in which the patients died, death due to the primary disease was observed in six cases, death due to other diseases was observed in one case, and there were no details regarding the death in one case.

The average interval between ER and recurrence was 19.7 ± 9.2 months. Among the 18 cases in which recurrence was observed, 16 cases showed recurrence within 3 years after ER. Among the 18 cases in which recurrence was observed, in all cases the lesions did not satisfy the curative conditions after ER for submucosal CRC.

## RELATIONSHIP BETWEEN DEPTH OF SUBMUCOSAL INVASION AND POSITIVE RATE OF VERTICAL MARGIN IN EACH MACROSCOPIC TYPE OF SUBMUCOSAL CRC

We examined the relationship between depth of submucosal invasion and positive rate of vertical margin according to the

**Table 4.** Cases with recurrence after ER for submucosal CRC

| No. | Gender | Age | Location | Macroscopic type | Size (mm) | ER technique | Vertical margin | Lateral margin | Depth of SM (μm) | Lymphatic/ venous involvement | Histological grade | Budding | Local recurrence | Metastatic recurrence | Alive/ death | Interval after ER (month) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 68 | C | Protruded | ≧20 | Piecemeal | ? | + | 240 | – | well | – | IM | + | Alive | 4 |
| 2 | M | 68 | S | Superficial | ≧20 | Piecemeal | + | ? | 250 | + | mod | – | SM | + | Alive | 15 |
| 3 | M | 62 | S | Protruded | <20 | En bloc | – | + | SM scanty | ? | well | – | IM | – | Alive | 14 |
| 4 | M | 63 | S | Protruded | ≧20 | En bloc | – | – | 1000 | + | mod | + | SM | + | Death | 16 |
| 5 | F | 69 | R | Superficial | <20 | En bloc | – | – | 1024 | – | well | – | ? | + | Alive | 14 |
| 6 | M | 73 | R | Protruded | <20 | En bloc | – | – | 1300 | – | mod | – | SM | + | Death | 20 |
| 7 | F | 60 | S | Protruded | <20 | En bloc | – | – | 1572 | – | well | – | SM | + | Alive | 89 |
| 8 | M | 61 | R | Protruded | ≧20 | En bloc | + | – | 1800 | + | mod | – | ? | + | Death | 12 |
| 9 | F | 71 | A | ? | ≧20 | Piecemeal | – | – | 2200 | + | mod | + | SM | + | Alive | 24 |
| 10 | F | 78 | C | Superficial | <20 | Piecemeal | + | ? | 2433 | – | well | – | SM | – | Alive | 16 |
| 11 | M | 59 | A | Protruded | <20 | En bloc | – | – | 3000 | + | por | + | ? | + | Death | 18 |
| 12 | F | 80 | R | Protruded | <20 | En bloc | – | – | 3500 | – | well | – | SM | + | Alive | 60 |
| 13 | M | 68 | S | Protruded | ≧20 | En bloc | ? | ? | 3800 | + | mod | + | IM | – | Alive | 8 |
| 14 | M | 74 | S | Protruded | <20 | En bloc | – | – | 4200 | + | mod | – | SM | + | Death | 0 |
| 15 | M | 66 | R | Protruded | <20 | En bloc | ? | – | 5300 | – | well | + | SM | – | Death | 26 |
| 16 | M | 65 | R | Protruded | ≧20 | En bloc | – | – | 6886 | + | mod | + | SM | + | Death | 22 |
| 17 | M | 81 | R | Protruded | <20 | En bloc | + | – | SM3 | – | ? | – | SM | – | Death | 10 |
| 18 | F | 80 | R | Superficial | ≧20 | En bloc | ? | + | ? | – | ? | – | IM | + | Alive | 10 |

A, ascending colon; C, cecum; F, female; IM, intramucosa; M, male; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; R, rectum; S, sigmoid colon; SM, submucosa; well, well-differentiated adenocarcinoma.

**Table 5.** Relationship between the depth of submucosal invasion and positive rate of vertical margin in each macroscopic type of submucosal CRC

| Depth of submucosal invasion (μm) | Macroscopic type Protruded type $n = 286$ | Superficial type $n = 82$ |
|---|---|---|
| ~1000 | 7.1% (11/156) | 2.9% (2/68) |
| 1001~2000 | 10.2% (6/59) | 8.3% (1/12) |
| 2001~3000 | 14.7% (5/34) | 0% (0/7) |
| 3001~4000 | 18.8% (3/16) | |
| 4001~ | 9.5% (2/21) | 0% (0/2) |
| Total | 9.4% (27/286) | 3.7% (3/82) |

CRC, colorectal carcinoma.

**Table 6.** Relationship between vertical margin and recurrence in endoscopically resected submucosal CRC without additional surgical resection

| Vertical margin | Recurrence Positive | Negative | Total |
|---|---|---|---|
| Positive | 1 (3.2) | 31 (96.8) | 32 (100) |
| Negative | 9 (2.5) | 347 (97.5) | 356 (100) |

There were no intramucosal recurrent cases.
CRC, colorectal carcinoma.

macroscopic type (protruded or superficial type) in the 368 cases in which the depth of submucosal invasion was reported (Table 5). The overall positive rate of vertical margin was 8.2% (30/368), and the positive rate of protruded and superficial type lesions was 9.4% (27/286) and 3.7% (3/82), respectively. There were no significant differences between each macroscopic type. The positive rate of vertical margin of the protruded and superficial type lesions with submucosal invasion ≦1000 μm was 7.1% (11/156) and 2.9% (2/68), respectively. The positive rate of vertical margin of the protruded and superficial type lesions with submucosal invasion >1000 μm was 6.2% (16/259) and 4.8% (1/21), respectively. With regard to the relationship between vertical margin and recurrence, the recurrence rate for the vertical margin-positive cases was 3.1% (1/32) and that for the vertical margin-negative cases was 2.5% (9/356). There were no significant differences between the values for these two groups (Table 6).

## DISCUSSION

This multi-institution questionnaire survey had several limitations. Owing to the retrospective-examination model, the average follow-up period was 38.7 months, and a central review was not carried out on the pathological specimens. However, valuable data were obtained by analyzing the prognoses of non-surgical submucosal CRC cases after ER, which were provided by multiple institutions. Our data showed that all non-surgical submucosal CRC cases with recurrence after

ER did not satisfy the curative conditions according to the Guidelines for Colorectal Cancer Treatment, 1st Edition by JSCCR.[1] As the curative conditions after ER for submucosal CRC stated in the currently used Guidelines for Colorectal Cancer Treatment, 2nd Edition by JSCCR, 2009[5] (a factor of budding grade was added to the curative condition of the 1st Edition) were derived from examinations of the cases in which surgical resection was accompanied by LN metastasis, micrometastasis was not taken into consideration. Clinical verification of the curative conditions can be proved by the prognosis of the non-surgical submucosal CRC cases after ER. However, as these results were obtained on the basis of the histopathological diagnosis in different institutions, we presumed that a certain amount of scattering existed among the data from different institutions.

ER is a therapeutic technique as well as an important diagnostic method that can be used as the total incisional biopsy. Complete resection of the lesions, including vertical margin-negative, is indispensable for curative conditions after ER for submucosal CRC. Currently, among the factors in the curative conditions, only the depth of submucosal invasion can be diagnosed prior to the surgical operation. LN metastasis of submucosal CRC with invasion depth deeper than 1500 μm and 2000 μm was not observed under certain conditions when the histological grade at the deepest invasive portion was taken into consideration.[6] Our data showed that the incidence of the histopathological vertical margin-positive was 8.2%, and there was no significant relationship between the vertical margin-positive and recurrence. This result may show that there is a difference between the histologically vertical margin-positive and submucosal residual tumors on the colorectal wall. To avoid local recurrence after ER, it is important to observe an ulcer in detail using colonoscopy. A previous report has described that residual tumors caused by incomplete ER have a higher growth potential than tumors before ER.[7] Therefore, to avoid a potential disadvantage to the patients, the preoperative diagnosis must be carried out precisely, and an appropriate therapy must be selected.

Regarding surveillance for non-surgical submucosal CRC cases after ER, the results obtained in this study revealed that distant metastasis or death due to primary disease within 3 years after ER was observed in 89% of the patients showing recurrence. Therefore, surveillance must be strictly carried out for 3 years after ER for submucosal CRC with non-curative condition. The examinations conducted in other institutions revealed that in many cases, recurrence took place within 5 years after ER.[8–10] Currently, there is no consensus as to the ideal surveillance method and period after ER for submucosal CRC.

This unstable questionnaire survey had several limitations. However, the current status regarding the mid-term prognosis after ER for submucosal CRC without additional surgical operation in Japan is not available. To investigate curative condition after ER for submucosal CRC and the appropriate interval between surveillances, a long-term prognosis survey from a large number of cases must be analyzed in the near future.

## CONCLUSION

This questionnaire survey was conducted in institutions affiliated with the Colorectal Endoscopic Resection Standardization Implementation Working Group in JSCCR. The results obtained by analysis of the prognosis of the non-surgical submucosal CRC cases after ER proved that there is no risk of recurrence, and that surveillance could be carried out without additional surgical resection when the lesions satisfied the curative conditions after ER for submucosal CRC according to the Guidelines for Colorectal Cancer Treatment, 1st Edition by JSCCR,[1] and recurrence was observed within 3 years after ER.

## ACKNOWLEDGMENT

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## ORIGINAL ARTICLE

# COMPARISON OF MAGNIFYING CHROMOENDOSCOPY AND NARROW-BAND IMAGING IN ESTIMATION OF EARLY COLORECTAL CANCER INVASION DEPTH: A PILOT STUDY

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**Background:** Several previous studies have identified narrow-band imaging (NBI) with magnification as being useful in evaluating early colorectal cancer invasion depth, but comparative diagnostic accuracy of invasion depth between pit pattern analysis using magnifying chromoendoscopy and NBI remains unclear. The aim of this retrospective study was to compare NBI and pit pattern analysis using magnifying chromoendoscopy in estimating early colorectal cancer invasion depth and to assess interobserver agreement.

**Patients and Methods:** We analyzed a total of 72 early colorectal cancers in 72 patients fulfilling the inclusion criteria. Each lesion image was subsequently reviewed by two experienced colonoscopists (A, B) and then classified clinically based on invasive/non-invasive pattern and Sano's capillary pattern classification with a five-point scale of confidence.

**Results:** In terms of diagnostic accuracy with confidence for A and B, the areas under the receiver operating characteristics curve were 0.84 and 0.81 for pit pattern analysis and 0.82 and 0.79 for NBI, respectively. Interobserver agreement for the diagnosis of submucosal deep (>1000 μm) invasion was evaluated for both modalities and indicated substantial agreement with pit pattern analysis ($\kappa = 0.63$) and moderate agreement with NBI ($\kappa = 0.44$).

**Conclusion:** Estimating invasion depth of early colorectal cancer using NBI appeared to have been comparable to pit pattern analysis, but there was greater interobserver variability using NBI.

**Key words: early colorectal cancer, narrow-band imaging, magnifying chromoendoscopy, invasion depth.**

## INTRODUCTION

Endoscopic therapy represents a major advance in the management of early gastrointestinal cancers. In the colorectum, lymph node metastasis invariably occurs only with submucosal deep invasion (≥1000 μm, SM-d).[1,2] Lesions diagnosed as well-differentiated adenocarcinomas limited to the mucosa (intramucosal, M) or as superficially invading the submucosa (<1000 μm from the muscularis mucosa, SM-s) without lymphovascular invasion or a poorly differentiated component (or both) are generally regarded as not involving lymph node metastasis.[3] Of these factors, however, only invasion depth can be endoscopically estimated before treatment. This characteristic emphasizes the importance of accurate estimation of depth prior to any therapeutic decision-making.

The efficacy of magnifying chromoendoscopy (MCE), not only in differentiating between colorectal neoplastic and non-neoplastic lesions,[4-6] but also in accurately determining invasion depth of early colorectal cancer, has widely been demonstrated.[7-13] Chromoendoscopy is operator-dependent and labor-intensive, however, and requires the use of staining solutions, spraying catheters, and several water rinses. These requirements have hampered its wider acceptance, particularly in Western countries, despite its demonstrated effectiveness.

Narrow-band imaging (NBI) is an innovative optical technology that uses interference filters to spectrally narrow the bandwidth used in conventional white light medical videoscopy. NBI allows more detailed visualization of the mucosal architecture and capillary pattern without the need for dye spraying. Although the usefulness of the NBI system in differentiating colorectal neoplastic from non-neoplastic lesions, as well as in estimating invasion depth, has been reported,[14-23] few studies have compared the usefulness of pit pattern analysis using MCE and NBI to estimate invasion depth of early carcinoma.

Here, we evaluated the use of NBI to estimate invasion depth in early colorectal cancer with diagnostic confidence in comparison with MCE using the invasive/non-invasive pattern classification of Matsuda and colleagues.[13] Additionally, we also assessed interobserver agreement for the two endoscopic modalities.

## METHODS

### Subjects

Seventy-two patients with 72 early colorectal cancers fulfilling the inclusion criteria were enrolled in this retrospective study (Table 1). A total of 3520 cases were present on our database and inclusion criteria were applied to these cases. These included all lesions observed with MCE using crystal

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violet staining and the NBI system; and all lesions diagnosed endoscopically as early colorectal cancer that underwent subsequent endoscopic or surgical resection. Images were taken of all lesions in the same condition using both MCE and NBI. Lesions diagnosed histopathologically as adenoma or advanced colorectal cancer as well as lesions with images judged to be of poor quality were excluded (Fig. 1). Images were taken by experienced colonoscopists, who were not reviewers, and analyzed by another experienced colonoscopist, who was also not a reviewer. The study protocol was approved by the ethics committee of the National Cancer Center Hospital, and written informed consent was obtained from all patients.

**Table 1.** Inclusion and exclusion criteria

| |
|---|
| Inclusion criteria |
| 1) All lesions observed by magnifying chromoendoscopy using crystal violet staining and NBI with magnification between April 2007 and March 2008 |
| 2) All lesions endoscopically diagnosed as early colorectal cancer that were subsequently treated by endoscopic or surgical resection |
| 3) Images taken of lesions in the same area |
| Exclusion criteria |
| 1) Lesions diagnosed histopathologically as adenoma or advanced colorectal cancer |
| 2) Images judged to be of poor quality |

NBI, narrow-band imaging.

### Endoscopic examination

All patients were prepared for colonoscopy with 2–3 L of polyethylene glycol-electrolyte solution administered on the morning of the examination. Scopolamine butylbromide (10 mg) or Glucagon (0.5 mg) was administered i.v. in patients without contraindications beforehand to minimize bowel movement. All procedures were performed by colonoscopists who had each performed more than 500 colonoscopies per year using magnifying colonoscopes (CF-H260AZI or PCF240ZI; Olympus, Tokyo, Japan), which enhance images up to 80–100 times using a one-touch operation power magnification system. A standard videoendoscopic system (EVIS LUCERA system; Olympus Optical, Tokyo, Japan) with two light sources was used, one for the standard optical broadband filter and the second for the NBI system.

Whenever a lesion was detected by standard colonoscopy, the system was switched to NBI by a single touch of the control section button to allow examination of the microvascular architecture. Indigo-carmine (0.4%) was then sprayed directly on the mucosal surface for pit pattern analysis after washing with proteinase to remove any overlying mucous. When high magnification observation with indigo-carmine spraying revealed an irregular pit pattern suspected of being type V, 0.05% crystal violet was applied for staining purposes.[9] In this study, all lesions were observed by MCE using crystal violet staining. After detailed observation, including imaging, all lesions were resected endoscopically or surgically.

### Histopathological examination

Resected specimens were fixed in 10% buffered formalin and cut into serial 5 mm slices for surgical specimens and 2 mm

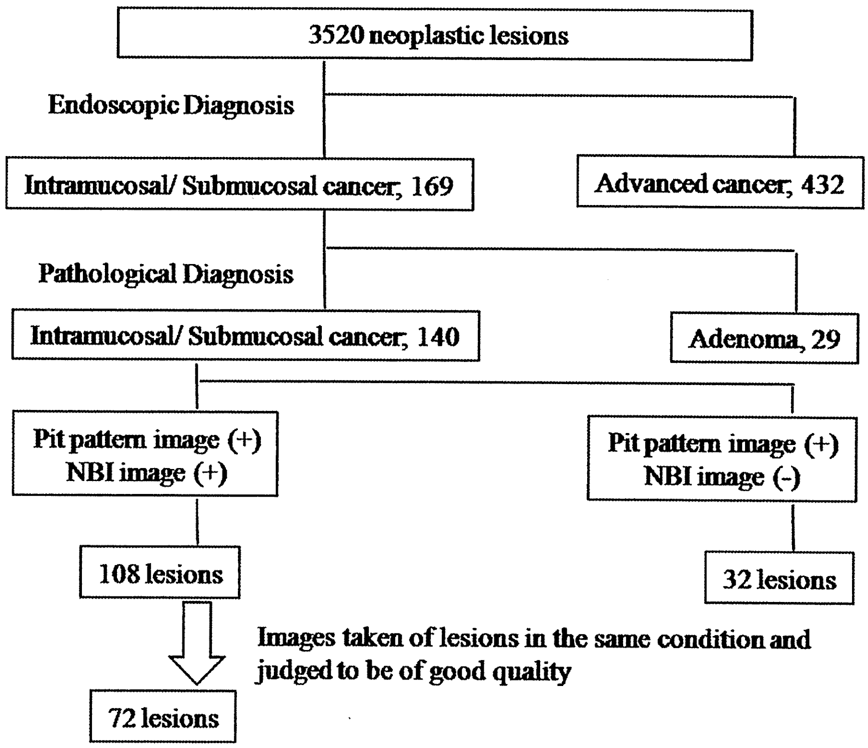


**Fig. 1.** Subject selection process in this study. NBI, narrow-band imaging.

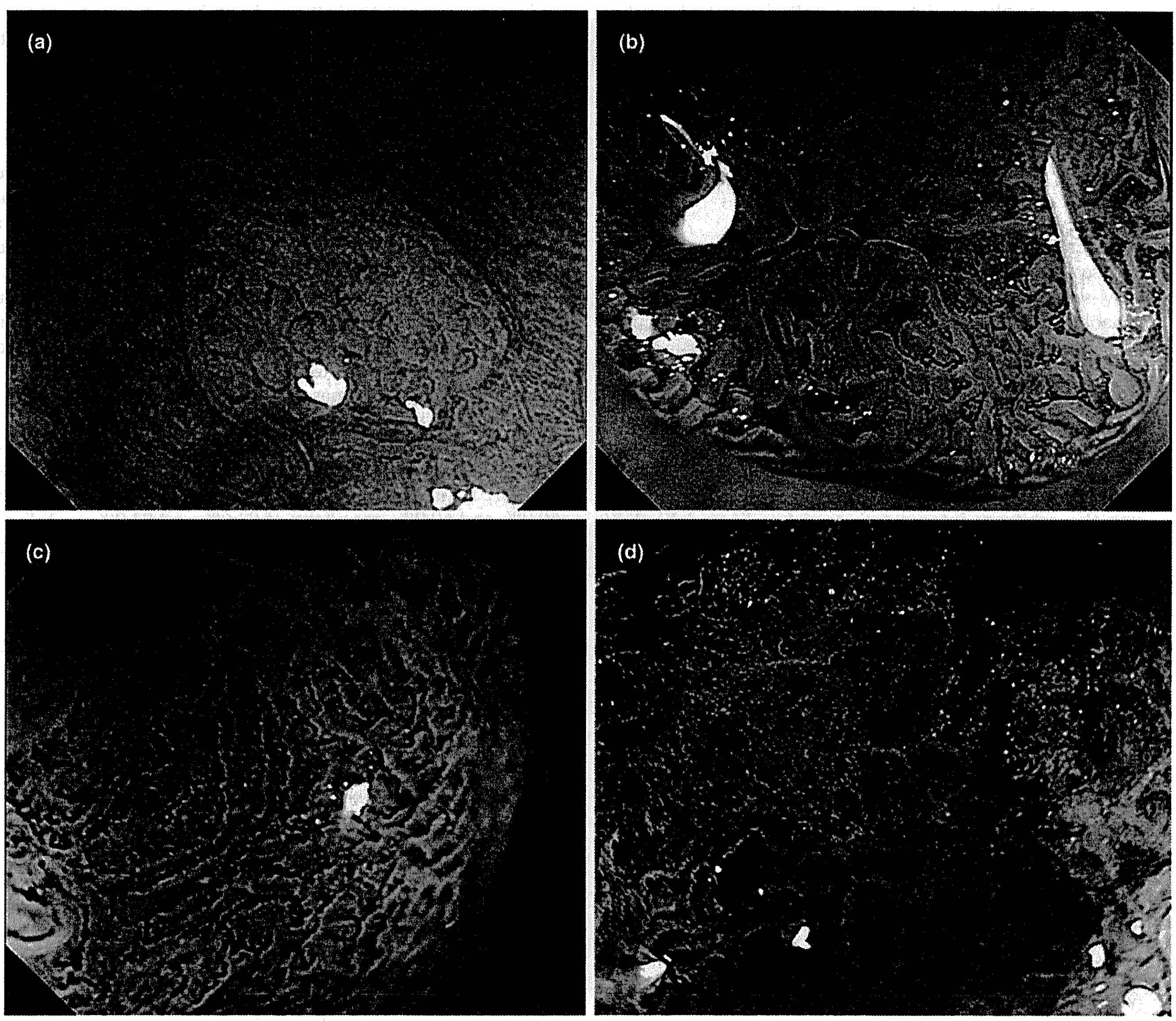


**Fig. 2.** Illustration of Sano's narrow-band imaging capillary pattern classification. (a) Faintly visible micro-vessels surrounding the pits (type I). (b) Elongated and increased thicker vessels surrounding the pits (type II). (c) Increased thick vessels unevenly sized with branching and curtailed irregularity (type IIIA). (d) Nearly avascular or loose vessels with fragmentation (type IIIB).

slices for endoscopic resection specimens. The slices were embedded in paraffin, cut into 3 μm sections and stained with hematoxylin–eosin, and microscopically examined for histological type by pathologists who specialized in gastrointestinal pathology. Histological diagnosis was based on the Japanese Research Society for Cancer of the Colon and Rectum and the Vienna classification.[24,25]

### Image evaluation

A total of 246 images of 72 lesions, excluding conventional images, were selected and grouped into two diagnostic modalities (i.e. MCE with crystal violet, 123 images; NBI with magnification, 123 images) in random order. The images were independently reviewed by two other senior colonoscopists (A and B), each with experience in more than 5000 cases of chromoendoscopy and NBI. Invasion depth was evaluated separately for each modality group without knowledge of lesion histopathology. Interobserver agreement in estimating invasion depth in early colorectal cancer was also assessed.

After review of mucosal crypt patterns observed with MCE, the lesions were classified using the clinical classification of Matsuda and colleagues.[13] All neoplastic lesions were classified into two categories: a non-invasive pattern predicting adenoma or carcinoma with M/SM-s invasion and an invasive pattern predicting carcinoma with SM-d invasion.

On reviewing microvascular architecture with NBI, four different patterns were identified according to Sano's classification.[19–22] In this classification, capillary pattern type III suggests 'carcinoma', and invasion depth was subsequently classified by examining the lesion's microvessel pattern with NBI as either M/SM-s (high-density vessels showing unevenly sized thicker capillaries with branching and curtailed irregularity; capillary pattern IIIA) or SM-d (nearly avascular or loose microvessel diameters; capillary pattern IIIB) (Fig. 2). Diagnostic accuracy of the two endoscopic modalities was determined by reference to the histopathological findings.

### Statistical analysis

Reviewers graded the estimated invasion depth using a five-point scale of diagnostic confidence: 1, definite adenoma or M/SM-s; 2, probable adenoma or M/SM-s; 3, indeterminate; 4, probable SM-d; and 5, definite SM-d. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) analysis based on calculation of the area under the ROC curve (Az). In addition, the sensitivity, specificity and overall accuracy of diagnosis of invasion depth were evaluated for each modality by comparing endoscopic and final histopathological diagnoses. Kappa (κ) statistics with 95% confidence intervals (CI) were used to test for interobserver agreement using the arbitrary interpretation of Landis and Koch (0, 'poor' agreement; 0.00–0.20, 'slight' agreement; 0.21–0.40, 'fair' agreement; 0.41–0.60, 'moderate' agreement; 0.61–0.80, 'substantial' agreement; and 0.80–1.00, 'almost perfect' agreement).[26]

**Table 2.** Clinicopathological features of colorectal lesions

| | |
|---|---|
| No. of lesions | 72 |
| Macroscopic type | |
| Polypoid | 14 |
| Flat elevated | 34 |
| Depressed† | 24 |
| Mean size of lesions (range) (mm) | 20 (10–120) |
| Location | |
| Right colon† | 25 |
| Left colon‡ | 23 |
| Rectum | 24 |
| Invasion depth | |
| M/SM-s | 49 |
| SM-d | 23 |
| Histopathology | |
| W/D | 65 |
| W/D + M/D | 6 |
| M/D | 1 |

†Cecum-transverse colon; ‡Descending-sigmoid colon.
M, mucosal invasion; M/D, moderately differentiated adenocarcinoma; SM-d, submucosal deep invasion; SM-s, submucosal superficial invasion; W/D, well-differentiated adenocarcinoma.

## RESULTS

Clinicopathological features of the lesions are summarized in Table 2. Morphologically, there were 14 polypoid, 34 flat elevated, and 24 depressed lesions. Mean size of the lesions was 20 mm (range 10–120 mm). Twenty-five were right-sided colon lesions, 23 were left-sided colon lesions, and 24 were rectal lesions. Histopathological analysis revealed carcinoma with M/SM-s in 49 lesions (68%) and carcinoma with SM-d in 23 (32%). Sixty-five (90%) lesions were well-differentiated adenocarcinomas, six (8%) were well- and moderately differentiated adenocarcinomas and one (2%) was a moderately differentiated adenocarcinoma.

Table 3 shows the results of each modality by reviewer. For reviewer A, visualization of lesions by the pit pattern analysis with MCE and NBI with magnification revealed sensitivity of 60.9% and 60.9%, specificity of 93.6% and 93.9%, and diagnostic accuracy of 82.9% and 83.3%, respectively, for SM-d invasion; while reviewer B achieved a sensitivity of 82.6% and 78.3%, specificity of 73.5% and 77.6%, and diagnostic accuracy of 76.4% and 77.8%, respectively.

Az was 0.84 for pit pattern analysis with MCE versus 0.82 with NBI for reviewer A and 0.81 versus 0.79 for reader B, respectively (Fig. 3).

Interobserver agreement for diagnosis of SM-d invasion for each modality indicated substantial interobserver agreement for pit pattern analysis with MCE ($\kappa = 0.63$) and moderate agreement for NBI with magnification ($\kappa = 0.44$) (Table 4).

## DISCUSSION

To our knowledge, this is the first report to compare the diagnostic performance of NBI with magnification and magnifying chromoendoscopy (i.e. pit pattern analysis) in evaluating the depth of invasion of colorectal neoplasms, based on diagnostic confidence and interobserver agreement. Conventional images were excluded because they would have been a major bias in the course of this study. Results showed that NBI had comparable accuracy to pit pattern analysis using MCE, which has been reported to be one of the most reliable methods for this assessment.[13,27,28]

**Table 3.** Performance of endoscopic modalities in estimation of invasion depth

| Reviewer A | Sensitivity (95%CI) | Specificity (95%CI) | Accuracy (95%CI) |
|---|---|---|---|
| Pit pattern | 60.9 (46.6–69.0) | 93.6 (86.7–97.6) | 82.9 (73.5–88.2) |
| NBI | 60.9 (46.6–69.0) | 93.9 (87.2–97.7) | 83.3 (74.2–88.5) |
| **Reviewer B** | **Sensitivity (95%CI)** | **Specificity (95%CI)** | **Accuracy (95%CI)** |
| Pit pattern | 82.6 (66.7–92.5) | 73.5 (66.0–78.1) | 76.4 (66.2–82.7) |
| NBI | 78.3 (62.2–89.3) | 77.6 (70.0–82.7) | 77.8 (67.5–84.8) |

CI, confidence interval; NBI, narrow-band imaging.

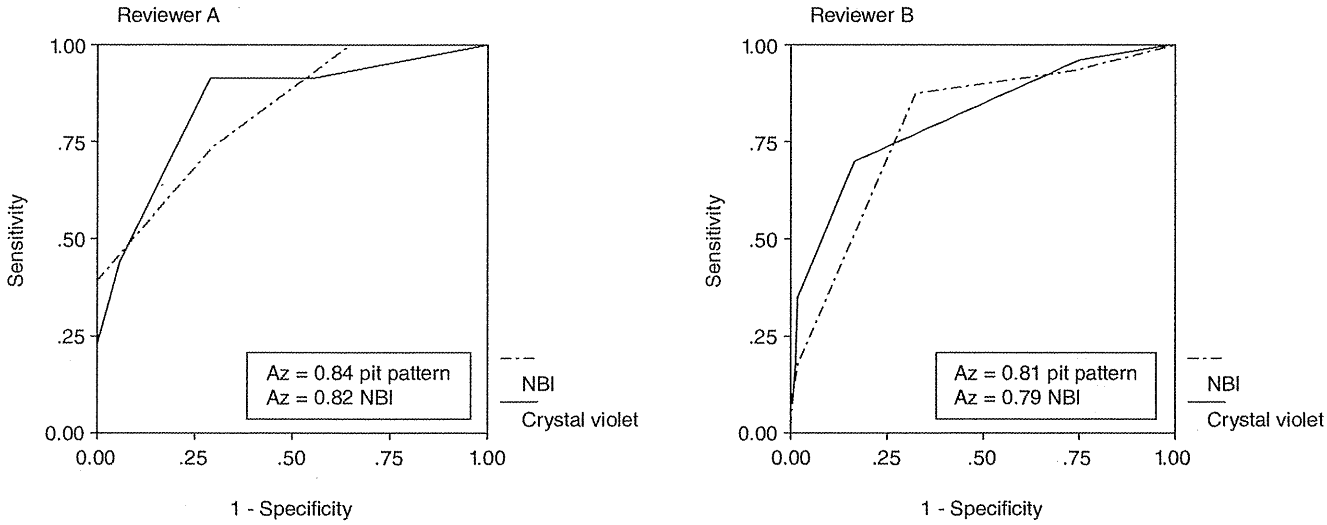


**Fig. 3.** Receiver operating curves of two reviewers. NBI, narrow-band imaging.

**Table 4.** Agreement between colonoscopists for each modality

| Modality | Value of κ (95%CI) | Strength of agreement |
|---|---|---|
| Pit pattern | 0.63 (0.44–0.82) | Substantial |
| NBI | 0.44 (0.22–0.67) | Moderate |

CI, confidence interval; NBI, narrow-band imaging.

Although sensitivity and specificity are generally accepted methods for quantifying morphological diagnostic ability, no study has reported diagnostic ability based on relative levels of confidence. In this study, the estimated depth of invasion of all lesions was scored on a five-point confidence scale. The data were analyzed by ROC analysis, which has been widely used in medical radiology imaging studies to investigate the effects of individual parameters on an imaging system or to compare the performance of different systems.[29,30] ROC analysis is considered optimal with regard to sensitivity if the Az is between 0.75 and 0.80.[31] Our ROC curves were therefore close to optimal. Based on the plotted ROC curves, the NBI system is also comparable to pit pattern analysis with MCE in terms of estimating invasion depth.

We also assessed interobserver agreement in estimating depth invasion for each modality and found 'substantial' agreement for pit pattern analysis with MCE and 'moderate' agreement for NBI with magnification. This moderate result indicates some variation in the reviewers' interpretation of irregularity in the microvascular architecture observed by the NBI system with magnification. As for such lower interobserver agreement in the interpretation of the NBI findings, we should remember that the NBI system is still a relatively new diagnostic method with an unknown learning curve and several different classifications for the evaluation of mucosal morphology in colorectal neoplasms have been proposed recently in Japan, further complicating the matter. As for consensus on microvascular architecture and the classification of findings, there has not yet been enough discussion worldwide as to how use of NBI can become a reality.

Chromoendoscopy with magnification requires considerable time for removing mucous and dye spraying. In contrast, the advantages of NBI include its convenience without the need and additional cost of dye spraying, and the ability to alternate between conventional and NBI images with a single touch of a button on the handle of the scope. If interobserver agreement appreciably improves and a consensus can be reached with regard to microvascular architecture and the classification of findings, it is conceivable that NBI could replace MCE for the diagnosis of invasion depth.

Several limitations of our study warrant mention. First, as this was a pilot study, all images were taken and evaluated by only two colonoscopists experienced in magnification endoscopy. Second, all evaluations were based on the retrospective analysis of still images, which can differ considerably from live endoscopic assessment of specific areas because it does not permit examination of a lesion from different angles and distances. Third, subjects were limited to those with intramucosal and submucosal carcinoma diagnosed pathologically. In this study, we focused on the relevance of diagnostic performance in estimating the depth of invasion in early colorectal cancer, based on our consideration that this is one of the most important clinical purposes of magnifying endoscopy. Moreover, we considered that investigation of the endoscopic differentiation and histopathological characteristics of adenoma and carcinoma was outside the scope of this study. Comprehensive evaluation of the effectiveness of conventional colonoscopy, MCE and NBI with magnification will require prospective multi-center trials involving endoscopists with varying backgrounds and degrees of experience.

In conclusion, our results suggest that the accuracy of the NBI system with magnification in estimating the invasion depth of colorectal neoplasms is comparable to that of pit pattern analysis with MCE. However, NBI showed greater variability in the interpretation of irregularities in microvascular architecture. These findings indicate that further evaluation of pit pattern analysis with MCE in estimating the invasion depth of early colorectal cancer should be undertaken as a matter of priority.

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REVIEW ARTICLE

# Endoscopic management of colonoscopic perforations (with videos)

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## INTRODUCTION

Colonoscopic perforation is a potentially life-threatening complication. Visual recognition of perforation or sites that are high risk to perforate at the time of the colonoscopy and its immediate closure offer the best potential for preventing any sequelae and for reducing its morbidity and mortality. Significant progress in endoscopic closure has been made since its first report by Yoshikane et al[1] over a decade ago. Herein, we summarize the literature on the prevalence, mechanisms, and diagnosis of perforations; review the results of experimental and clinical studies; and offer practical tips on the endoscopic closure of colonoscopic perforations (Fig. 1).

## INCIDENCE

The incidence rates of colonoscopic perforations range from 0.07% to 0.1% in diagnostic and therapeutic colonoscopies, respectively (Table 1).[2-10] Most perforations occur in the rectosigmoid colon (53%), followed by the cecum (24%), the ascending and transverse colon (9% each), and the descending colon (5%).[9]

Risk factors for colonoscopic perforations include older age, female sex, increased comorbidity, diverticulosis, bowel obstruction, and biopsy or polypectomy.[7,8,10] The risk of colonoscopic perforation is lower for gastroenterologists as compared with surgeons and family physicians and further reduced for gastroenterologists with high procedure volumes.[10-12]

## MECHANISMS

Colonoscopic perforation can result from a number of mechanisms including blunt trauma from the endoscope, unintended resection or dissection of the muscularis propria and serosa, and coagulation necrosis of the muscularis propria (Fig. 1) and serosa. Characteristics of perforations include:

(1) Blunt trauma (direct trauma, torque from the colonoscope, or retroflexion injury) accounts for the majority of colonoscopic perforations. Most are large (mean diameter 2 cm) and are located in the rectosigmoid colon.

(2) Unintended endoscopic resection or dissection (electrocoagulation biopsy, snare resection, EMR, or endoscopic submucosal dissection [ESD]) are the second most common reported cause of perforations. Most are small (mean diameter 1.4 cm) and are located in the cecum and right side of the colon.

- Electrocoagulation biopsy: The degree and duration of electrocautery used determine the risk of colon perforation.[13]
- Snare polypectomy: In a prospective study of 3976 snare polypectomies among 2257 patients from 13 German institutions, perforations occurred in 26 patients (1.2%). Polyps larger than 1 cm in the right side of the

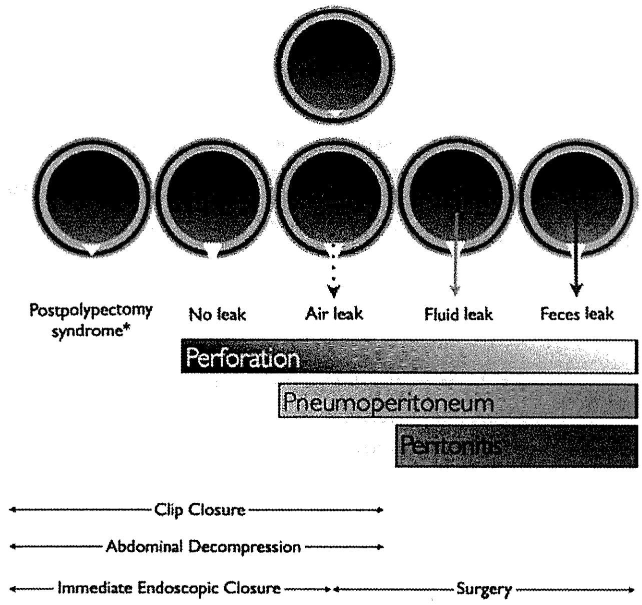


**Figure 1.** Perforation after colonoscopic resection can begin as postpolypectomy syndrome (serositis from transmural burn) that could evolve into a perforation or as a free perforation with air and fluid leakage, resulting in pneumoperitoneum and peritonitis. Immediate endoscopic closure could be useful before peritonitis develops. Prevention of postpolypectomy syndrome and its potential sequalae is most important.

*Abbreviations:: ESD, endoscopic submucosal dissection.*

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**TABLE 1. Summary of perforation rate in studies reporting over 10,000 colonoscopies**

| Study | Study period, (no. of colonoscopies) | Origin | Perforation rate (mortality) |
|---|---|---|---|
| 1 | 1989-1999 (n= 23,508) | Australia[2] (Teaching hospitals) | 1/1000 (0.04/1000) |
| 2 | 1987-1996 (n= 10,486) | United States[3] (Mayo Clinic, Scottsdale) | 0.019/1000 (0.0019/1000) |
| 3 | 2002-2004 (n= 12,407) | United States[4] (Community GI group practice) | 0.002/1000 (no deaths) |
| 4 | 2000-2004 (n= 50,138) | Poland[5] (40 centers) | 0.1/1000 (no deaths) |
| 5 | 1991-1998 (n= 39,286) | United States[6] (Medicare beneficiaries ≥65 y) | 2/1000 |
| 6 | 1994-2002 (n= 16,318) | United States[7] (Kaiser Permanente ≥40 y) | 0.9/1000 (0.06/1000) |
| 7 | 2002-2003 (n= 97,091) | Canada[8] (British Columbia, Alberta, Ontario, and Nova Scotia) | 0.85/1000 (0.074/1000) |
| 8 | 1980-2006 (n=258,248) | United States[9] (Mayo Clinic, Rochester) | 0.7/1000 |
| 9 | 2004-2006 (n= 24,509) | Canada[10] (Winnipeg hospitals) | 1.0/1000, colonoscopy alone 0.8/1000, sigmoidoscopy alone 0.5/1000, colonoscopy + biopsy 1.8/1000, colonoscopy + polypectomy 59.8/1000, colonoscopy + dilation (0.04/1000) |

colon or 2 cm in the left side of the colon and multiple polyps carry an increased complication risk.[14]

- EMR: The risk of perforation after EMR is about 1 in 500 from pooled analysis of 17 reports.[15-31] The low perforation rate (0.7%) may be related to submucosal injection before snaring and electrocautery and routine use of clips to approximate the mucosal defect.[32]
- ESD: The risk of perforation after ESD can be as high as 1 in 20 (5%), although most were small and successfully treated by clips.[33-40] Thus, perforation during ESD rarely requires surgical closure. Inaccurate identification of the cutting line and underestimation of the depth of the submucosal layer may result in perforation. Endoscopist's experience of less than 50 ESDs, tumors larger than 5 cm, and underlying submucosal fibrosis (recurrent tumors and lateral spreading tumors of the nongranular type with converging folds) increase the risk of perforation.[41,42] Tumor location and morphology and the type of resection knives have no effect on the risk of ESD perforation.[40]

(3) Thermal injury (argon beam coagulation or electrocautery to ablate tissue or control bleeding) accounts for 18% of cases. Most of these perforations are small (0.9 cm) and are located in the cecum.

## DIAGNOSIS

Recognition of perforation at the time of colonoscopy or high-risk sites for delayed perforation is important to prevent the dreadful complication of colonoscopy. About a third of perforations are diagnosed during the procedure and the remaining within 1 to 2 days after the procedure; a few cases present as late as 14 days.[2-4,10,14,43] Thus, the 14-day reporting period is important to capture all colonoscopic perforations.[43]

### Diagnosis of perforation at the time of colonoscopy

Examination of the resection site is essential to ensure that perforation has not occurred. Routine injection of diluted indigo carmine into the submucosa can be helpful in determining the plane of resection—a blue resection base indicates intact submucosa; a white resection base indicates deeper resection into the muscularis propria. This has been described as a "target sign"—white center (muscularis propria), with surrounding blue area (indigo carmine stained submucosa).[44,45] A more subtle perforation may be recognized as shiny serosa seen through the defect (Fig. 2). Perforation also may appear as a rent in the muscularis propria during ESD or as an obvious tear in the sigmoid colon or rectum after blunt trauma.[40,46-51]

Another important physical sign is the development of tension pneumoperitoneum.[52] Thus, periodic assessment of the anterior abdominal wall tone is important.

### Diagnosis of perforation after completion of the procedure

Perforation should be considered and appropriate workup performed when a patient complains of abdominal pain. A CT scan of the abdomen and pelvis are most sensitive in the detection of retroperitoneal air, even in the absence of free air under the diaphragm on plain abdominal radiographs.[53]

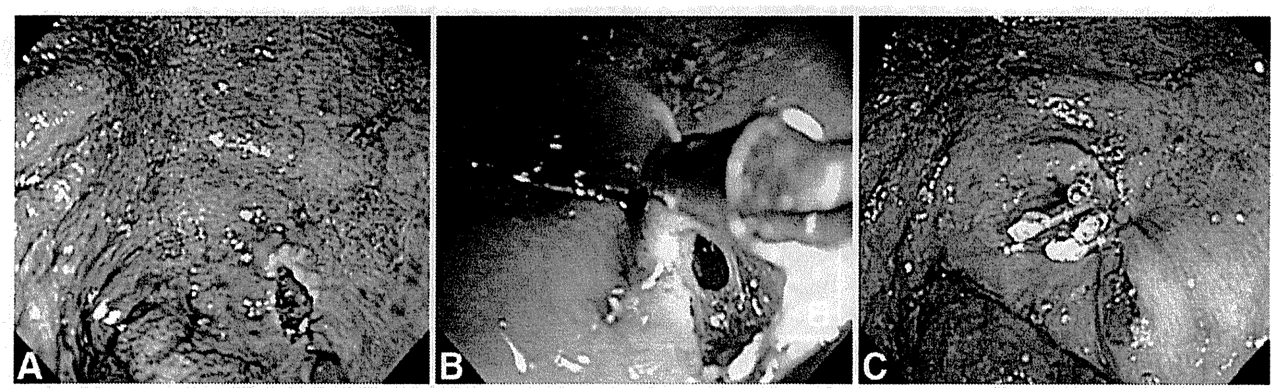


**Figure 2.** Colonoscopic clip closure of a small, linear perforation. **A,** A small, linear perforation is recognized after en bloc EMR of a cecal adenoma in a patient with ulcerative colitis being treated with steroids. **B,** The first clip is deployed, partially closing the tear. **C,** Completed closure is achieved with deployment of 4 clips. (Reproduced with permission from the ASGE)

## MANAGEMENT

Until recently, surgery was the mainstay of treatment in the majority of patients, with nonoperative medical management in a select group (Fig. 1). Surgery is indicated in patients with large perforations, generalized peritonitis, or ongoing sepsis as well as in patients with concomitant pathology, such as a large sessile polyp, which is likely to be a carcinoma, unremitting colitis, or perforation complicating an obstructing colonic lesion. Other candidates for surgery include those whose conditions deteriorate with conservative management.[54] Surgery is associated with a significant morbidity (36%) and mortality (7%).[9] Conservative management may be undertaken in patients with asymptomatic perforations, those with localized peritonitis who improve clinically, and those with postpolypectomy coagulation syndrome.[53,55-57]

Endoscopic clips can be successful in the closure of colonoscopic perforations recognized during the colonoscopy. These clinical observations have been supported by a series of animal studies. Endoscopic closure is effective in creating a leak-proof seal of the perforation, healing of the perforation, preventing peritonitis, limiting peritoneal adhesions, and avoiding surgery.[47,58-70]

## PREVENTION OF COLONOSCOPIC PERFORATION

Prevention is the most important factor in the management of colonic perforation. A number of precautions could be undertaken to avoid a perforation and complications arising from such an event.

### Colon preparation

**Poor bowel preparation.** Defer colonoscopy in patients with poor bowel preparation to avoid the risk of fecal peritonitis.[9] In addition, deferring colonoscopy in these patients avoids the risk of colonic explosion from cautery-induced ignition of combustible gases.[71] A split-dose preparation of 4 L of polyethylene glycol solution or having the patient drink 2 to 3 liters of polyethylene glycol solution the morning of the procedure results in excellent preparation. Checking the color of the stools before each procedure and administering additional polyethylene glycol solution when necessary assures excellent preparation.[72,73]

**Dry field.** Suctioning of all the fluid and drying the operating field segment, along with upstream and downstream segments, prevent escape of luminal contents through a perforation. Moving the patient to the nondependent position so that the target lesion can be located may prevent fluid escape and peritonitis with perforation. Conscious sedation allows patient repositioning during the procedures.

### Colonoscopy technique

A detailed review of the patient's demographics, comorbidities, and prior surgical procedures facilitates the risk assessment for colonoscopic perforation and selection of appropriate closure techniques, technologies, and precautions to prevent it (Fig. 3).

**Fixed colon.** Avoid excessive pushing of the colonoscope. Use of a smaller-caliber colonoscope along with careful tip deflection to negotiate the acute angles of a fixed colon in patients with adhesions from prior pelvic and abdominal surgeries is advised. Change of the patient's position, use of balloon-assisted endoscopy, use of a water immersion technique, or use of carbon dioxide insufflation also may be helpful.[74-79]

**Redundant colon.** Use of an enteroscope along with the application of abdominal compression at appropriate places, techniques to stiffen the endoscope further (deploying variable stiffness function, insertion of a biopsy forceps through the biopsy port, use of overtubes that lock and stiffen on demand), or holding the loops down (balloon-assisted endoscopy) may be effective.[80,81]

**Prolonged procedures and failed procedures.** Use of carbon dioxide, periodically venting the air out (by releasing the biopsy port cap), or intermittent suctioning may release the luminal pressure.

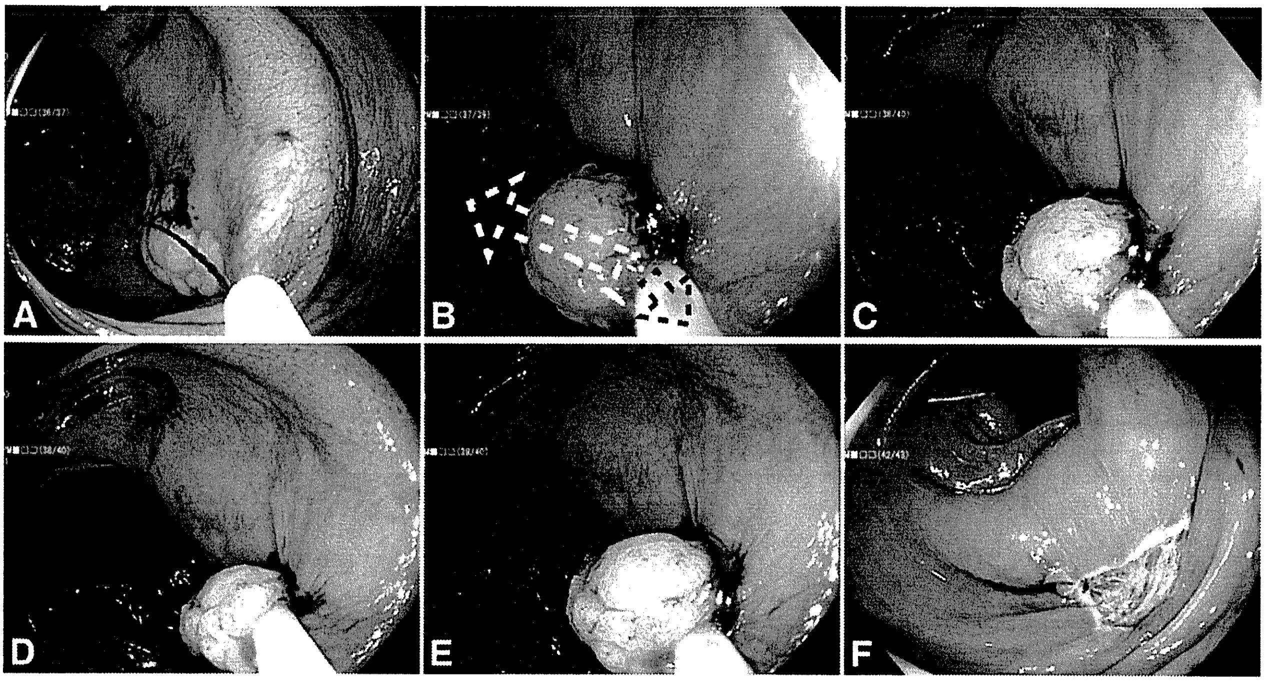


**Figure 3.** Prevention of perforation during EMR. **A,** A flat lesion after a submucosal injection of saline solution with a few drops of indigo carmine being captured with a stiff snare. **B,** After the snare was closed, the tip of the endoscope was moved to the left and upward (*white arrow*) while the snare was slightly pulled back (*black arrow*). **C,** The lesion after being tented away from its underlying muscularis propria. **D,** The endoscopist then asked the assistant to loosen the snare slightly, without loosening the lesion. **E,** The snare was closed snugly again. **F,** The lesion was resected.[92]

**Small rectum.** Avoid retroflexion in patients with small rectums.[82] Examine the rectal vault before endoscope withdrawal from the colon, because retroflexion-induced perforations could be identified and closed immediately with clips.[48,49,83-86]

**Procedure note.** Details of procedure duration, technical difficulties, and measures undertaken to overcome them should be noted to plan future endoscopies.

### Management of lesions

**Referral versus resection.** It is important to decide whether it is better to refer to endoscopists with expertise in the endoscopic resection or undertake the resection if it could be done safely.[87,88]

**Referral without biopsy.** If a decision is made to refer, defer biopsies, because they cause submucosal fibrosis, which prevents subsequent adequate lifting and the ability to successfully resect the lesion. Avoid tattoo injection into the lesion because this leads to fibrosis in the submucosa.[89] Instead, inject it a fold away from the lesion.

**Resection of diminutive polyps.** Cold snare resection of diminutive polyps is safer than hot biopsy.[90,91]

**Resection of pedunculated polyps.** Apply a snare on the stalk of a pedunculated polyp away from the wall, and tent it up before cautery to limit transmural burn and perforation.

**Resection of sessile and flat lesions.** Ample injection of submucosal fluid to separate the lesion from the muscularis propria is critical to prevent thermal injury to the muscle.[32] The dynamic submucosal injection technique creates a large, submucosal cushion.[92] Piecemeal resection of large polyps (>2 cm) may limit deeper injury to the muscle compared with large, en bloc resections. Specific routine steps to prevent perforation during EMR have been described (Fig. 3).[93]

**ESD of large, flat lesions.** Accurate identification of the cutting plane is critical to avoiding perforation during ESD. Starting the submucosal dissection close to the mucosal layer and after the submucosal layer has been expanded and well-visualized allows dissection to be performed at the lower third or just above the muscle layer to avoid a perforation. When fibrosis is encountered, the short-type, small-caliber-tip, transparent hood is useful for exposing the muscularis propria.

## ENDOSCOPIC MANAGEMENT OF COLONOSCOPIC PERFORATION

Endoscopic closure of colonic perforation has been successful, provided that the perforation is immediately recognized and closed without delay. This could be accomplished with a variety of devices. Through-the-scope clips have been used extensively over the last decade for endoscopic closure of colon perforations.[37,40,45,46,49,63,66-68,70,94-100] Recently, over-the-scope clips have been introduced in Europe and in the United

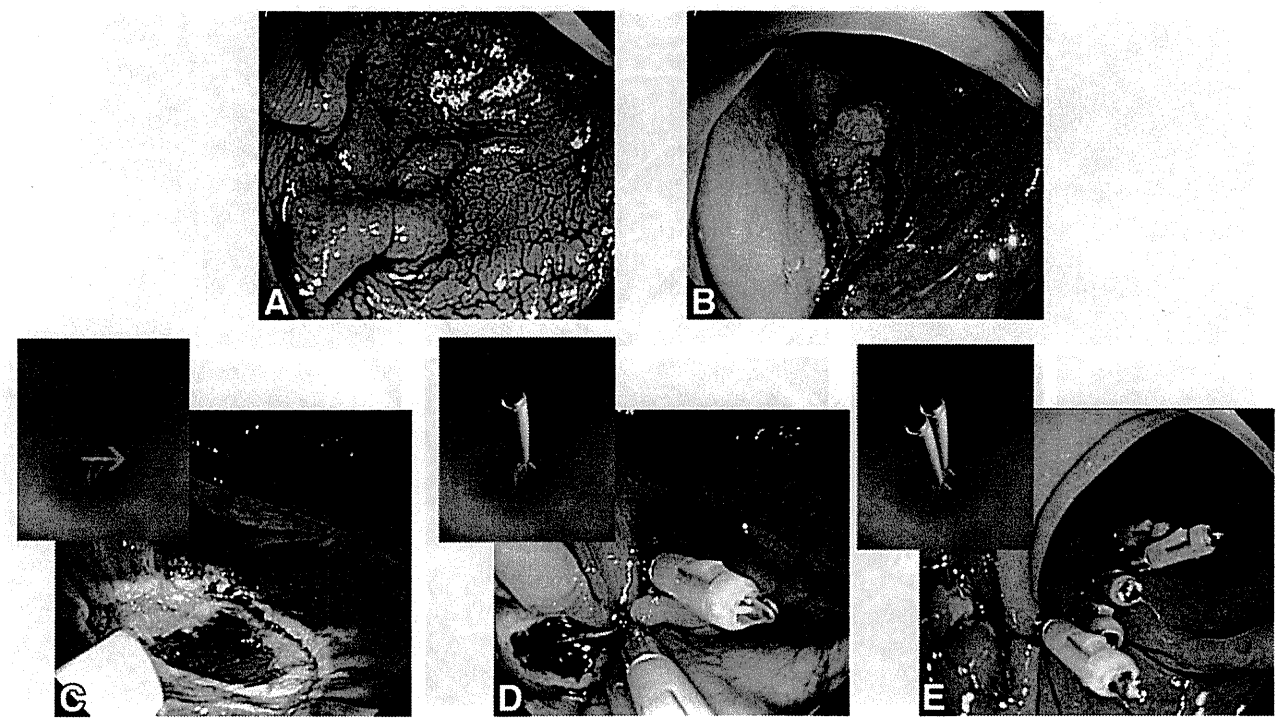


**Figure 4.** Colonoscopic clip closure of a perforation after EMR. **A, B, C,** EMR of a 2-cm, flat lesion with high-grade dysplasia resulted in a large linear perforation. **C, D, E,** This perforation was closed with clips starting at the top of the perforation and working downward. (Reproduced with permission from the ASGE)

States.[65,69,97,101-105] Suturing devices such as T-tags have been extensively investigated in animal models, especially in the closure of large, gaping perforations with everted edges that are not amenable to clip closure and closure of large defects after full-thickness resection of the colon, but these devices are not available in the market.[62,64,106,107] Both through-the-scope clips and over-the-scope clips produce results comparable to hand-sewn colostomy closure in terminal animal studies.[107,108] Through-the-scope clips can be deployed anywhere in the colon; hence they are ideal for immediate closure of perforations without leaving the site of perforation, thereby avoiding leakage of colon contents. Clips are useful in the closure of small (1 cm) nongaping perforations.[40,58-61,72] However, through-the-scope clips have been reported to be unsuccessful in the closure of large, gaping perforations with everted edges and defects after full-thickness resection, which might be closed with through-the-scope suturing devices such as T-tags.[62,107,109]

Emergency decompression of accumulated air in the peritoneum with a wide-bore needle is important to reduce respiratory compromise, to prevent circulatory decompensation, and to prevent air embolism in the portal venous system. Practical tips of the endoscopic management of colonic perforations are available through the American Society for Gastrointestinal Endoscopy Learning Center and as follows:

## Through-the-scope clips

Clips can be used to close perforations immediately after their recognition during the colonoscopy. Both the endoscopist and assistant must be well-versed with the use of clips before undertaking endoscopic closure of perforations. Depending on the size and shape of the perforation, the following techniques can be used for closure of colonoscopic perforations and management of pneumoperitoneum (Figs. 3-6) (Videos 1-4, available online at www.giejournal.org. Reproduced with permission from the ASGE.).

## Closure of a large perforation

Keeping the clip close to the end of the endoscope, with the hinge of the clip blades just outside the endoscope, allows the clip–endoscope to be maneuvered as a single unit. Open the clip and rotate the blades to align them at right angles to the defect. After engaging the lower blade to the lower edge of a transverse perforation, gently push the clip–endoscope unit while applying gentle suction to collapse the lumen so that as much tissue as possible from the opposite edge of the perforation can be grasped while the clip is slowly closed. For longitudinal perforations, apply the clip just above the upper end of a longitudinal perforation to pucker the edges below for easier application of subsequent clips, one below the other. Place additional clips from the top, down, in longitudinal perforations or left-to-right in circular perforations