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5 十二指腸憩室 duodenal diverticulum

- 消化管の憩室の中で，十二指腸は大腸，空腸に次いで多い．
- 十二指腸内では，下行部の内側に多い．
- 多発例は5人に1人程度である（右頁第1症例）．
- ほとんどの場合は憩室内に炎症はみられないが，まれに急性憩室炎を起こし，緊急手術を行ったとの報告がある．
- 十二指腸乳頭の近くに多い（傍乳頭憩室）．
- この中でも膵頭部の後方にできやすい（右頁第3症例）．
- 傍乳頭憩室はレンメル症候群をきたすことがあり，これに黄疸を合併した場合は手術適応となる．
- 憩室内に食物残渣が貯留することもある（右頁第4症例）．
- 内視鏡的に憩室内の食物残渣を除去したところ，レンメル症候群が軽快したとの報告がある．

Reference

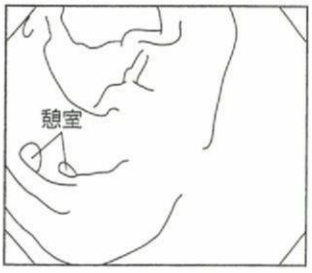
レンメル症候群 Lemmel syndrome

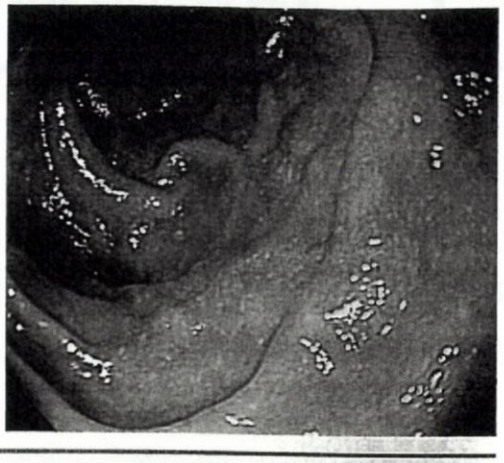
乳頭近くにできた憩室が胆管あるいは膵管を圧迫して，胆管炎・胆石症・膵炎などを起こすことがあり，レンメル症候群（傍乳頭憩室症候群）という．

十二指腸憩室

多発憩室

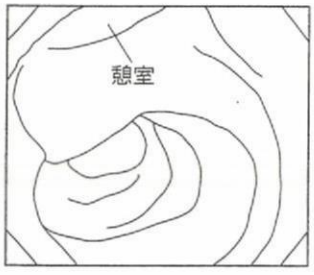
十二指腸下行部内側に，小さな憩室を 2 個認める．これ位の大きさでは，蠕動や送気の程度によってみえなくなることがある．

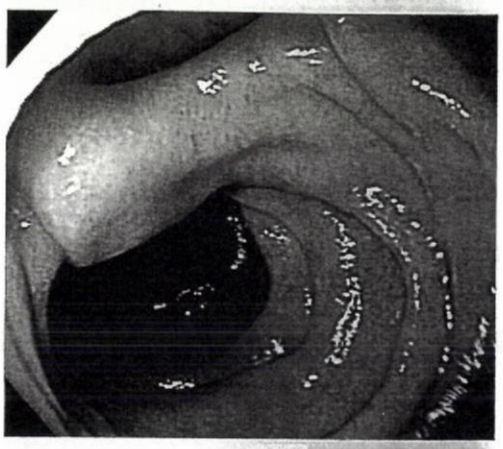




やや大きな憩室

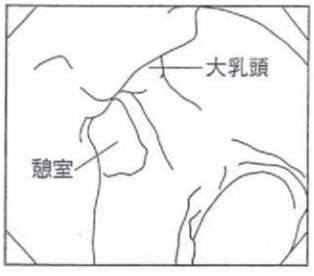
SDA 直下に，やや大きな憩室を認める．誤って憩室内にスコープを勢いよく挿入しないよう注意する必要がある．

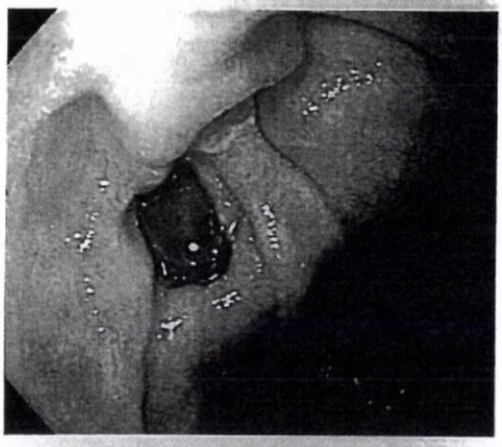




傍乳頭憩室

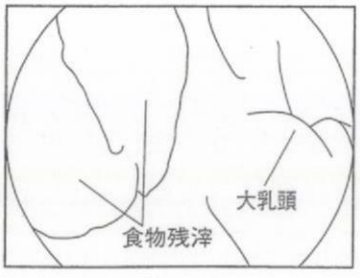
大乳頭に接して憩室を認め，位置的には膵頭部の後方に相当する．急性膵炎を繰り返しており，レンメル症候群と考えられる．





傍乳頭憩室内の食物残渣

大乳頭のすぐ口側の憩室内に食物残渣が充満している．本症例は胆石があり，慢性膵炎と肝機能障害を伴っていた．



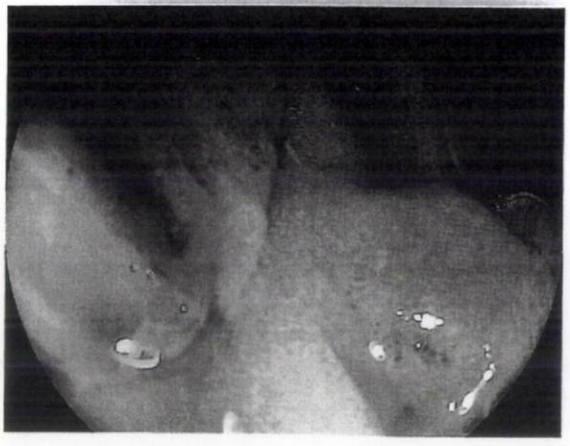


Image of the Month

Endoscopic Submucosal Dissection of a Large Laterally Spreading Tumor in the Rectum is a Minimally Invasive Treatment

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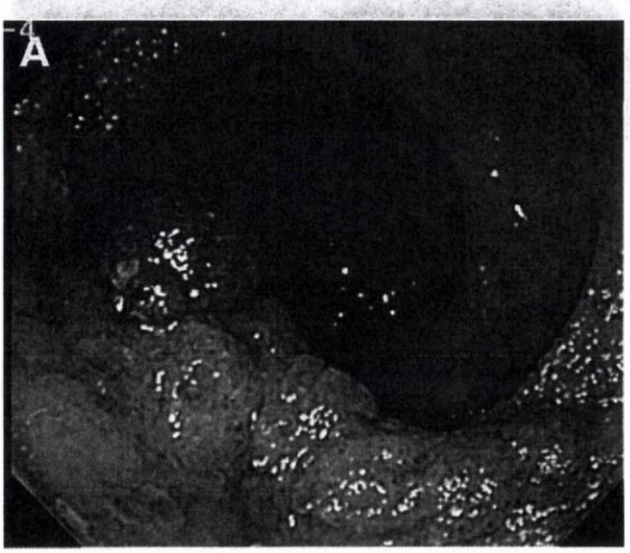
Division of Endoscopy, National Cancer Center Hospital, Tokyo, Japan



A 65-year-old man was referred for endoscopic removal of a large (13 cm), laterally spreading, granular-type tumor in the rectum with its distal margin located 0.5 cm from the dentate line (Figure *A*). The lesion was classified as intramucosal by magnified chromoendoscopy.[1]

Endoscopic submucosal dissection (ESD) was performed under conscious sedation using a bipolar current needle knife (B-knife; XEMEX Co, Tokyo, Japan; Figure *B*) and an insulation-tipped electrosurgical knife (IT knife; Olympus Optical Co, Tokyo, Japan).[2,3] No major complications occurred and the total duration of the procedure was 3 hours (Figure *C*). The specimen was retrieved en bloc and measured 12 × 9 cm (Figure *D*). Histologic assessment revealed a well-differentiated adenocarcinoma limited to the mucosal layer without any evidence of vascular infiltration and/or poorly differentiated adenocarcinoma component.

We report an ESD of a large, rectal, laterally spreading, granular-type tumor with its distal margin located close to the dentate line. In this case, ESD was technically easier and safer to perform in addition to having lower rates of morbidity and mortality compared with other treatment modalities.

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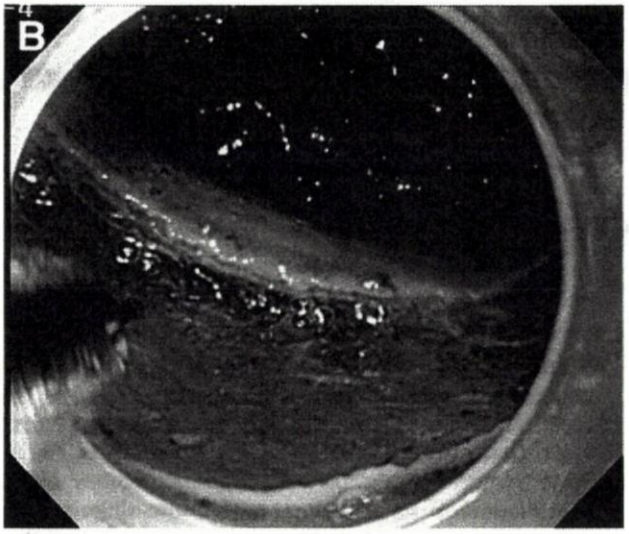
doi:10.1016/j.cgh.2007.10.024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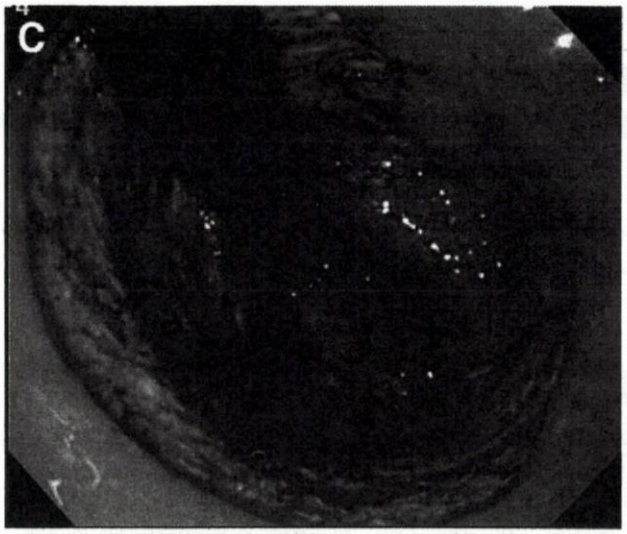
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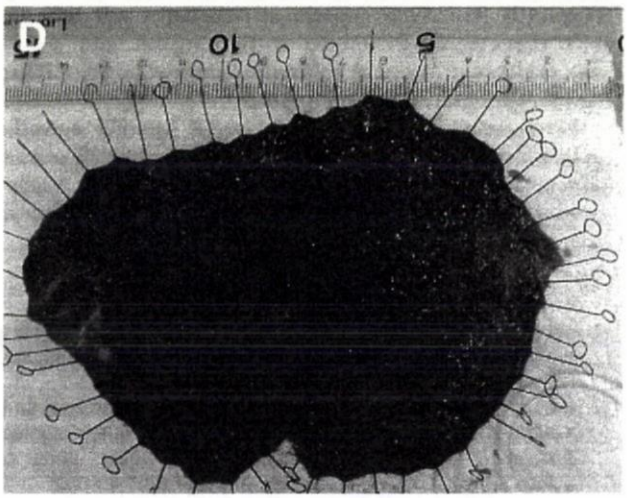
D

Endoscopic submucosal dissection of recurrent or residual superficial esophageal cancer after chemoradiotherapy

Yutaka Saito, MD, PhD, Hajime Takisawa, MD, Haruhisa Suzuki, MD, Kouhei Takizawa, MD, Chizu Yokoi, MD, Satoru Nonaka, MD, Takahisa Matsuda, MD, Yukihiro Nakanishi, MD PhD, Ken Kato, MD

Tokyo, Japan

Background: Treatment of local recurrent or residual superficial esophageal squamous-cell carcinoma (SCC) with conventional EMR often results in a piecemeal resection that requires further intervention.

Objective: The aim of this study was to evaluate the efficacy of endoscopic submucosal dissection (ESD).

Design: A case series.

Patients: Between January 2006 and September 2006, 4 local recurrent or residual superficial esophageal SCCs were treated by ESD.

Interventions: ESD procedures were performed by using a bipolar needle knife and an insulation-tipped knife. After injection of glycerol into the submucosal (sm) layer, a circumferential incision was made, and an sm dissection was performed. All lesions were determined to be intramucosal or sm superficial, without lymph-node metastasis by EUS before treatment.

Main Outcome Measurements: Tumor size, en bloc resection rate, tumor-free lateral margin rates, and complications were recorded.

Results: All 4 ESD cases were successfully resected en bloc, and the tumor-free lateral margin rate was 75% (3/4) by histopathology examination. The mean tumor size of the resected specimens was 35 mm (range, 15-50 mm). There were no complications.

Limitations: The number of ESDs in our series was limited, and there are no long-term follow-up data.

Conclusions: ESD for recurrent or residual superficial esophageal tumors after chemoradiotherapy achieves the goal of an en bloc resection, with a low rate of incomplete treatment without any greater risk than the EMR technique.

Esophageal cancer is one of the most difficult GI cancers to detect at an early stage, even by endoscopy. Recently, a narrow-band imaging endoscope was developed and was shown to be advantageous for the early detection of squamous-cell carcinoma (SCC) in the esophagus and the pharynx, although it still is not widely in use.[1,2]

Some esophageal cancers have been detected as invasive tumors, and surgery has been the standard treatment for such lesions. However, higher mortality rate because of surgery has been reported (range 2.1% to 13.7%), as has poor patient quality-of-life after surgery.[3,4]

There is a current preference to treat esophageal SCC by primary chemoradiotherapy (CRT),[5,6] but 13% of patients treated for esophageal SCC with CRT have a recurrence or a residual tumor. Surgery after CRT is unsatisfactory,[7,8] and endoscopic treatment can be proposed when the tumor is superficial,[9-13] but a strip biopsy is difficult, because fibrosis and piecemeal resection frequently occur even for small lesions. A search of the literature confirmed that en bloc resection by endoscopic submucosal dissection (ESD) provides better results in the stomach.[14-17] ESD was recently reported to be useful in the treatment of superficial esophageal SCC[18-20]; however, the feasibility and safety of ESD for local recurrent or residual tumors is unclear. Previously, we reported on

Abbreviations: B-knife, bipolar needle-knife; CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; IT-knife, insulation-tipped-knife; NCCH, National Cancer Center Hospital; SCC, squamous-cell carcinoma; sm, submucosal.

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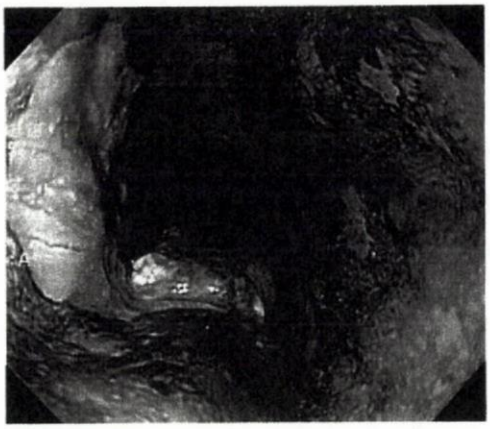

Figure 1. The primary tumor before CRT was diagnosed as a type 1 SCC, with a circumferential intraepithelial lesion, which had been located in the mid esophagus at a previous hospital.

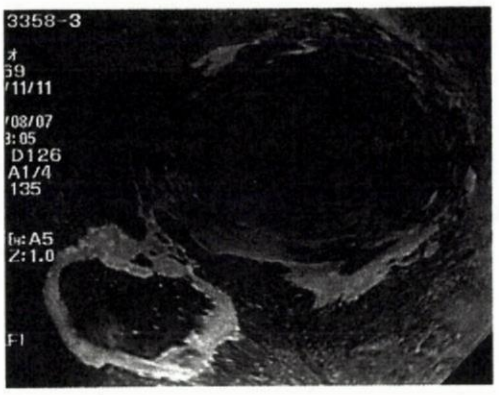

Figure 2. An endoscopy revealed a 0-IIC superficial residual lesion, 40 mm in diameter, located in the mid esophagus. After iodine staining, the lesion became more apparent and was larger than 50% in circumference.

the effectiveness and safety of ESD for colorectal tumors by using a bipolar needle-knife (B-knife) and an insulation-tipped knife (IT-knife), neither of which has any coagulation effect at the needle tip.[21-24] The aim of our study was to evaluate the efficacy and safety of ESD for local recurrent or residual esophageal tumors by using a B-knife and an IT-knife.

PATIENTS AND METHODS

Four patients with esophageal SCC, each of whom had developed a local recurrent or residual tumor (2 recurrent tumors and 2 residual tumors) after CRT, were included in this study, which was conducted between January 2006 and September 2006 at the National Cancer Center Hospital (NCCH) in Tokyo. Three of the ESD cases involved stage I lesions treated by CRT, and the other case was of a stage II lesion. The 4 ESDs were performed from 217 days to 1377 days after the initial CRT.

ESDs by using a B-knife and an IT-knife were performed on all 4 patients, with Glyceol (Chugai, Tokyo, Japan)[25] used in each case as the submucosal (sm) injection solution to maintain proper sm elevation. All of the local recurrent or residual tumors were confirmed as intramucosal or sm superficial, without lymph-node metastasis, by EUS and a CT before treatment.

Endoscopic operating system

ESD procedures were performed by using video endoscopes (GIF-Q240 or GIF-Q260; Olympus Optical Co, Ltd, Tokyo, Japan).

ESD procedure

A transparent disposable attachment (D-201-1074; Olympus) was fitted onto the tip of the endoscope to retract the sm layer and to facilitate dissection. Lesion margins were delineated before ESD by using 1.5% iodine staining (Figs. 1 and 2). After sm injection of Glyceol, a circumferential incision in the mucosa was made by using a B-knife and an IT-knife.[21-24] Additional Glyceol was then injected into the sm layer to lift the lesion, and the thickened sm layer was dissected by using an IT-knife (Figs. 3 and 4). The B-knife was mainly used for the dissection of fibrosis caused by CRT.[21-24] The operation time was recorded for all patients.

Sedation

Midazolam (3-5 mg intravenously) was administered in all cases. An additional 2 mg was given as necessary, whenever indicated, based on the individual endoscopist's judgment.

Histologic assessment

All specimens were evaluated after being cut into 2-mm slices; they were examined microscopically for histologic type, depth of invasion, lateral resection margin, and vertical resection margin.

Follow-up care

All patients who had an ESD at the NCCH were regularly observed, with annual endoscopic and EUS examinations and CTs. Complete follow-up care was available for all 4 patients in the ESD group.

Statistical analysis

All variables in this study were described as mean (SD). All statistical analyses were performed by using SAS version 8.0 (SAS Institute Inc, Cary, NC). The P value was 2 sided, and $P < .05$ was used to determine statistical significance.

Ethics

The ethics committee at the NCCH approved the study protocol, and written informed consent was obtained from all 4 patients in the ESD group before entering the study.

Figure 3. An en bloc resection was achieved without complication in 100 minutes.

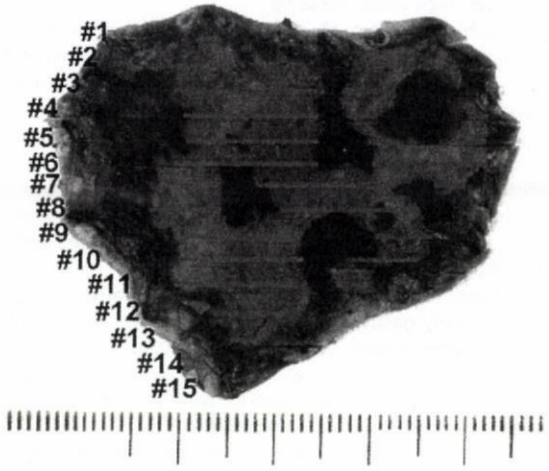

Figure 4. The resected specimen was 50 mm in diameter, with both the lateral and vertical margins negative by endoscopy. Both the lateral and vertical margins were negative on histopathologic examination, and the depth of invasion was m2. A curative local resection was achieved in this case.

RESULTS

During the study period, 4 patients were treated with ESD. All 4 lesions were eligible for outcome analysis. Clinical characteristics of the patients are presented in Table 1. Each of the 4 ESD cases was successfully resected en bloc, with no complications. The mean (SD) ESD time was 58 ± 42 minutes (range 15-100 minutes), and the mean (SD) size of the resected specimens was 35 ± 15 mm (range 15-50 mm). On histopathologic examination, the lateral and vertical margins were negative in 3 of 4 ESD cases, but the depth of invasion was sm1 in 2 of those cases, so additional CRT was performed on those patients. A curative local resection was achieved in the other case. None of the patients developed local recurrence or distant metastasis in the follow-up period. There were no immediate or late complications related to ESD procedures reported. The median (SD) follow-up time was 3 ± 2 months (range 0-6 months) for the ESD group.

TABLE 1. Clinical characteristics of patients

No. lesions	4
Stage before CRT (stage I/II)	3/1
Days after CRT (median)	749 (range 217-1377)
Residual/recurrent	2/2
Tumor depth (m/sm)	2/2
Tumor size (mean [SD]) (mm)	35 ± 15 (range 15-50)
Procedure time (mean [SD]) (min)	58 ± 42
En bloc resection rate	100% (4/4)
Tumor-free lateral margin rate	75% (3/4)
Local recurrence rate	0% (0/4)
Complication (perforation)	0 (0%)

DISCUSSION

The ESD technique, by using a B-knife[21-24] and an IT-knife,[17,23,24] enhanced the en bloc resection rate, thereby increasing the likelihood of curative results for local residual or recurrent tumors. In fact, ESDs with a B-knife and an IT-knife are performed to treat superficial neoplastic lesions, such as gastric and colonic neoplasms, at the NCCH.[17,22-24] ESD has enabled us to treat recurrent gastric cancers after EMR. As indicated in our previous reports,[26] about 5% of such cases involved perforations, although virtually all of the perforation cases were successfully treated by means of endoscopic clipping, without the need for additional surgery.

The esophagus is located in the mediastinum, so the risks of ESD are further enhanced, and perforations must be avoided. The newly developed B-knife results in a safer ESD, because the electric current is localized at the needle tip.[21] The IT-knife [17,23,24] also decreases the risk of perforation as a result of the insulated tip attached to the end of the needle. A B-knife was mainly used for the dissection of fibrosis caused by CRT. The combined use of these two instruments has enabled us to safely perform ESDs even for local recurrence of residual tumors after CRT with successful results similar to our experience in the colorectum.[23,24] Although the number of patients who underwent ESD in our series was limited and the follow-up periods were short, there were no cases of recurrence after ESD during any of the follow-up periods. Further follow-up data are required, however, for meaningful recurrence and survival analyses.

For comparison, 17 local recurrent or residual tumors (10 recurrent tumors, 7 residual tumors) in 14 patients treated at the NCCH between January 2005 and December

2005 by conventional strip biopsy (EMR) were included as historical controls. Ten of the EMR lesions were stage I treated by CRT, and the other 7 were stage II lesions. The 17 EMRs were performed from 134 days to 636 days after the initial CRT.

Analysis showed a significant difference between the 2 treatment groups in terms of en bloc resection rates, with 100% (4/4) in the ESD group compared with 47% (8/17) in the EMR group ($P = .05$), despite the tumor size being significantly larger in the ESD group. Further analysis showed a difference between the 2 groups in terms of resection margin involvement, with 25% (1/4) in the ESD group and 65% (11/17) in the EMR group (not significant). The higher en bloc resection rate and lower incidence of margin involvement in the ESD group compared with the EMR group resulted in a higher curability rate.

It is recognized that ESD for local recurrent or residual tumors is difficult because of fibrosis, which results after CRT. Although it is still not technically feasible to perform either EMR or ESD for an invasive SCC deeper than sm2 (close to the muscle layer), ESD enables us to resect invasive SCC for both sm1 and sm2. Surgical treatment for esophageal SCC is difficult, with a poor quality-of-life reported for patients after surgery, whereas a higher recurrence rate has been reported after CRT treatment. ESD or EMR should be performed initially, therefore, followed by CRT to treat possible lymph node metastasis when EUS or magnifying endoscopy examinations reveal no evidence of deeper invasion to the muscle layer as previously reported.[27]

In conclusion, ESD for recurrent or residual superficial esophageal tumors after CRT with a B-knife or an IT-knife achieves the goal of an en bloc resection with a low rate of incomplete treatment without greater risk than the EMR technique. ESD should be the reference procedure, therefore, for treating such lesions.

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DISCLOSURES

The authors report that there are no disclosures relevant to this publication.

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GASTROENTEROLOGY

Endoscopic submucosal resection with a ligation device is an effective and safe treatment for carcinoid tumors in the lower rectum

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Abstract

Background and Aims: Various methods for complete endoscopic resection of rectal carcinoid tumors have been reported; however, the number of cases investigated in each study has been limited. The aim of the present study was to clarify the clinical usefulness of a novel technique named endoscopic submucosal resection with a ligation device (ESMR-L) in a large number of rectal carcinoid tumors.

Patients and methods: Between January 1999 and March 2005, a total of 61 patients with 63 rectal carcinoid tumors estimated at 10 mm or less in diameter, without atypical features and resected by ESMR-L were recruited for this analysis. The complete resection rate, complications associated with the procedure, local recurrence, and distant metastases were evaluated.

Results: Sixty-one patients were 36 males and 25 females with a mean age of 59 ± 11 years (24–76 years). Tumor size ranged from 2 to 12 mm in diameter, with an average size of 6.4 ± 2.4 mm. Fifty-nine lesions (93.6%) were located in the lower rectum (Rb), three in the upper rectum (Ra) and one in the recto-sigmoid colon (Rs). In total, 60 out of 63 lesions (95.2%) were histologically determined to be completely resected. The complete resection rate for lesions located in the Rb was 98.3%, which was significantly higher than that for lesions in Ra and Rs (50%). Minor bleeding associated with the procedure occurred in five lesions (7.9%), but all cases were successfully managed with hemoclips. Histopathologically, all tumors were located in the submucosal layer, and all were classified as classical-type carcinoids without lymphovascular invasion. Neither local recurrence nor distant metastasis was detected during a median follow-up period of 24 months.

Conclusion: In a large number of cases, ESMR-L proved to be a useful and safe procedure to resect rectal carcinoid tumors 10 mm or less in diameter, especially for those located in the Rb.

Introduction

Approximately 90% of large intestinal carcinoid tumors develop in the rectum.[1] Generally, rectal carcinoid tumors are found incidentally during colonoscopy as submucosal tumors covered with yellow-discolored mucosa. Several parameters have been suggested as predictive criteria in the assessment of the malignant potential including tumor size, histological growth patterns, muscularis propria invasion, and lymphovascular invasion.[2,3] Among these parameters, size is considered to be the most simple and reliable parameter. Metastasis occurs in ≤3% of tumors ≤10 mm in diameter, and in 5–15% of tumors 10–19 mm in diameter; however, the frequency increases to 80% for those ≥20 mm.[4–6] Rectal carcinoid tumors ≤10 mm in diameter, confined to the submucosal layer, and without lymphovascular invasion, rarely metastasize. They are, therefore, considered good candidates for local excision, including endoscopic or transanal resections.

However, it is difficult to resect rectal carcinoids completely due to the presence of submucosal tumor involvement. Resection by polypectomy or conventional endoscopic submucosal resection (EMR) is often associated with involvement of the resection margin that necessitates further intervention.[7,8] Therefore, various methods of endoscopic resection for rectal carcinoid tumors have been developed and reported to be effective for complete resection[9–15] (Table 1). To resect the carcinoid tumors completely, we also have reported a novel endoscopic resection technique using an endoscopic variceal ligation (EVL) device, named endoscopic submucosal resection with a ligation device (ESMR-L).[13]

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Table 1 Series of endoscopic resections for rectal carcinoid tumors

Reference	Method	Injection solution	Complete resection rate
Iishi *et al.* (1996)[9]	Strip biopsy	None	90% (9/10)
	Polypectomy	None	28.6% (2/7)
Imada *et al.* (1996)[10]	EMR-C	Glycerol	100% (8/8)
Charles *et al.* (1999)[11]	ESMR-L	None	100% (5/5)
Oshitani *et al.* (2000)[12]	EMR-C	Saline	85.7% (6/7)
Ono *et al.* (2003)[13]	ESMR-L	Saline	100% (14/14)
	Polypectomy or EMR	None or saline	57.1% (8/14)
Nagai *et al.* (2004)[14]	EMR-C	Saline	100% (8/8)
	EMR		37.5% (3/8)
Kobayashi *et al.* (2005)[15]	Strip biopsy	None or saline	82.9% (34/41)

EMR-C, endoscopic mucosal resection with cap aspiration; ESMR-L, endoscopic submucosal resection with a ligation device.

However, previous studies using various methods of endoscopic resection were based on a limited number of cases.

The present study was conducted with a large number of cases treated by ESMR-L. We retrospectively analyzed and re-evaluated the clinical usefulness and safety of ESMR-L for carcinoid tumors < 10 mm in diameter with the primary end-points being as follows.

1 Complete resection status in the horizontal and vertical resection planes using histopathology as the gold standard.
2 Resection complications including bleeding and perforation.
3 Local recurrence.

Methods

Patients and lesions

Rectal carcinoid tumors, endoscopically estimated at ≤10 mm in diameter, without atypical features, including ulceration or depressed areas, were considered good candidates for endoscopic resection.[16]

Between January 1999 and March 2005, a total of 61 patients (36 males, 25 females; mean age, 59 ± 11 [range, 24–76] years) with 63 rectal carcinoid tumors considered as good candidates, were treated by ESMR-L at the National Cancer Center Hospital Tokyo, East, and the Takahiro Fujii Clinic. All lesions were investigated for this study. Informed written consent for endoscopic resection was obtained from all patients prior to the treatment. The tumor size was estimated endoscopically with a measuring forceps (Olympus Optical Co., Tokyo, Japan).

Informed consent for treatment of rectal carcinoid was obtained from all patients.

Endoscopic procedures

ESMR-L was carried out with a conventional single-channel endoscope (PCF-Q200I or PCF-Q240ZI; Olympus Optical Co.) with attached band ligator device (EVL Device; Sumitomo Bakelite Co., Tokyo, Japan).

The procedure of ESMR-L was as follows.

1 Submucosal saline solution was injected beneath the tumor to elevate it and thereby reduce the risks of perforation and resection margin involvement.
2 The lesion was then aspirated into the ligator device, followed by deployment of the elastic band.
3 Snare resection was performed below the band by using blended electrosurgical current at 50 W on the coagulation setting (ICC 200 ERBE).
4 The resection specimen was then removed by aspirating it into the cap or retrieving it with a grasping forceps (Olympus Optical Co.).

Histopathological evaluation

All removed specimens were fixed in 10% formalin, sectioned at 2 mm, stained with hematoxylin and eosin, and examined histologically with respect to cut-margin involvement, depth of invasion, lymphovascular invasion, and histopathological type.[17]

Follow up

All patients were examined endoscopically 1 year after their ESMR-L. We recognized their resection sites by the scars using indigo-carmine dye spraying and pictures taken during the previous treatment. Patients continued to undergo annual follow-up examinations including chest radiograph, abdominal and pelvic computed tomography (CT) or ultrasound (US).

Statistical analysis

Statistical differences were analyzed using chi-squared tests. A *P*-value of less than 0.05 was considered statistically significant. Calculations were made using the Statistical Package for the Social Sciences (SPSS) program (SPSS, version 8.0 for Windows, Tokyo, Japan).

Results

The sizes of resected tumors ranged from 2 to 12 mm in diameter, with an average of 6.4 ± 2.4 mm (≤5 mm, 27 lesions [43%]; ≥6 mm, 36 lesions [57%]). Regarding tumor site, 59 lesions (93.6%) were located in the lower rectum (Rb), three in the upper rectum (Ra) and one in the recto-sigmoid colon (Rs).

We defined complete resection as no lateral and vertical margin involvement of the resected specimen, histopathologically. The complete resection rate was 95.2% (60/63). The complete resection rates for lesions located in the Rb and in the Ra or Rs were

Table 2 Complete resection rates (negative vertical cut margin rate)

		Complete resection rate
All lesions		95.2% (60/63)
Location	Rb	98.3 (58/59)
	Rs, Ra	50.0% (2/4)
Size	≤5 mm	92.6% (25/27)
	≥6 mm	97.2% (35/36)

*$P = 0.79$.

Ra, upper rectum; Rb, lower rectum; Rs, recto-sigmoid colon.

98.3% and 50%, respectively (Table 2). The complete resection rates for lesions ≤5 mm and ≥6 mm were 92.6% (25/27) and 97.2% (35/36), respectively (Table 2).

According to histopathological evaluation, all tumors were located in the submucosal layer, and all were classified as classical-type carcinoids. No lymphovascular invasion was observed in any of the tumors. Three lesions in three patients had margin involvement of the resected specimen (Ra, two lesions: 8 mm and 5 mm; Rb, one lesion: 4 mm). Because the three patients declined further surgical intervention, careful follow up without additional surgery was conducted. No local recurrence or distant metastasis was observed at the last follow-up examinations at 3, 11, and 18 months after treatment (Table 3).

Complications associated with the procedures did not include perforation; however, minor bleeding occurred in five cases (7.9%): four lesions exhibited minor bleeding during the procedure and, in one lesion, bleeding occurred for 4 h after the endoscopic resection. Hemostasis was achieved in all cases with hemoclips; thus, no blood transfusions or surgery was necessary. Neither local recurrence nor distant metastasis has been observed at a median follow up of 24 months (range, 3–54 months).

Discussion

The majority of rectal carcinoid tumors are small, 66% being ≤10 mm in diameter.[2] Rectal carcinoid tumors estimated endoscopically as ≤10 mm in diameter without atypical features and confined to the submucosal layer without lymphovascular invasion rarely metastasize, and are thus considered good candidates for local excision, including endoscopic or transanal resection.[3,16]

Endoscopic resection such as polypectomy or conventional EMR is a more simple and less invasive procedure than surgical resection; however, complete resection of rectal carcinoid tumors is difficult using these techniques, as these tumors, even though small in diameter, are located in the submucosal layer of the rectal wall.[7,8] To resect rectal carcinoid tumors completely, various types of endoscopic resection techniques such as strip biopsy, aspiration resection, band-snare resection, and endosonography probe-guided band ligation have been described as effective[9–15,18] (Table 1). Most of these articles include only a limited number of cases. We have reported that ESMR-L is superior to conventional EMR or polypectomy for complete resection, although the number of cases we investigated was small and included only 14 patients.[13] We conducted this retrospective analysis to establish the effectiveness and safety of ESMR-L in a large number of lesions.

In our study, ESMR-L provided an overall high complete resection rate, 95.2% (60/63) (Table 2). Three lesions resulted in margin involvement after ESMR-L, and were histopathologically considered as incomplete resections. No additional treatment but careful follow up was conducted as the patients wished; however, no local recurrence or distant metastasis was detected within a short period after ESMR-L (Table 3).

Kobayashi *et al.* reported that EUS could be used to determine whether rectal carcinoid tumors are candidates for endoscopic complete resection.[15] They categorized rectal carcinoid tumors with submucosal invasion into the following two groups: SM-D (–), if narrowing of the submucosa (third layer on EUS) by tumor is within the upper two-thirds of the submucosa, and SM-D (+), if narrowing extends to the lower one-third of the submucosa. They reported that the rate of complete endoscopic resection was significantly higher in the SM-D (–) group (96%; 23/24) compared with the SM-D (+) group (73%; 8/11) and concluded that lesions with SM-D (+) invasion on EUS should be treated by transanal endoscopic microsurgery (TEM) or local surgical resection. However, if they applied these criteria to their lesions, eight lesions in the SM-D (+), which could be treated by endoscopic resection, would have been overtreated by surgical resection. EUS is a useful tool for assessing the depth of invasion and size of rectal carcinoid tumors. However, we are concerned that using EUS to determine the treatment indication for rectal carcinoid tumors ≤10 mm, according to their suggestion would result in overtreatment, such as surgical resection.

Ishikawa *et al.* have reported that the wall of the Rb was significantly thicker than that of other sites in the rectum and colon, and they also described that the wall thickness of the upper rectum was not significantly greater than that of the sigmoid colon.[19] Regarding the site of rectal carcinoid tumors, in the present study, the complete resection rate was 98.3% (58/59) in the Rb; in contrast, the complete resection rate was 50% (2/4) in the Ra and Rs (Table 2). As the rectal wall of the Rb is thick and supported by surrounding connective tissue, ESMR-L could be performed with full suction to achieve a deeper vertical margin without perforation. Therefore, it provided a higher complete resection rate in our series. However, rectal carcinoid tumors located in the Ra or Rs resulted in a low complete resection rate. This may have occurred because suction was not sufficient enough to obtain a deeper margin in order to avoid perforation.

The actual number of cases in each location was relatively small, however, so we should increase the number of cases in the future.

Rectal carcinoid tumors are most frequently detected in the rectum, 8 cm from the anorectal junction.[2] Therefore, almost all rectal carcinoid tumors are detected in the Rb, and could be deeply resected by ESMR-L. The most frequent complications associated with endoscopic resection are bleeding and perforation. In our study, we had no perforations Only five lesions resulted in minor bleeding, and all could be easily treated with hemoclips. We experienced no complications requiring surgery or blood transfusions. Therefore, ESMR-L could be performed safely for the resection of rectal carcinoid tumors.

In conclusion, our study showed that, in a large number of cases, ESMR-L has been proven to be a useful and safe procedure to completely resect rectal carcinoid tumors ≤10 mm in diameter, especially those located in the Rb.

Table 3 Characteristics of three lesions with margin involvement

Case	Tumor size (mm)	Location	Depth of invasion	Additional treatment	Recurrence or distant metastasis	Follow-up period (months)
1	4	Rb	sm	(–)	(–)	18
2	5	Ra	sm	(–)	(–)	11
3	8	Ra	sm	(–)	(–)	3

Ra, upper rectum; Rb, lower rectum; sm, submucosal.

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GASTROENTEROLOGY

Detectability of colorectal neoplastic lesions using a narrow-band imaging system: A pilot study

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Abbreviations: HDC, high definition colonoscopy; HNPCC, hereditary nonpolyposis colorectal cancer; IC, indigo carmine; NBI, narrow-band imaging; NCCH, National Cancer Center Hospital; RCCPS, National Cancer Center Research Center for Cancer Prevention and Screening.

Abstract

Background and Aim: Flat and depressed colorectal neoplastic lesions can be difficult to identify using conventional colonoscopy techniques. Narrow-band imaging (NBI) provides unique views especially of mucosal vascular network and helps in visualization of neoplasia by improving contrast. The aim of this study was to assess the feasibility of using NBI for colorectal neoplasia screening.

Methods: Forty-seven consecutive patients, who underwent high definition colonoscopy (HDC) screening examinations revealing neoplastic lesions, were enrolled in our prospective study. No biopsies or resections were performed during the initial HDC, but patients in whom lesions were detected underwent further colonoscopies using NBI, with the results of the first examination blinded from the colonoscopist. They then received appropriate treatment. We compared diagnostic detection rates of neoplastic lesions for HDC and NBI procedures using total number of all identified neoplastic lesions as reference standard.

Results: Altogether, 153 lesions were detected and analyzed in 43 patients. Mean diagnostic extubation times were not significantly different ($P = 0.18$), but the total number of lesions detected by NBI was higher (134 *vs* 116; $P = 0.02$). Based on macroscopic type, flat lesions were identified more often by NBI ($P = 0.04$). As for lesion size, only flat lesions < 5 mm were detected more frequently ($P = 0.046$). Lesions in the right colon were identified more often by NBI ($P = 0.02$), but NBI missed two flat lesions ≥ 10 mm located there.

Conclusions: Narrow band imaging colonoscopy may represent a significant improvement in the detection of flat and diminutive lesions, but a future multi-center controlled trial should be conducted to fully evaluate efficacy for screening colonoscopies.

Introduction

Early detection and removal of colorectal adenomas have been shown to reduce both the incidence of cancer and cancer-related mortality.[1–3] Colonoscopy is considered to be an effective examination method for the detection of colorectal neoplastic lesions,[1,4] but adenomatous polyps are sometimes missed during routine colonoscopies. Studies using back-to-back examinations have found that the undetected rate for adenomatous polyps was approximately 25%[5,6] and even adenomas greater than 1 cm have been missed.

Recent studies have shown that flat and depressed colorectal neoplasms may contribute to the development of colorectal cancers[7–11] although it is difficult to detect such lesions endoscopically. A need exists for better endoscopic visualization, therefore, especially of flat and depressed colorectal lesions. Endoscopic techniques that improve detection of such adenomas will help maximize effectiveness of colonoscopic examinations in diagnosing colorectal cancers.

Narrow-band imaging (NBI) technology is based on modifying spectral features by narrowing spectral transmittance bandwidth using various optical filters.[12] We first reported that it provided a unique view particularly of the mucosal vascular network and the surface structure.[13] Usefulness of NBI has been reported in endoscopic diagnosis of the gastrointestinal tract,[14–21] oro-hypopharynx[22] and bronchus.[23] In the colorectum, previous research on the usefulness of NBI with magnification for differential diagnosis between neoplastic and non-neoplastic lesions has been conducted,[14–16] but there are only a few reports on its effectiveness in actually detecting neoplastic lesions.[24,25]

The aim of our prospective study was to assess the feasibility of using NBI for colorectal neoplasia screening.

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Methods

Patients and study design

The Research Center for Cancer Prevention and Screening (RCCPS) of the National Cancer Center (NCC), Tokyo, Japan, conducted a prospective cohort study including screening colonoscopy on study participants at baseline.[26] High definition colonoscopies (HDCs) using magnification were performed on patients at RCCPS to detect and diagnose neoplastic lesions, but no treatments or biopsies were performed there because of government insurance-imposed restrictions and the need to comply with existing RCCPS and NCC policies. The RCCPS performs colorectal examinations on patients only for screening purposes in order to detect and diagnose neoplastic lesions so this study utilized the cancer screening and treatment system that had already been developed in close cooperation between RCCPS and the adjacent National Cancer Center Hospital (NCCH).

Subjects found to have neoplastic lesions were enrolled in this study and treated at NCCH. Exclusion criteria included patients with advanced colorectal cancer; genetic syndromes such as hereditary non-polypoid colon cancer (HNPCC) and familial adenomatous polyposis; inflammatory bowel disease; or a previous colonic resection. In addition, patients with polypoid lesions $\geq$ 20 mm in size were excluded because such lesions could be readily identified during intubation prior to NBI so those patients were unsuitable for our purposes in comparing detectability between HDC and NBI. Patients with inadequate bowel preparation also were excluded from this study. A total of 47 consecutive patients with neoplastic lesions 5 mm or larger in size detected at RCCPS, who subsequently were scheduled to undergo removal of such lesions at NCCH, were originally enrolled and informed consent was obtained from all of them prior to their participation in this study.

We compared diagnostic detection rates for neoplastic lesions and extubation times using NBI at NCCH to the initial HDCs performed at RCCPS. Colonoscopies were completed to the cecum at both RCCPS and NCCH on every patient in this study.

NBI system

A medical video endoscopic system (EVIS, Lucera Spectrum, Olympus Optical Co., Tokyo, Japan) equipped with sequential illumination was used for the NBI examinations. The filter wheel in the illumination unit had three optical filters[12–14] so that when those filters were placed in the optical illumination system, they eliminated all illumination wavelengths except for two narrow wavelength bands. The central wavelengths of each band were 415 nm and 540 nm, respectively. Video endoscopic systems with CF-H260AZI magnification colonoscopes (Olympus) were used at both RCCPS and NCCH while the NBI system was used only at NCCH.

Adenomatous lesions including those that were flat and depressed could be seen as dark brown lesions without any dye or staining solution and were easily detected while withdrawing the NBI-equipped colonoscope. Capillary enhancement further contributed to improved visibility with this view.[14–16]

High definition colonoscopy (first examination) at RCCPS

Between December 2004 and November 2005, HDCs with magnification were performed at RCCPS for screening purposes only, by five highly experienced colonoscopists who had been trained and previously performed over 1000 colonoscopies at NCCH. The method of colonoscopic examination and diagnostic procedures followed at RCCPS were virtually identical to those followed at NCCH. All detected lesions were sprayed with 0.4% indigo carmine (IC) dye and then classified into one of the three macroscopic types: flat, polypoid or depressed lesions and diagnosed as either neoplastic or non-neoplastic by chromoendoscopy with magnification using Kudo's classification of pit pattern analysis[27] in which Types I and II are non-neoplastic and Types III_L, III_S, IV and V are neoplastic lesions.[28] Detected lesions were diagnosed using magnification chromoscopy, but no biopsies or resections were performed at RCCPS due to NCC intra-institutional restrictions against such procedures. A stopwatch was used to measure withdrawal time during each examination.

Colonoscopy using NBI (second examination) at NCCH

After their first colonoscopic examinations at RCCPS, patients with detected neoplastic lesions 5 mm or larger in size underwent further colonoscopies at NCCH using NBI during withdrawal examinations, with the results from the initial findings blinded from the performing colonoscopists. The further examinations were performed by three highly experienced, but completely different colonoscopists than at RCCPS. Intubations using HDC were performed and then the colonoscope was changed to NBI mode immediately after reaching the cecum. The study's exclusion criteria included patients with inadequate bowel preparation as determined immediately before their withdrawal examinations using NBI. Three colonic segments (right colon; proximal to the splenic flexure; and left colon and rectum) were examined by NBI during extubation without the colonoscopist having prior knowledge of the results from the first HDC until procedure completion. During each NBI colonoscopy, an independent observer with detailed knowledge of findings from the first HDC including polyp location and type watched the entire procedure.

When undergoing magnification for diagnosis of a detected lesion as either neoplastic or non-neoplastic, the NBI system could be changed to standard mode with the touch of a single button. The independent observer determined whether detected lesions were identical between the two colonoscopies based on RCCPS colonoscopic reports and photographs using the back-to-back method. All identified neoplastic lesions were then removed endoscopically unless the patient requested otherwise.

Withdrawal examination results were compared after completion of each colonic segment observation for matching purposes. If the independent observer determined that a lesion had been missed by NBI, the NBI examination was immediately interrupted and the colonoscope was changed to standard mode to look for the missed lesion in that specific segment to determine whether only HDC could identify that particular lesion.

During the NBI colonoscopy, measurement of withdrawal time was stopped temporarily whenever the colonoscopist performed a

Table 1 Examination technique comparisons: withdrawal time, total lesion number and size

	HDC	NBI	*P*-value
Withdrawal Time (Minutes; Mean ± SD)	12.2 ± 5.4	11.2 ± 4.2	0.18
Total Number of Detected Lesions	116	134	0.02
Size of Detected Lesions (mm; Mean ± SD)	5.5 ± 3.1 (Range: 2–20)	5.3 ± 2.8 (Range: 2–20)	0.89

HDC, high definition colonoscopy; NBI, narrow-band imaging; SD, standard deviation.

therapeutic procedure such as a polypectomy, endoscopic mucosal resection (EMR) or hot biopsy, or searched for a missed lesion using the standard mode. As a result, withdrawal times accurately reflected the actual amount of time spent examining the colonic mucosa for lesions using NBI.

Statistical analysis

Using the total of all detected neoplastic lesions including HDC findings at RCCPS and NBI results at NCCH as the reference standard, we compared diagnostic detection rates for neoplastic lesions and extubation times between HDC and NBI examinations. Statistical comparisons were made for each category of data using chi-square, Mann–Whitney *U* and McNemar's tests.

Results

Of the 47 consecutive patients enrolled in this study within an average of 3.4 months (range: 1–7 months) after their first colonoscopic examinations at RCCPS, we comparatively assessed the accuracy of HDC and NBI systems in 43 of those patients including 33 men and 10 women. Four patients (9%) were excluded because of inadequate bowel preparation prior to their NBI examinations. The independent observer was able to ascertain without discrepancy which lesions were detected at RCCPS, NCCH or both facilities. No invasive cancers were identified in any HDC or NBI examinations. Altogether, 153 identified neoplastic lesions were detected and analyzed with no significant difference in mean diagnostic extubation times (HDC/12.2 ± 5.4 min *vs* NBI/11.2 ± 4.2 min; $P = 0.18$).

Detectability in HDC and NBI examinations

The number of neoplastic lesions detected by NBI was higher than the number of neoplastic lesions detected using HDC (NBI/134 lesions *vs* HDC/116 lesions; $P = 0.02$) although mean size of detected neoplastic lesions was not significantly different (HDC/5.5±3.1 mm *vs* NBI/5.3 ± 2.8 mm; $P = 0.89$) (Table 1). Table 2 shows no significant difference in detection rates between the two techniques based on lesion size (< 5 mm, 5–9 mm and ≥ 10 mm in diameter). According to macroscopic type, flat lesions were identified by NBI more often than HDC (flat: NBI/72 lesions *vs* HDC/58 lesions; $P = 0.04$; and polypoid: NBI/62 lesions *vs* HDC/58 lesions; $P = 0.45$), but when lesion size was taken into account, only flat lesions < 5 mm were detected more often by NBI (NBI/44 lesions *vs* HDC/33 lesions; $P = 0.046$) (Table 3). There were no depressed lesions detected by either type of examination. According to location, lesions in the right colon were identified by NBI more often (NBI/87 lesions *vs* HDC/72 lesions; $P = 0.02$) than in the other two colonic locations (Table 2).

Table 2 Detected lesion comparisons: size, macroscopic type and location

	HDC	NBI	*P*-value
Lesion size			
< 5 mm	48	57	0.15
5–9 mm	58	68	0.06
≥ 10 mm	10	9	0.61
Macroscopic type			
Flat Lesion	58	72	0.04
Polypoid Lesion	58	62	0.45
Location			
Right Colon	72	87	0.02
Left Colon	31	36	0.45
Rectum	13	11	> 0.99

HDC, high definition colonoscopy; NBI, narrow-band imaging.

Table 3 Detected lesion comparisons: flat and polypoid lesions by number and size

	HDC	NBI	*P*-value
Total Number of Flat Lesions	58	72	
Number of Lesions			
< 5 mm	33	44	0.046
5–9 mm	22	27	0.27
≥ 10 mm	3	1	0.48
Total Number of Polypoid Lesions	58	62	
Number of Lesions			
< 5 mm	15	13	0.68
5–9 mm	36	41	0.18
≥ 10 mm	7	8	> 0.99

HDC, high definition colonoscopy; NBI, narrow-band imaging.

Among 153 identified neoplastic lesions, 141 were removed endoscopically and histopathological examinations confirmed three intramucosal cancers, 134 tubular adenomas, three hyperplastic polyps and one normal tissue specimen. In terms of the three intramucosal cancers, only one was detected by HDC, but NBI was able to detect all three of them. The positive predictive value for magnification diagnosis of neoplastic lesions was 97.2% (137/141).

Miss rate in HDC and NBI examinations

The overall miss rate using NBI was 12% (19/153). The NBI miss rate was 15% of the 85 flat lesions detected compared to 9% of the 68 polypoid lesions detected, however, there was no significant difference ($P = 0.32$). The NBI miss rates based on lesion size

were < 5 mm, 16%; 5–9 mm, 8%; and ≥ 10 mm, 18%. The NBI miss rates in individual colonic segments were right colon, 11%; left colon, 15%; and rectum, 14%. None of these differences was significant. In comparison, the HDC miss rate for flat lesions (32%; 27/85) was significantly higher than for polypoid lesions (15%; 10/68) ($P = 0.01$) and HDC missed 33% (20/60) of all flat neoplastic lesions located in the right colon. As for sensitivity, NBI was 88% (134/153) and HDC was 76% (116/153) for total lesions and NBI was 87% (52/60) and HDC was 67% (40/60) for flat neoplastic lesions located in the right colon.

In relation to missed lesions ≥ 10 mm, one polypoid lesion was missed during HDC and two flat lesions were missed during NBI. The missed lesion during HDC was an intramucosal cancer 12 mm in diameter in the left colon while the two flat lesions missed during NBI were located in the right colon. One of these two flat lesions was a tubular adenoma 10 mm in size with low grade atypia and the other one, also a tubular adenoma with low grade atypia, was one of 12 lesions detected in a single patient during HDC examination at RCCPS. A repeat HDC at NCCH after changing to standard mode still could not detect this flat lesion 15 mm in size. It was only after chromoendoscopy was performed that this lesion was detected once again.

Discussion

A number of prospective studies in Western countries previously have indicated both the significant prevalence and the clinicopathological relevance of flat and depressed type colorectal lesions. Such lesions are, however, difficult to detect using HDC, a situation that is all the more significant because both adenomas and carcinomas have a higher malignant potential compared to polypoid lesions of similar size.[7–11]

While the NBI system has been shown to be helpful in visualizing neoplasia by improving contrast and is considered to be a new type of 'optical equipment-based image enhanced endoscopy (IEE)',[21] the feasibility of its use for colorectal screening had not been clarified previously. Since it is important to improve detection of neoplastic lesions, particularly flat and depressed type lesions, we decided to evaluate the effectiveness of colonoscopy examinations using NBI compared to HDC.

In this study, NBI improved detection of neoplastic lesions as well as the detection rate of flat and diminutive lesions particularly in the right colon. Since NBI is a contrast detection method that highlights the mucosal vascular network by narrowing spectral transmittance bandwidth using optical color separation filters, we believed that NBI would be useful specifically for enhancing detection of neoplastic lesions especially flat and diminutive lesions.

Although most flat lesions have been reported to be located in the right colon,[7,8] HDC has a higher miss rate in the right colon compared to the left colon.[29,30] In our study, initial HDCs missed 33% of flat neoplastic lesions in the right colon despite such examinations having been performed by highly skilled endoscopists well versed in the significance of non-polypoid lesions. In comparison, the NBI contrast detection method found many lesions that had been overlooked during HDC. As a result, the detection rate for flat lesions in the right colon for the NBI group showed considerable improvement in comparison to HDC. No significant difference in detection rates between NBI and HDC in the left colon or rectum, however, might have been due to the lower prevalence of flat lesions in those locations.

Diminutive lesions seem to have little clinical significance in Western countries because the majority of polyps 5 mm or smaller are hyperplastic and not thought to confer any increased risk for development of colon carcinoma.[31,32] Flat and depressed lesions, however, are considered to have greater malignant potential compared to polypoid lesions of similar size.[7–11] Since there is a possibility of invasive cancers developing from diminutive flat and depressed lesions, we cannot ignore them.

Recently, the use of NBI in HNPCC patients has been reported to significantly increase the detection of flat and diminutive neoplastic lesions in the proximal colon similar to our results.[25] Flat and small adenomas that are particularly prone to malignant transformation occur with greater frequency in the right colon of HNPCC patients[33,34] so it is feasible that NBI will be used in the future for improved surveillance in such patients.

The mechanism for detection of lesions by NBI depends on angiogenic and vascular morphological changes such as elongation of capillaries and venules and moderate increases in microvascular diameters of neoplastic lesions. It has been reported that angiogenesis is critical to the transition of pre-malignant lesions in a hyperproliferative state to the malignant phenotype[16,35] so NBI is a promising advancement in detection of pre-malignant flat lesions. In this study, NBI missed two flat lesions that were tubular adenomas 15 mm and 10 mm in size both with low grade atypia. This could have been because those lesions might have had poor vascularity. It was not ascertained in our study whether NBI was able to emphasize capillary pattern and surface structure of neoplastic lesions with less angiogenic or vascular morphological changes. It is anticipated that further modification and refinement of the NBI system's optical filters will result in improved visualization of even flat lesions with histopathologically low grade atypia that are the most difficult to detect by HDC.

Pancolonic chromoscopy using an IC diffusion spray catheter during extubation from the cecum, which highlighted subtle mucosal irregularities, has been reported to significantly increase detection of diminutive, flat neoplastic lesions in the right colon similar to our results.[36,37] Brooker's extubation times for the IC group, however, were almost twice as long as for the control group.[36] Subsequently, a considerable amount of 0.5% IC was required (median 68 mL; range: 65–90 mL) as indicated in Hurlstone's report.[37] Our NBI examinations took no longer in terms of withdrawal time compared to HDC. In addition, NBI did not require any specialized colonoscopy techniques, suction time for IC was unnecessary and there was no dye solution cost compared to pancolonic chromoscopy using IC. The simple, one-touch conversion from conventional to NBI mode and back again was shown also to be very useful.

This study had several limitations. All patients had at least one lesion as determined by HDC so it was more likely that additional lesions would be found during NBI examinations in this subset of patients with an increased prevalence for lesions. Although it can be argued that colonoscopists doing NBI withdrawal examinations might have been more careful in their observations so as not to miss any lesions detected during HDC, in fact, there was no significant difference in mean diagnostic extubation times. Since the stated aim of our study was to assess the feasibility of using NBI for the screening of colorectal neoplasia, a controlled trial

should be conducted in the future to fully evaluate the efficacy of the NBI system for clinical purposes such as screening colonoscopies. Specificity of NBI and HDC also were not indicated because magnification colonoscopies were used and diagnoses based on Kudo's classification of pit pattern analysis in which Type I and II are non-neoplastic lesions. As a result, we were unable to calculate specificity, but considered it to be over 90% based on a previously reported prospective study.[38] Finally, all HDC and NBI examinations were performed by highly experienced colonoscopists with extensive training at NCCH. It is uncertain whether other colonoscopists would have achieved the same results, especially those with less experience.

During NBI colonoscopy examinations, intestinal fluid and stool were seen as reddish in color similar to blood[14] so a high-quality bowel preparation was a prerequisite for using NBI and advocating reliable bowel preparation should be an important consideration.

In conclusion, colonoscopic examinations using NBI increased the number of neoplastic lesions detected and improved the detection rate of flat and diminutive lesions in the right colon. The NBI system was used to detect and differentiate neoplastic lesions from non-neoplastic lesions without using any dye or staining solutions. Proper and adequate bowel preparation was essential, however, for maximum NBI detection as well as for better results during HDC examinations. As one of the most technologically advanced optical equipment-based IEE systems, NBI has the potential for becoming a new modality in the future for colorectal screening examinations provided there are further improvements in current limitations, most notably better NBI visualization. If NBI is to meet our optimistic expectations, we should begin a multi-center trial as soon as possible.

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