Table 2 Clinical characteristics of patients

	EMR/EPMR	ESD	*p*-Value
Number of lesions	228 (74/154)	145	
Pathology	77/151	45/100	NS
(Adenoma/M-SM1; %)	(34%/66%)	(31%/69%)	NS
Macroscopic type	80/114/34/0	5/63/71/6	
(Is/LST-G/LST-NG/recurrence[a])	(35%/50%/15%/0)	(3%/43%/49%/4%)	<0.0001
Location (Rt/Lt/rectum)	89/52/110	44/28/73	
Tumor size (mean ± SD)	28 ± 8 mm	37 ± 14 mm	0.0006
(range)	(20–95 mm)	(20–140 mm)	
Age (mean ± SD; years)	64 ± 4	64 ± 11	NS

[a] Recurrence included local recurrence after EMR and residual tumor after incomplete en bloc resection

EMR endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *M* intramucosal; *SM* submucosal; *LST-G* laterally spreading tumor granular type; *LST-NG* laterally spreading tumor nongranular type; *Rt* right colon; *Lt* left colon; *SD* standard deviation; *NS* not significant

Table 3 Clinical outcomes

	EMR/EPMR	ESD	*p*-Value
Number of lesions	228 (74/154)	145	
Endoscopic follow-up times (mean ± SD; number)	2.4 ± 1.6	2.0 ± 1.1	NS
(range)	(1–8)	(1–5)	
Endoscopic follow-up periods (mean ± SD; months)	26 ± 17	20 ± 13	NS
(range)	(6–68)	(6–61)	
En bloc resection (%)	74 (33%)	122 (84%)	<0.0001
Recurrence rate (%)	33 (14%)	3 (2%)	<0.0001
En bloc/piecemeal recurrences	2/31	0/3	
Complications			
Perforation	3 (1.3%)	9 (6.2%)	NS
Delayed bleeding	7 (3.1%)	2 (1.4%)	NS
Procedure time (mean ± SD; min)	29 ± 25	108 ± 7	<0.0001
(range)	(3–120)	(15–360)	

EMR endoscopic mucosal resection; *EPMR* endoscopic piecemeal mucosal resection; *ESD* endoscopic submucosal dissection; *SD* standard deviation; *NS* not significant

carcinomas was 69% in the ESD group and 66% in the EMR group (p = NS) (Tables 2 and 3).

Local recurrences rates

There were only three cases (2.1%) of local recurrence in the ESD group during a mean endoscopic follow-up period of 20.0 ± 12.9 months (range 6–61 months). In comparison, local recurrence occurred in 14.5% (33/228) of the lesions in the EMR group during a mean endoscopic follow-up period of 25.9 ± 17.0 months (6–68 months). All three recurrences in the ESD group had previously been resected on a piecemeal basis and each recurrence required one additional EMR. Each of these recurrences was diagnosed histologically as a tubular adenoma and curative resections were achieved for all three. The 33 recurrences in the EMR group involved 2/74 (2.7%) en bloc resections and 31/174 (17.8%) piecemeal resections (Table 3). Twenty-six of the 33 EMR recurrent cases were successfully treated by one additional EMR with the other seven cases needing two sessions of repeat EMR. Two EPMRs required surgery because of invasive recurrence (Fig. 4A–F) while a third piecemeal resection also required surgery because of technical difficulty in performing another EMR despite the intramucosal nature of that particular recurrence.

Duration of recurrence detection

Mean duration of recurrence detection was 6 months (2–18 months) in the EMR group and 6 months (4–6 months) in the ESD group (Table 3).

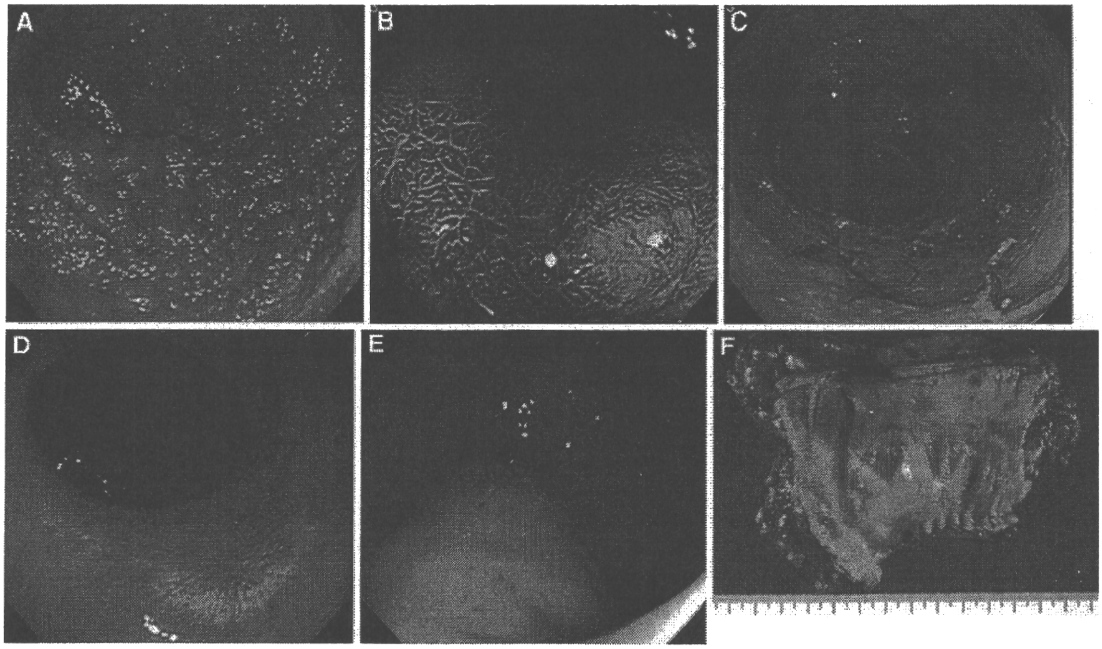

Fig. 4 **A** This case originally involved a large LST-G lesion >3/4 in circumference. **B** Magnified colonoscopy using 0.05% crystal violet staining revealed a noninvasive pattern on the large nodule. **C** An EPMR consisting of more than ten pieces finally resected the entire lesion. Histology revealed an intramucosal carcinoma without any evidence of lymphovascular invasion or a poorly differentiated component so we followed this patient closely without surgery. **D** The third follow-up colonoscopy after 18 months revealed no recurrence. **E** A fourth follow-up was performed 1 year later, at which time a submucosal tumor-like recurrence was found 1 cm from the original EPMR scar. **F** Surgery was performed on this lesion and histology revealed the recurrence of an invasive cancer

Early and late complications

Perforations occurred in 9 out of 145 patients (6.2%) in the ESD group, which was higher compared with the perforation rate of 1.3% (3/228) in the EMR group (p = NS). None of the 12 perforations was delayed and all of them were successfully treated endoscopically using endoclips and managed conservatively.

Minor delayed bleeding occurred in two patients (1.4%) in the ESD group and seven (3.1%) patients in the EMR group (p = NS), but all nine cases were successfully managed conservatively using endoclips with no blood transfusions or additional procedures necessary (Table 3).

Procedure times

The procedure time for ESDs was 108 ± 71 min (15–360 min) compared with 29 ± 25 min (3–120 min) for EMRs, resulting in a significantly shorter procedure time for the EMR group ($p < 0.0001$) (Table 3).

Discussion

This study is, to the best of our knowledge, the first to compare clinical outcomes for colorectal ESD with EMR/EPMR including mid-term follow-up.

For many years, conventional EMR and surgery were the only available treatments for large colorectal tumors, even those detected at an early stage. Conventional EMRs usually resulted in EPMRs particularly for large LSTs ≥20 mm with reports of local recurrence rates ranging from 7.4% to 17% [8, 12, 32]. Most of those recurrences, however, received repeated endoscopic treatment with excellent results regarding preservation of the colorectum [32].

In our series, the introduction of ESD enabled us to effectively treat large colorectal tumors that were LST-NGs and carcinomas, resulting in higher en bloc resection and curability rates compared with conventional EMR. EPMR also was effective in treating many LST-Gs ≥20 mm, with only three cases requiring surgery after such piecemeal resections, including two invasive recurrences cases. Those two cases were originally diagnosed histologically as intramucosal carcinomas without lymphatic or vascular invasion, but both recurrences consisted of invasive carcinomas. We suspect that each case may have originally involved either sm invasion or lymphatic invasion that was not diagnosed histologically because of the increased difficulty in assessing a piecemeal resection. Based on our results, therefore, EPMRs must be performed carefully and close follow-up is required in the event that additional treatment becomes necessary because accurate histological evaluation can be difficult or impossible in

such cases. As an alternative, greater consideration should be given to either ESD or laparoscopic surgery rather than EPMR.

Conventional EMRs in this study had an overall local recurrence rate that was similar to in previous reports [12, 33], as en bloc resection cases resulted in a low recurrence rate of 3%, but piecemeal resections had a considerably higher recurrence rate of 20%. In contrast, ESDs resulted in a significantly higher en bloc resection rate and, consequently, a significantly lower recurrence rate. In those ESDs in which en bloc resections were not achieved, however, the local recurrence rate was approximately 13%, which was much closer to the local recurrence rate for EPMRs. According to our findings, EPMR resulted in a higher recurrence rate compared with ESD, although EPMR produced results similar to those of ESD in relation to preservation of the colorectum.

In this study, we conducted follow-up examinations on patients 6 month after EPMRs and 1 year after EMR en bloc resections, regardless of the lateral margin findings. This was based on our preliminary data [33] indicating that EPMR recurrences were more frequent compared with EMR en bloc resection recurrences and most such EPMR recurrences occurred within 6 months. This current study once again confirmed that most EPMR recurrences were detected after the first 6 months, so such recurrences could continue to be successfully treated endoscopically, supporting the propriety of our follow-up program after EPMR.

As for complications, the perforation rate in the ESD group was 6.2%, which was considerably higher than the 1.3% perforation rate in the EMR group, although there was no statistical difference between the two groups. In other reported series, the perforation rates for colorectal ESDs [8, 27, 28] and EMRs [42] ranged from 1.4% (1/71) to 5.5% (11/200) and 0.31% to 0.93%, respectively, which were similar to our results. The target lesions for ESD in this study, however, were large LSTs that would have been treated by surgery in the past because of the technical difficulty [43]. In fact, the mean tumor size was significantly larger in the ESD group compared with the EMR group so conventional EMRs performed on such lesions undoubtedly would have resulted in a higher complication rate for the EMR group.

All perforation cases were successfully treated conservatively without surgery by endoscopic clipping. As a result, the perforation rate of 6.2% in the ESD group was considered to be acceptable, although further instrument improvements and technique refinements will both be necessary to reduce the perforation rate. The delayed bleeding rate was relatively low in both groups, but particularly in the ESD group, probably because small vessels were coagulated during the ESD procedure.

Considering the additional procedure time and increased cost of ESD devices, it would be difficult to standardize the colorectal ESD procedure on a widespread basis at the present time. We currently select lesions with more serious indications for colorectal ESD that would otherwise be treated surgically. Such ESD patients usually are discharged from the hospital sooner than if surgery had been performed, resulting in reduced medical costs.

Finally, the long-term efficacy of colorectal ESD needs to be established by evaluating an extended follow-up period, although ESD certainly appears to be a feasible alternative to conventional EMR, particularly for certain kinds of colorectal cancers. This study was not a randomized controlled trial, however, and eligibility criteria for the two endoscopy procedures were sometimes unclear for different kinds of lesions. It will be necessary, therefore, to prospectively assess the clinical outcome comparison between ESD and EMR for large colorectal tumors in the future. Another limitation of this study that may have been a source of bias was the exclusion of 40% of the total EMR/EPMR cases from our analysis because follow-up colonoscopy examinations were not carried out at NCCH or could not be ascertained by us.

In conclusion, ESD was selected more often for treating large colorectal tumors because it provided higher en bloc resection and curability rates compared with EMR despite the longer procedure time and higher perforation rate associated with ESD. All ESD perforations, however, could be successfully managed by conservative endoscopic treatment. EMR effectively treated many large colorectal tumors, and only three cases required surgery after EPMRs; such procedures should be carefully performed because it can be more difficult and occasionally impossible to make an accurate histological evaluation, meaning that close follow-up is required in the event that additional treatment is necessary in such cases.

Acknowledgement The authors wish to thank Christopher Dix for helping to edit this manuscript.

References

1. Ahmad NA, Kochman ML, Long WB, Furth EE, Ginsberg GG (2002) Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. Gastrointest Endosc 55: 390–396
2. Yokota T, Sugihara K, Yoshida S (1994) Endoscopic mucosal resection for colorectal neoplastic lesions. Dis Colon Rectum 37: 1108–1111
3. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N (2003) Endoscopic mucosal resection. Gastrointest Endosc 57:567–579
4. Tada M, Murakami A, Karita M, Yanai H, Okita K (1993) Endoscopic resection of early gastric cancer. Endoscopy 25:445–450

5. Deyle P, Largiader F, Jenny S, Fumagalli I (1973) A method for endoscopic electrosection of sessile colonic polyp. Endoscopy 5: 38–40
6. Kudo S (1993) Endoscopic mucosal resection of flat and depressed type of early colorectal cancer. Endoscopy 25:455–461
7. Saito Y, Fujii T, Kondo H, Mukai H, Yokota T, Kozu T et al (2001) Endoscopic treatment for laterally spreading tumors in the colon. Endoscopy 33:682–686
8. Tanaka S, Haruma K, Oka S, Takahashi R, Kunihiro M, Kitadai Y et al (2001) Clinicopathologic features and endoscopic treatment of superficially spreading colorectal neoplasms larger than 20 mm. Gastrointest Endosc 54:62–66
9. Kudo S, Kashida H, Tamura T, Kogure E, Imai Y, Yamano H et al (2000) Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. World J Surg 24:1081–1090
10. Uraoka T, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D et al (2006) Endoscopic indications for endoscopic mucosal resection of laterally spreading tumors in the colorectum. Gut 55:1592–1597
11. Min BH, Lee JH, Kim JJ, Shim SG, Chang DK, Kim YH et al (2009) Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: Comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). Dig Liver Dis 41:201–209
12. Walsh RM, Ackroyd FW, Shellito PC (1992) Endoscopic resection of large sessile colorectal polyps. Gastrointest Endosc 38: 303–309
13. Hosokawa K, Yoshida S (1998) Recent advances in endoscopic mucosal resection for early gastric cancer. Jpn J Cancer Chemother 25:476–483 (in Japanese with English abstract)
14. Ohkuwa M, Hosokawa N, Boku N, Ohtsu H, Tajiri S, Yoshida S (2001) New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 33:221–226
15. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D et al (2001) Endoscopic mucosal resection for treatment of early gastric cancer. Gut 48:225–229
16. Kondo H, Gotoda T, Ono H, Oda I, Kozu T, Fujishiro M et al (2004) Percutaneous traction-assisted EMR by using an insulation-tipped electrosurgical knife for early stage gastric cancer. Gastrointest Endosc 59:284–288
17. Kobayashi T, Gotohda T, Tamakawa K, Ueda H, Kakizoe T (2004) Magnetic anchor for more effective endoscopic mucosal resection. Jpn J Clin Oncol 34:118–123
18. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D et al (1999) A new endoscopic resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. Gastrointest Endosc 50:560–563
19. Kodashima S, Fujishiro M, Yahagi N, Kakushima N, Omata M (2006) Endoscopic submucosal dissection using flexknife. J Clin Gastroenterol 40:378–384
20. Sano Y, Fu KI, Saito Y, Doi T, Hanafusa M, Fujii S et al (2006) A newly developed bipolar-current needle-knife for endoscopic submucosal dissection of large colorectal tumors. Endoscopy 38(Suppl 5):E95
21. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y et al (2007) A pilot study to assess safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection under conscious sedation. Gastrointest Endosc 65: 537–542
22. Yamamoto H, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K et al (2002) Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. Gastrointest Endosc 56: 507–512
23. Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T et al (2003) Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 35:690–694
24. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y et al (2007) Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc 66(5):966–973
25. Antillon MR, Bartalos CR, Miller ML, Diaz-Arias AA, Ibdah JA, Marshall JB (2008) En bloc endoscopic submucosal dissection of a 14-cm laterally spreading adenoma of the rectum with involvement to the anal canal: expanding the frontiers of endoscopic surgery (with video). Gastrointest Endosc 67:332–337
26. Uraoka T, Kato J, Ishikawa S, Harada K, Kuriyama M, Takemoto K et al (2007) Thin endoscope-assisted endoscopic submucosal dissection for large colorectal tumors (with videos). Gastrointest Endosc 66:836–839
27. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S et al (2007) Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. Clin Gastroenterol Hepatol 5(6):674–677
28. Tamegai Y, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E et al (2007) Endoscopic submucosal dissection: a safe technique for colorectal tumors. Endoscopy 39:418–422
29. Fujii T, Hasegawa RT, Saitoh Y, Fleischer D, Saito Y, Sano Y et al (2001) Chromoscopy during colonoscopy. Endoscopy 33:1036–1041
30. Saito Y, Emura F, Matsuda T, Saito D, Fujii T (2004) Invasive pattern is an indication for surgical treatment (letter to the editor). Gut online (serial online), Mar. Available at http://gut.bmjjournals.com/cgi/eletters/53/2/284
31. Matsuda T, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N et al (2008) Efficacy of the invasive/non-invasive pattern by magnifying estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 103(11):2700–2706
32. Uraoka T, Fujii T, Saito Y, Sumiyoshi T, Emura F, Bhandari P et al (2005) Effectiveness of glycerol as a submucosal injection for EMR. Gastrointest Endosc 61:736–740
33. Yamamoto H, Sekine Y, Higashizawa T, Kihira K, Kaneko Y, Hosoya Y et al (2001) Successful en-bloc resection of a large superficial gastric cancer by using sodium hyaluronate and electrocautery incision forceps. Gastrointest Endosc 54:629–632
34. Kitajima K, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H et al (2004) Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol 39: 534–543
35. Japanese Research Society for Cancer of the Colon and Rectum (1998) General rules for clinical and pathological studies on cancer of the colon, rectum and anus: histopathological classification, 6th edn. Kanehara Syuppan, Tokyo, pp 60–90
36. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM et al (2000) The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47:251–255
37. Hotta K, Fujii T, Saito Y, Matsuda T (2009) Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 24(2):225–230
38. Hurlstone DP, Cross SS, Brown S, Sanders DS, Lobo AJ (2004) A prospective evaluation of high-magnification chromoscopic colonoscopy in predicting completeness of EMR. Gastrointest Endosc 59:642–650
39. Kato S, Fujii T, Koba I, Sano Y, Fu KI, Parra-Blanco A et al (2001) Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying: can significant lesions be distinguished? Endoscopy 33:306–310
40. Fu KI, Sano Y, Kato S, Fujii T, Nagashima F, Yoshino T et al (2004) Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for

differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. Endoscopy 36:1089–1093
41. Emura F, Saito Y, Taniguchi M, Fujii T, Tagawa K, Yamakado M (2007) Further validation of magnifying chromocolonoscopy to differentiate colorectal neoplastic polyps in a health screening center. J Gastroenterol Hepatol 22:1722–1727
42. Taku K, Sano Y, Fu KI, Saito Y, Matsuda T, Uraoka T et al (2007) Iatrogenic perforation associated with therapeutic colonoscopy: a multicenter study in Japan. J Gastroenterol Hepatol 22(9):1409–1414
43. Kobayashi N, Saito Y, Uraoka T, Matsuda T, Suzuki H, Fujii T (in press) Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of colorectal endoscopic submucosal dissection. J Gastroenterol Hepatol

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i3.392

World J Gastroenterol 2010 January 21; 16(3): 392-394
ISSN 1007-9327 (print)

CASE REPORT

A laterally-spreading tumor in a colonic interposition treated by endoscopic submucosal dissection

Hideaki Bando, Hiroaki Ikematsu, Kuang-I Fu, Yasuhiro Oono, Takashi Kojima, Keiko Minashi, Tomonori Yano, Takahisa Matsuda, Yutaka Saito, Kazuhiro Kaneko, Atsushi Ohtsu

Hideaki Bando, Hiroaki Ikematsu, Yasuhiro Oono, Takashi Kojima, Keiko Minashi, Tomonori Yano, Kazuhiro Kaneko, Atsushi Ohtsu, Department of Gastrointestinal Oncology & Endoscopy, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan
Kuang-I Fu, Department of Gastroenterology, Juntendou University Nerima Hospital, Tokyo 177-0033, Japan
Takahisa Matsuda, Yutaka Saito, Endoscopy Division, National Cancer Center Hospital, Tokyo 104-0045, Japan
Author contributions: Bando H designed the research, collected, analyzed and interpreted the data; Ikematsu H, Fu KI, Oono Y, Kojima T, Minashi K, Yano T, Matsuda T, Saito Y, Kaneko K and Ohtsu A wrote and revised the paper.
Correspondence to: Hiroaki Ikematsu, MD, Department of Gastrointestinal Oncology & Endoscopy, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan. hikemats@east.ncc.go.jp
Telephone: +81-4-71331111 Fax: +81-4-71346928
Received: September 5, 2009 Revised: October 13, 2009
Accepted: October 20, 2009
Published online: January 21, 2010

Abstract

Herein we describe an early colonic carcinoma which developed in a colonic interposition 14 years after surgery for esophageal cancer, which was successfully treated by endoscopic submucosal dissection (ESD). An 80-year-old man underwent colonic interposition between the upper esophagus and stomach after surgery for an early esophageal squamous cell carcinoma in 1994. He received a surveillance endoscopy, and a laterally-spreading tumor of granular type, approximately 20 mm in size, was identified in the colonic interposition. An endoscopic biopsy revealed moderately differentiated adenocarcinoma histologically, however, we diagnosed the lesion as an intramucosal carcinoma based on the endoscopic findings. The lesion was safely and completely removed *en bloc* by ESD using a bipolar knife. Histologically, the lesion was an intramucosal moderately differentiated adenocarcinoma in a tubular adenoma.

Key words: Colonic interposition; Early colonic carcinoma; Endoscopic submucosal dissection

Peer reviewers: Christopher Mantyh, MD, Associate Professor, Department of Surgery, Duke University Medical Center, Box 3117, Durham, NC 2771, United States; Ming-Te Huang, Professor, Department of Surgery, Taipei Medical University-Shuang Ho Hospital, Taipei 23561, Taiwan, China

Bando H, Ikematsu H, Fu KI, Oono Y, Kojima T, Minashi K, Yano T, Matsuda T, Saito Y, Kaneko K, Ohtsu A. A laterally-spreading tumor in a colonic interposition treated by endoscopic submucosal dissection. *World J Gastroenterol* 2010; 16(3): 392-394 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i3/392.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i3.392

INTRODUCTION

Although rarely reported, adenoma and adenocarcinoma can occur as a late complication in colon segments used to replace the esophagus. Herein, we describe an early colonic carcinoma which developed in a colonic interposition 14 years after surgery for esophageal cancer, which was successfully treated by endoscopic submucosal dissection (ESD).

CASE REPORT

An 80-year-old man underwent colonic interposition between the upper esophagus and stomach after surgery for an early esophageal squamous cell carcinoma (T1, N0, M0, stage I according to the TNM classification) in 1994. He received an esophagogastroduodenoscopy for surveillance and a laterally-spreading tumor of granular type (LST-G), approximately 20 mm in size, was identified in the colonic interposition. On conventional view, a

Table 1 Summary of reported cases of neoplasia arising in a colonic interposition

Case	Authors	Age	Gender	Size (mm)	Histology	Period after surgery (yr)	Follow up	Therapy	Course
1	Goldsmith *et al*[5], 1968	48	F	50	Adenocarcinoma	2	+	Surgery	Follow up
2	Szántó *et al*[6], 1981	65	M	5	Adenomatous polyp	1	-	Polypectomy	Follow up
3	Haerr *et al*[7], 1987	72	M	NI	Adenocarcinoma	9	+	Radiation chemotherapy	Death
4	Houghton *et al*[8], 1989	64	M	NI	Adenocarcinoma	20	-	Surgery	Follow up
5	Theile *et al*[9], 1992	68	M	29	Adenocarcinoma	12	NI	Surgery	Follow up
6	Lee *et al*[10], 1994	75	F	NI	Adenocarcinoma	20	+	Surgery	Follow up
7	Altorjay *et al*[11], 1995	NI	M	60	Adenomatoid polyp	6	+	Surgery	Death
				NI	Carcinoma				
8	Kovacs *et al*[12], 1997	8	M	9	Tubular adenoma	13	+	Polypectomy	Follow up
				11	Tubular adenoma				
9	Altomare *et al*[13], 2006	64	M	6	Tubular adenoma	7	+	Polypectomy	Follow up
10	Present case, 2008	80	M	25	Adenocarcinoma in tubular adenoma	14	-	ESD	Follow up

ESD: Endoscopic submucosal dissection; NI: No information.

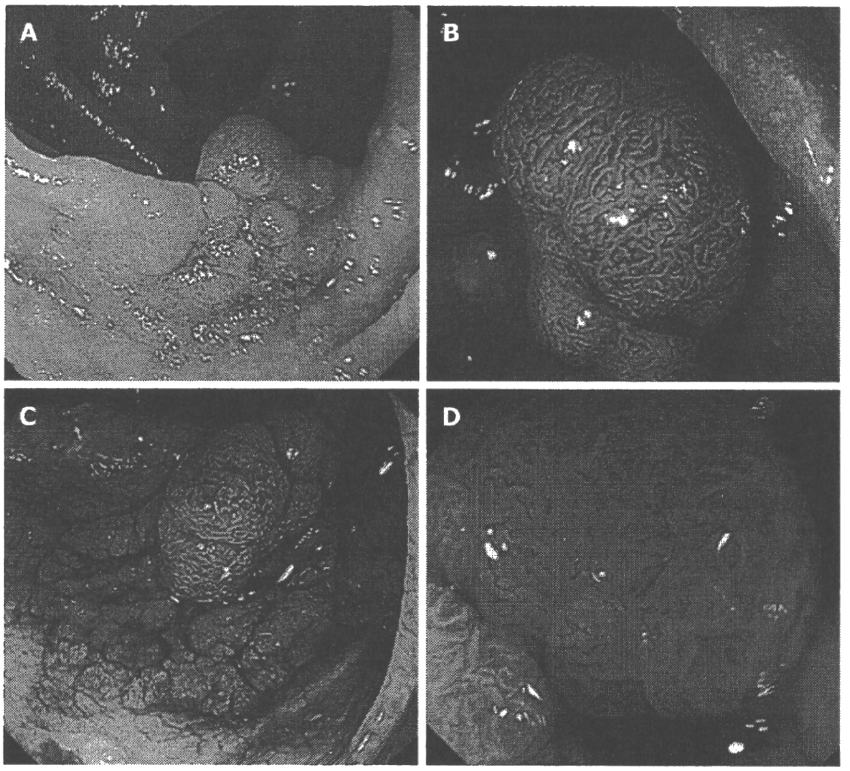

Figure 1 A laterally-spreading tumor of granular type (LST-G) in the colonic interposition was shown at colonoscopy. Narrow-band imaging with magnification revealed a capillary pattern type Ⅱ. Magnifying chromoendoscopy using 0.4% indigo carmine revealed a type Ⅳ pit pattern. A: Conventional view; B: Narrow-band imaging with magnification; C: Chromoendoscopy with 0.4% indigo carmine; D: Magnifying chromoendoscopy using 0.4% indigo carmine dye spraying.

Figure 2 Histologically, the resected specimen showed an intramucosal adenocarcinoma in a tubular adenoma. Cross sectional view (HE, magnification × 5).

large, reddish nodule was detected in the lesion. With magnifying narrow-band imaging (NBI) observation, the lesion revealed a capillary pattern type Ⅱ according to Sano's classification[1], and a type Ⅳ pit pattern according to Kudo's classification was detected under magnifying chromoendoscopy using 0.4% Indigo carmine dye spraying[2]. An endoscopic biopsy was taken from the large nodule and a histological diagnosis of moderately differentiated adenocarcinoma was established, however, we diagnosed the lesion as an intramucosal carcinoma based on the above endoscopic findings (Figure 1). Thus, the lesion was considered a good candidate for endoscopic

resection. The lesion was safely and completely removed *en bloc* by ESD using a bipolar knife (B-knife® XEMEX Co. Ltd. Tokyo, Japan)[3,4]. Histologically, the lesion was an intramucosal moderately differentiated adenocarcinoma in a tubular adenoma. Lateral and vertical margins of the specimen were negative. There was no lymphatic and venous invasion (Figure 2). The patient was hospitalized for 6 d after ESD to confirm the absence of complications such as delayed perforation, and was then discharged.

DISCUSSION

Despite the fact that many interposition grafts are performed for malignant esophageal disease, to the best of our knowledge, there have only been 10 reported cases, including four adenomatous polyps and six adenocarcinomas, arising in a colonic interposition (Table 1)[5-13]. Because the sizes of the adenomatous polyps in the reported cases were small, they were treated with polypectomy. Reoperation or chemoradiotherapy was performed in patients with cancers. Therefore, this is the first case of an early adenocarcinoma in a colonic interposition resected by ESD.

We performed ESD instead of endoscopic mucosal resection (EMR) in this case, as the lesion was not well-elevated even after submucosal injection of glycerol. This phenomenon is the so-called "non-lifting sign positive" as determined by Uno *et al*[14]. As our endoscopic diagnosis of an intramucosal carcinoma was established with magnifying NBI and chromoendoscopy, submucosal benign fibrosis rather than desmoplastic reaction created by invasive cancer was considered to cause the non-lifting sign positive. EMR for the lesion with the non-lifting sign positive may result in incomplete resection or unfavorable complications such as colonic perforation. During ESD, hyaluronic acid was additionally injected into the submucosal layer and a transparent hood was attached to the tip of the scope for better submucosal dissection[15]. To reduce deep burn to the muscle layer, we used a bipolar knife instead of a monopolar knife. To reduce operating time, we used a bipolar snare to remove the lesion after adequate dissection. These efforts enabled us to completely and safely remove the lesion *en bloc* without complication. Furthermore, the patient's colonic interposition was reconstructed using the subcutaneous route, and thus the risk of mediastinitis even if perforation occurred was lower than that if reconstructed substantially.

Despite the fact that many interposition grafts are performed for malignant esophageal disease, few reports of adenocarcinoma arising in a colonic interposition have been reported. It is commonly thought that patients who have esophageal malignancy carry a dismal prognosis, and few of these patients will survive long enough to develop colonic adenocarcinoma. However, with recent progress in chemotherapy, many patients have long-term survival. Almost all case reports presenting with adenoma or adenocarcinoma arise five or more years after colonic interposition surgery, and there are only two case reports where adenoma or adenocarcinoma in the colonic interposition has arisen 1 or 2 years after surgery (Table 1). In our case, adenocarcinoma in a tubular adenoma was detected 14 years postoperatively. Colonoscopic screening is usually performed before colonic interposition. However, Heresbach *et al*[16] reported an overall miss rate of 23.4% in the colonoscopic detection of neoplasia including both adenomas and colorectal cancers. Therefore, we recommend upper endoscopic screening within 1 year of colonic interposition and periodic surveillance, as lesions may be detected early and removed safely by endoscopy.

REFERENCES

1 **Sano Y**, Ikematsu H, Fu KI, Emura F, Katagiri A, Horimatsu T, Kaneko K, Soetikno R, Yoshida S. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. *Gastrointest Endosc* 2009; **69**: 278-283

2 **Kudo S**, Rubio CA, Teixeira CR, Kashida H, Kogure E. Pit pattern in colorectal neoplasia: endoscopic magnifying view. *Endoscopy* 2001; **33**: 367-373

3 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973

4 **Sano Y**, Fu KI, Saito Y, Doi T, Hanafusa M, Fujii S, Fujimori T, Ohtsu A. A newly developed bipolar-current needle-knife for endoscopic submucosal dissection of large colorectal tumors. *Endoscopy* 2006; **38** Suppl 2: E95

5 **Goldsmith HS**, Beattie EJ Jr. Malignant villous tumor in a colon bypass. *Ann Surg* 1968; **167**: 98-100

6 **Szántó I**, Kiss J, Vámosi-Nagy I, Vörös A. Endoscopic polypectomy in the segment of colon used for oesophageal replacement. *Endoscopy* 1981; **13**: 134

7 **Haerr RW**, Higgins EM, Seymore CH, el-Mahdi AM. Adenocarcinoma arising in a colonic interposition following resection of squamous cell esophageal cancer. *Cancer* 1987; **60**: 2304-2307

8 **Houghton AD**, Jourdan M, McColl I. Dukes A carcinoma after colonic interposition for oesophageal stricture. *Gut* 1989; **30**: 880-881

9 **Theile DE**, Smithers BM, Strong RW, Windsor CJ. Primary adenocarcinoma in a colonic 'oesophageal' segment. *Aust N Z J Surg* 1992; **62**: 158-160

10 **Lee SJ**, Koay CB, Thompson H, Nicolaides AR, Das Gupta AR. Adenocarcinoma arising in an oesophageal colonic interposition graft. *J Laryngol Otol* 1994; **108**: 80-83

11 **Altorjay A**, Kiss J, Vörös A, Szanto I, Bohak A. Malignant tumor developed in colon-esophagus. *Hepatogastroenterology* 1995; **42**: 797-799

12 **Kovacs BJ**, Griffin RA, Chen YK. Synchronous adenomas in a colonic interposition graft and the native colon. *Am J Gastroenterol* 1997; **92**: 2303-2304

13 **Altomare JF**, Komar MJ. A tubular adenoma arising in a colonic interposition. *J Clin Gastroenterol* 2006; **40**: 765-766

14 **Uno Y**, Munakata A. The non-lifting sign of invasive colon cancer. *Gastrointest Endosc* 1994; **40**: 485-489

15 **Yamamoto H**, Yahagi N, Oyama T, Gotoda T, Doi T, Hirasaki S, Shimoda T, Sugano K, Tajiri H, Takekoshi T, Saito D. Usefulness and safety of 0.4% sodium hyaluronate solution as a submucosal fluid "cushion" in endoscopic resection for gastric neoplasms: a prospective multicenter trial. *Gastrointest Endosc* 2008; **67**: 830-839

16 **Heresbach D**, Barrioz T, Lapalus MG, Coumaros D, Bauret P, Potier P, Sautereau D, Boustière C, Grimaud JC, Barthélémy C, Sée J, Serraj I, D'Halluin PN, Branger B, Ponchon T. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. *Endoscopy* 2008; **40**: 284-290

S-Editor Wang JL **L-Editor** Webster JR **E-Editor** Tian L

Surg Endosc (2010) 24:2231–2235
DOI 10.1007/s00464-010-0939-8

Transcutaneous monitoring of partial pressure of carbon dioxide during endoscopic submucosal dissection of early colorectal neoplasia with carbon dioxide insufflation: a prospective study

Tsuyoshi Kikuchi · Kuang-I Fu · Yutaka Saito · Toshio Uraoka · Masakatsu Fukuzawa · Syusei Fukunaga · Taku Sakamoto · Takeshi Nakajima · Takahisa Matsuda

Received: 24 June 2009 / Accepted: 15 November 2009 / Published online: 23 February 2010

Abstract
Background The authors have reported that carbon dioxide (CO_2) insufflation is safe and effective for lengthy endoscopic submucosal dissection (ESD) with the patient under conscious sedation. However, CO_2 monitoring has not been assessed to clarify whether partial pressure of carbon dioxide (PCO_2) increases during this type of long procedure. This study aimed to monitor CO_2 before, during, and after ESD to investigate whether CO_2 insufflation is safe for patients receiving a lengthy ESD of early colorectal neoplasia under conscious sedation.
Methods This study prospectively enrolled 35 consecutive patients who underwent ESD at the National Cancer Center Hospital. Transcutaneous PCO_2 ($PtcCO_2$) was measured with a noninvasive sensor before, during, and after ESD for patients under conscious sedation using midazolam.
Results The mean size of removed lesions was 44 ± 22 mm (range, 15–100 mm). The operation time was 90 ± 100 min (range, 15–600 mm). The dose of midazolam was 5.7 ± 4.0 mg (range, 2–19 mg). The mean $PtcCO_2$ was 41 ± 5 mmHg (range, 33–53 mmHg) before ESD and 44 ± 6 mmHg (range, 32–54 mmHg) afterward. The mean peak $PtcCO_2$ during ESD was 55 ± 7 mmHg (range, 39–78 mmHg), which was significantly higher than before or after ESD ($p < 0.0001$). However, no complication associated with CO_2 insufflation such as CO_2 narcosis, gas embolism, or arrhythmia needing treatment was seen in any of the cases.
Conclusions This study suggests that CO_2 insufflation is safe for patients receiving a lengthy colorectal ESD under conscious sedation.

Keywords Carbon dioxide insufflation · Endoscopic submucosal dissection · Transcutaneous measurement of PCO_2

Carbon dioxide (CO_2) insufflation is reported to reduce patient pain and abdominal discomfort during and after colonoscopy [1, 2]. The safety and efficacy of CO_2 insufflation during colonoscopy also has been assessed previously [3–5].

On the other hand, endoscopic submucosal dissection (ESD) is a novel and minimally invasive treatment for early gastrointestinal neoplasia [6]. However, even if performed by an expert, this therapeutic procedure often requires more than 1 or 2 h for the removal of a superficial colorectal tumor 40 mm or larger. For such long therapeutic procedures, if air insufflation is applied, a considerable amount of air enters the colonic lumen, causing severe intra- and postoperative abdominal discomfort or pain.

We have previously conducted a case–control study to show that CO_2 insufflation is safe and effective for colorectal ESD [7]. In the previous study, however, the arterial partial pressure of CO_2 (pCO_2) was measured only before and after ESD and showed no significant increase in CO_2 after ESD. It still is unknown whether CO_2 increases significantly during ESD. Furthermore, sedatives used during ESD also may cause hypoxemia and hypoventilation,

T. Kikuchi · Y. Saito (✉) · T. Uraoka · M. Fukuzawa · S. Fukunaga · T. Sakamoto · T. Nakajima · T. Matsuda
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: ytsaito@ncc.go.jp

K.-I. Fu
Department of Gastroenterology, Juntendo University Nerima Hospital, Tokyo, Japan

resulting in CO_2 retention [8]. Therefore, to determine whether CO_2 insufflation is safe during ESD, we conducted this study to monitor CO_2 throughout ESD.

Recently, a new sensor for combined assessment of pulse oximetry oxygen saturation (SpO_2) and transcutaneous measurement of PCO_2 ($PtcCO_2$) has been introduced (TOSCA monitor; Linde Medical Sensors, Basel, Switzerland). In the current study, we used this machine for continuous monitoring of ventilation because it provides a simple and noninvasive technique.

Patients and methods

Patients

This study enrolled 35 consecutive patients between February 2006 and November 2006 at the National Cancer Center Hospital (NCCH) in Tokyo. All ESD procedures were performed by two highly experienced colonoscopists (Y.S., T.U.). Patients with severe chronic occlusive pulmonary disease, severe heart disease (New York Heart Association [NYHA] classification 3 or 4), and known CO_2 retention were excluded from the study. Furthermore, arterial blood gas was measured for all patients before ESD, and the patients with abnormal levels of arterial blood gas were excluded from this study.

The ethics committee of the NCCH approved the study protocol. Written informed consents were obtained from all the studied patients before the ESD procedures.

Methods

Endoscopic procedures

The procedures were performed using Olympus video colonoscopes (OLYMPUS MEDICAL SYSTEMS, CORP., Tokyo, Japan). Carbon dioxide was administered using a CO_2 regulator (UCR; OLYMPUS MEDICAL SYSTEMS, CORP., Tokyo, Japan) connected to the endoscope supply tube by means of a "quick lock" connector, and a flow indicator provided visual confirmation that CO_2 was being delivered.

During the procedures, CO_2 was constantly set at 1.5 l/min. All the patients were prepared for colonoscopy with 2 to 3 l of polyethylene glycol-electrolyte solution administered the morning of examination day. To avoid bowel movement, scopolamine butylbromide (10 mg) or glucagon (0.5 mg) was administered intravenously (IV) for patients with no contraindication before examination. In all cases, midazolam (2 mg, IV) was used before insertion of the colonoscope. In addition, 2 mg was given repeatedly when necessary based on each endoscopist's judgment. To delineate the margin of the lesions before their removal, 0.4% indigo carmine dye spraying was performed (Fig. 1A, B).

A circumferential incision in the mucosa was made with a bipolar needleknife (B-knife) (XEMEX Co., Tokyo, Japan) after a submucosal injection of glycerol (Chugai Pharmaceutical Co, Ltd, Tokyo, Japan) [6]. Thereafter, a sodium hyaluronate solution was injected into the submucosa layer to lift the lesion, and the thickened submucosal layer was cut with a B-knife and an insulation-tip knife (IT-knife) (OLYMPUS MEDICAL SYSTEMS, CORP., Tokyo, Japan) (Fig. 1C, D). The operation time was recorded for all the patients.

Transcutaneous CO_2 monitoring

Transcutaneous PCO_2 ($PtcCO_2$) was measured with a noninvasive sensor (TOSCA Monitor) for combined assessment of pulse oximetry oxygen saturation (SpO_2) and $PtcCO_2$ in this study (Fig. 2) [9]. This fully digital sensor comprises the basic element of a Severinghaus-type PCO_2 sensor and the basic elements of a pulse oximeter sensor.

The sensor was attached to the ear lobe using an adhesive holder that integrates a reflective element positioned onto the inner surface of the ear lobe to allow transmissive-reflective pulse oximetry with red-infrared absorption analysis of the arterial pulse signal. The sensor temperature is selectable in a range of 37–45°C in steps of 0.5°C using two independent circuits to provide a safe and reliable control with an accuracy of +0.2°C.

For this study, we used the default temperature setting of 42°C to improve local arterialization and to accelerate CO_2 diffusion. Measurement of $PtcCO_2$ is based on the fact that CO_2 diffuses through body tissues and can be detected by a sensor with a gas-permeable membrane at the skin surface.

Statistical analysis

All the variables in this study are described as mean ± standard deviation. The *t*-test was used to compare the continuous variables of $PtcCO_2$ assessed before, during, and after ESD. All statistical analyses were performed by using SAS version 8.0 (SAS Institute Inc, Cary, NC, USA). The *p* values were two-sided, and those less than 0.05 were used to determine statistical significance.

Results

In this study, 35 patients (20 men and 15 women; mean age, 65.4 years; range, 32–85 years) with 35 lesions underwent ESD. The mean tumor size was 44 ± 22 mm (range, 15–100 mm). All the tumors were resected en bloc by ESD. The mean dosage of midazolam was 5.7 ± 3.5 mg

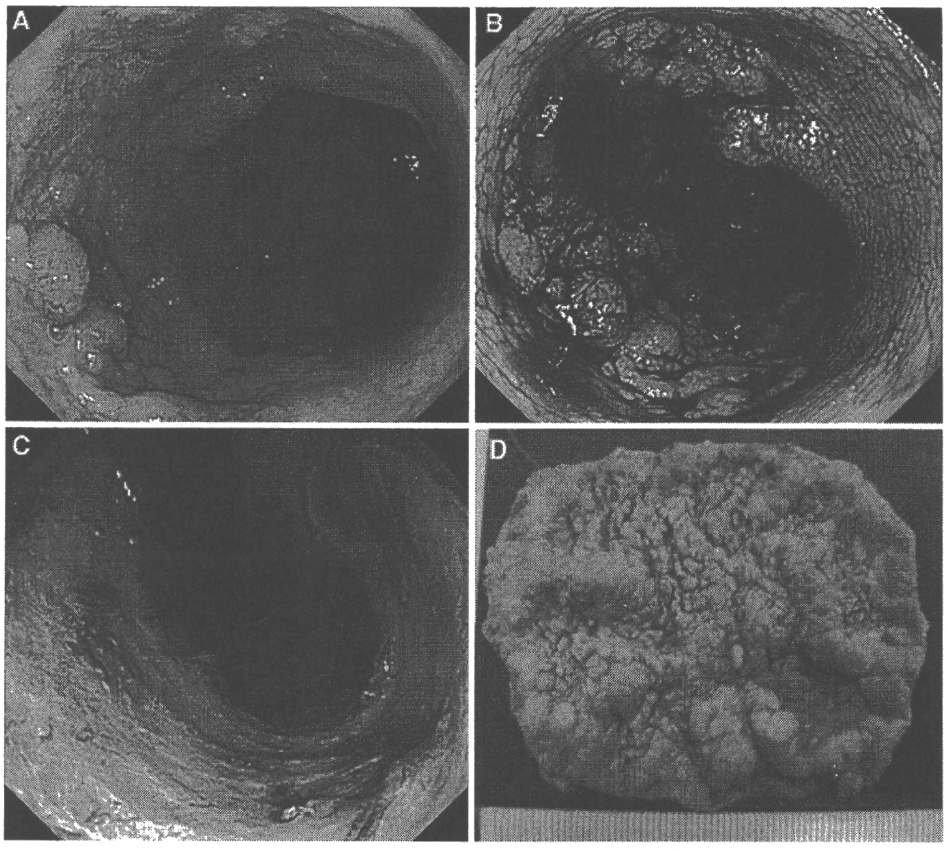

Fig. 1 **A** A laterally spreading tumor (granular type) detected in the sigmoid colon. **B** After 0.4% indigo-carmine dye spraying, the margin of the lesion was delineated, and the size was estimated endoscopically to be 75 mm. **C** The scope, retroflexed in the sigmoid colon, showed that the lesion was completely removed without complication by endoscopic submucosal dissection (ESD) using the B-knife and IT knife. **D** The resected specimen fixed by 10% formalin was 80 mm in size. Histologically, the lesion was an intramucosal carcinoma in adenoma, which was completely removed by ESD

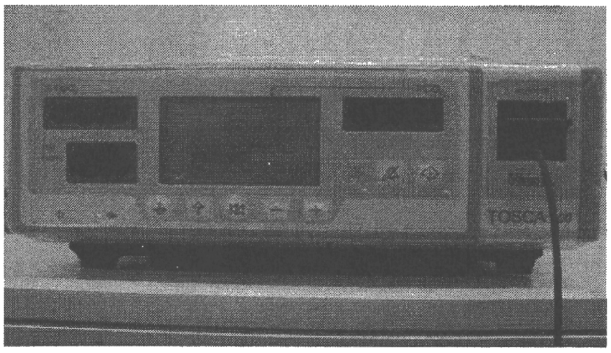

Fig. 2 TOSCA monitor (Linde Medical Sensors, Basel, Switzerland)

Table 1 Clinicopathologic characteristics of the resected patients

No. of cases	35
Gender (male/female)	20/15
Mean age: years (range)	65.4 ± 19.4 (32–85)
Tumor size: mm (range)	44 ± 22 (15–100)
Operation time: min (range)	90 ± 100 (15–600)
Dose of midazolam: mg (range)	5.7 ± 4.0 (2–19)
Tumor location	
Right colon	17
Left colon	13
Rectum	5

during the procedure. The median operation time was 90 min (mean, 100 min; range, 15–600 min). The clinicopathologic details are summarized in Table 1. No delayed bleeding, perforation, or other complication associated with ESD was observed in any of the cases in this study.

Transcutaneous CO_2 monitoring

The mean $PtcCO_2$ value before ESD was 41 ± 5 mmHg (range, 33–53 mmHg). The mean $PtcCO_2$ value after ESD was 44 ± 6 mmHg (range, 32–54 mmHg). The mean peak $PtcCO_2$ was 55 ± 7 mmHg (range, 39–78 mmHg), which was significantly higher than the mean $PtcCO_2$ values before and after ESD ($p < 0.0001$). Although, the $PtcCO_2$ peak value exceeded 60 mmHg in three cases, no complication associated with CO_2 insufflation such as CO_2 narcosis, gas embolism, or arrhythmia that needed treatment was seen in any of the cases. The trends of $PtcCO_2$ during ESD are shown in Fig. 3 (Table 2).

Discussion

The current study is, to the best of our knowledge, the first study to monitor CO_2 throughout ESD and subsequently show that CO_2 insufflation during ESD does not lead to a

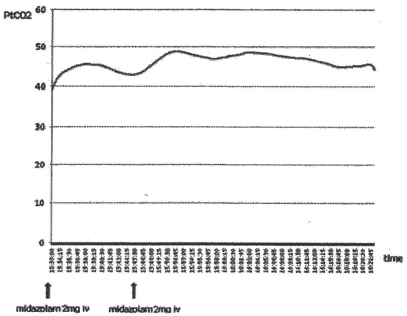

Fig. 3 The trends of transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) during endoscopic submucosal dissection (ESD)

Table 2 Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) monitoring before, during, and after endoscopic submucosal dissection (ESD)

Mean $PtcCO_2$ before ESD: mmHg (range)	41 ± 5 (33–53)
Peak $PtcCO_2$ during ESD: mmHg (range)	55 ± 7 (39–78)
$PtcCO_2$ after ESD: mmHg (range)	44 ± 6 (32–54)

clinically significant rise in the $PtcCO_2$ level, even for patients receiving conscious sedation. The importance of perioperative monitoring of pulmonary gas exchange is undisputed. Pulse oximeter (measurement of SpO_2) is a reliable and standard method for monitoring oxygenation, but it frequently is necessary to determine PCO_2 as well to assess the respiratory status of the patient, especially when CO_2 insufflation is used.

In the current study, we used a miniature combined SpO_2/PCO_2 sensor (TOSCA monitor) for the continuous and noninvasive measurement of oxygenation and CO_2 tension that can be applied at the ear lobe. Transcutaneous measurement of PCO_2 is based on the fact that CO_2 gas can diffuse through body tissue and skin and be detected by a sensor at the skin surface [10]. Moreover, measurements of $PtcCO_2$ obtained with this device are shown to have a good correlation with arterial CO_2 values [11]. Corrected $PtcCO_2$ measurements correlate well with $PaCO_2$ values in virtually all clinical conditions, and typically are higher by 5–6 mmHg. The difference is attributable to skin metabolism and arteriole-cellular CO_2 difference [12, 13].

Insufflation of CO_2 into the colon could lead to arterial CO_2 retention and subsequent acidosis because CO_2 acts as an acid in the human body [14, 15].Theoretically, the development of severe acidosis can subsequently lead to cardiac arrhythmia and circulatory collapse. Furthermore, it is well known that sedatives can lead to impaired respiration (hypoventilation and hypoxemia), causing changes in PCO_2 and other metabolic parameters [8]. Carbon dioxide insufflation is reported to be safe for patients undergoing colonoscopy under conscious sedation. However, compared with diagnostic colonoscopy, ESD is a much longer procedure and often needs more additional sedatives.

We have reported that CO_2 insufflation is safe and effective for patients receiving ESD under conscious sedation because we saw no significant CO_2 elevation after ESD, and less dosage of midazolam was needed in the CO_2 group [7]. In that study, however, arterial partial pressure of CO_2 (pCO_2) was measured only before and after the procedure. It is therefore also important to assess the safety of CO_2 insufflation during ESD. In this study, the mean peak $PtcCO_2$ during ESD was significantly higher than the mean $PtcCO_2$ before or after ESD. However, given that $PtcCO_2$ is typically higher than $PaCO_2$ by 5–6 mmHg, the mean peak $PtcCO_2$ during ESD can be considered within the normal range. Furthermore, a slight increase in $PtcCO_2$ was observed after additional sedation. However, only three patients transiently experienced more than 60 mmHg of $PtcCO_2$ for an extremely short period (data not shown).

There was no correlation of $PtcCO_2$ with longer procedure time, patient age, location, or total times of additional sedation (data not shown). In addition, no CO_2 retention or other side effects associated with CO_2 elevation were seen. Thus, sedation in addition to CO_2 insufflation could be the primary cause of CO_2 retention, but this is not clinically significant because the observed changes were within the reference range considering that $PtcCO_2$ is typically higher than $PaCO_2$ by 5 to 6 mmHg, as described previously. Furthermore, the slight increase in $PtcCO_2$ related to additional sedation also was associated with a slight decrease in PaO_2 in this study (data not shown). This also supported the fact that additional sedation would result in hypoventilation to a slight degree, which could be monitored by pulse oximeter.

Thereafter, we managed 200 or more cases of colorectal ESD using CO_2 insufflation monitored only with pulse oximeter, and no serious side effect was seen in the patients. Therefore, we can recommend that $PaCO_2$, which is more cost effective and more convenient, can replace $PtcCO_2$ for monitoring ESD with CO_2 insufflation. Because our study has shown that CO_2 insufflation can be used safely for colonic ESD, the use of CO_2 insufflation for ESD in the colon is subject to no limitation except in contraindicated cases (patients with severe cardiopulmonary diseases or CO_2 retention) and a little cost for CO_2.

In conclusion, the current study showed that CO_2 insufflation is safe during colorectal ESD. Additional sedation during ESD could lead to a slight but not clinically significant increase in CO_2, and it is associated with a slight decrease in PaO_2, which can be monitored using a less

expensive and more convenient device such as a pulse oximeter.

Disclosures Tsuyoshi Kikuchi, Kuang-I Fu, Yutaka Saito, Toshio Uraoka, Masakatsu Fukuzawa, Syusei Fukunaga, Taku Sakamoto, Takeshi Nakajima, and Takahisa Matsuda have no conflicts of interest or financial ties to disclose.

References

1. Hussein AM, Bartram CI, Williams CB (1984) Carbon dioxide insufflation for more comfortable colonoscopy. Gastrointest Endosc 30:68–70
2. Stevenson GW, Wilson JA, Wilkinson J, Norman G, Goodacre RL (1992) Pain following colonoscopy: elimination with carbon dioxide. Gastrointest Endosc 38:564–567
3. Bretthauer M, Thiis-Evensen E, Huppertz-Hauss G, Gisselsson L, Grotmol T, Skovlund E, Hoff G (2002) NORCCAP (Norwegian Colorectal Cancer Prevention): a randomized trial to assess the safety and efficacy of carbon dioxide versus air insufflation in colonoscopy. Gut 50:604–607
4. Church J, Delaney C (2003) Randomized, controlled trial of carbon dioxide insufflation during colonoscopy. Dis Colon Rectum 46:322–326
5. Bretthauer M, Lynge AB, Thiis-Evensen E, Hoff G, Fausa O, Aabakken L (2005) Carbon dioxide insufflation in colonoscopy: safe and effectiveness in sedated patients. Endoscopy 37:706–709
6. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D (2007) Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). Gastrointest Endosc 66:966–973
7. Saito Y, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Kozu T, Saito D (2007) A pilot study to assess the safety and efficacy of carbon dioxide insufflation during colorectal endoscopic submucosal dissection with the patient under conscious sedation. Gastrointest Endosc 65:537–542
8. Bell GD (2000) Premedication, preparation, and surveillance. Endoscopy 32:92–100
9. Hirabayashi M, Otani N, Kagawa S, Kamide M (2006) Method of evading the overshoot phenomenon of transcutaneous $P(CO_2)$ measurement at the ear lobe (in Japanese). Masui 55:1018–1022
10. Franklin ML (1995) Transcutaneous measurement of partial pressure of oxygen and carbon dioxide. Respir Care Clin North Am 1:119–131
11. Chhajed PN, Kaegi B, Rajasekaran R, Tamm M (2005) Detection of hypoventilation during thoracoscopy: combined cutaneous carbon dioxide tension and oximetry monitoring with a new digital sensor. Chest 127:585–588
12. Epstein MF, Cohen AR, Feldman HA, Raemer DB (1985) Estimation of $PaCO_2$ by two noninvasive methods in the critically ill newborn infant. J Pediatr 106:282–286
13. Bhavani-Shankar K, Steinbrook RA, Mushlin PS, Freiberger D (1998) Transcutaneous PCO_2 monitoring during laparoscopic cholecystectomy in pregnancy. Can J Anaesth 45:164–169
14. Magno R, Medegard A, Bengtsson R, Tronstad SE (1979) Acid-base balance during laparoscopy: the effect of intraperitoneal insufflation of carbon dioxide and nitrous oxide on acid-base balance during controlled ventilation. Acta Obstet Gynecol Scand 58:81–85
15. Wolf JS Jr (1996) Pathophysiologic effects of prolonged laparoscopic operation. Semin Surg Oncol 12:86–95

World Journal of Gastroenterology

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

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

ORIGINAL ARTICLE

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

Masakatsu Fukuzawa, Yutaka Saito, Takahisa Matsuda, Toshio Uraoka, Takao Itoi, Fuminori Moriyasu

Masakatsu Fukuzawa, Yutaka Saito, Takahisa Matsuda, Toshio Uraoka, Division of Endoscopy, National Cancer Center Hospital, Tokyo 1040045, Japan
Masakatsu Fukuzawa, Takao Itoi, Fuminori Moriyasu, Division of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo 1600023, Japan
Toshio Uraoka, Department of Endoscopy, Okayama University Hospital, Okayama 7008558, Japan
Author contributions: Fukuzawa M, Saito Y and Matsuda T performed the research, designed the study, analyzed the data and wrote the manuscript; Uraoka T, Itoi T and Moriyasu F contributed to the discussion and reviewed the manuscript.
Correspondence to: Masakatsu Fukuzawa, MD, Division of Endoscopy, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 1040045, Japan. masakatu8055@yahoo.co.jp
Telephone: +81-3-35422511 Fax: +81-3-35423815
Received: November 30, 2009 Revised: January 20, 2010
Accepted: January 27, 2010
Published online: April 14, 2010

Abstract

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

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

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

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

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

Peer reviewer: Dr. Oliver Mann, MD, Senior Attending Physician and Deputy Director, Department of General, Visceral and Thoracic Surgery, University of Hamburg, Martini Str. 52, D-20246 Hamburg, Germany

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

INTRODUCTION

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

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

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

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

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

MATERIALS AND METHODS

NBI system

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

Patients and evaluation methods

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

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

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

Chromoendoscopy with magnification

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

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

Microvascular architecture of ECC

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

Statistical analysis

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

RESULTS

Clinicopathological features of patients and lesions

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

Table 1 Clinicopathological features of evaluated colorectal lesions

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

[1]Update on the Paris classification of superficial neoplastic lesion in the digestive tract[26]. LST-G: Laterally spreading tumor-granuler type; LST-NG: Laterally spreading tumour-non granular type; m/sm-s: Mucosal/submucosal superficial; sm-d: Submucosal-deep.

Univariate analysis

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

Multivariate analysis

Multivariate analysis demonstrated that sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13133.1]; and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1) (Table 2). The sensitivity, specificity, PPV, NPV and diagnostic accuracy rate for each characteristic are shown in Table 3. The two vascular findings that were confirmed by multivariate analysis had the highest values for specificity, PPV and accuracy (non-dense vessel density: specificity 0.99, PPV 0.95, accuracy 90.2%; negative vessel regularity: specificity 0.99, PPV 0.95, accuracy 90.2%).

Pit pattern diagnosis

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

DISCUSSION

It has been reported previously that observation of intra-

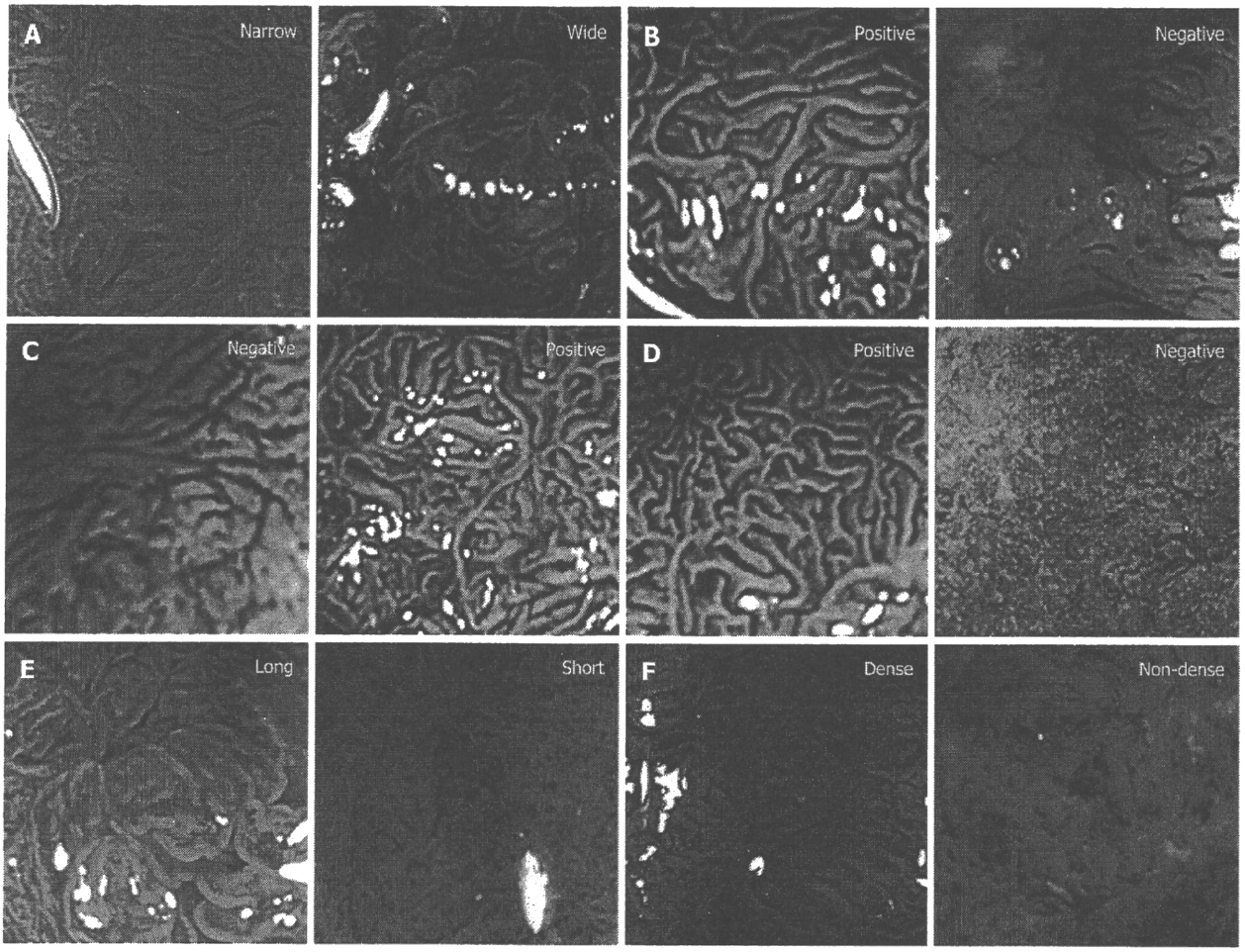

Figure 1 Microvascular architecture. A: Caliber, narrow: Capillaries are narrow diameter. Caliber, wide: Capillaries are wide diameter; B: Caliber regularity, positive: Capillaries are uniform thickness. Caliber regularity, negative: Capillaries are unequal thickness; C: Meandering, negative: Capillaries are linear. Meandering, positive: Capillaries are meandering; D: Vessel regularity, positive: Capillaries surround mucosal glands regularly. Vessel regularity, negative: Capillaries irregularly branching; E: Vessel length, long: Long capillaries. Vessel length, short: Short capillaries; F: Vessel density, dense: Dense capillaries. Vessel density, non-dense: Sparse capillaries.

Table 2 Microvascular architecture & invasion depth

Variables			Univariate analysis *P*-value[1]	Multivariate analysis *P*-value[1]	Odds ratio	95% CI
		Non-dense/dense				
Vessel density	m/sm-s	1/68	< 0.001	0.001	402.5	12.4-13133.1
	sm-d	33/10				
		Negative/positive				
Vessel regularity	m/sm-s	8/61	< 0.001	0.038	15.9	1.2-219.1
	sm-d	38/5				
		Negative/positive				
Caliber regularity	m/sm-s	44/25	< 0.001	0.056	17.3	0.9-323.4
	sm-d	42/1				
		Short/long				
Vessel length	m/sm-s	20/49	< 0.001	0.161	0.2	0.01-2.10
	sm-d	37/6				
		Positive/negative				
Meandering	m/sm-s	49/20	0.002	0.110	0.1	0.01-1.60
	sm-d	41/2				
		Wide/narrow				
Caliber	m/sm-s	62/7	NS			
	sm-d	41/2				

[1]χ^2 or Fisher's test. 95% CI: 95% confidence interval; NS: Not significant.

papillary capillary loops by magnification endoscopy is useful in the diagnosis of invasion depth of superficial esophageal cancer[10,11]. The intra-papillary capillary loops can be seen in the normal esophageal mucosa by mag-

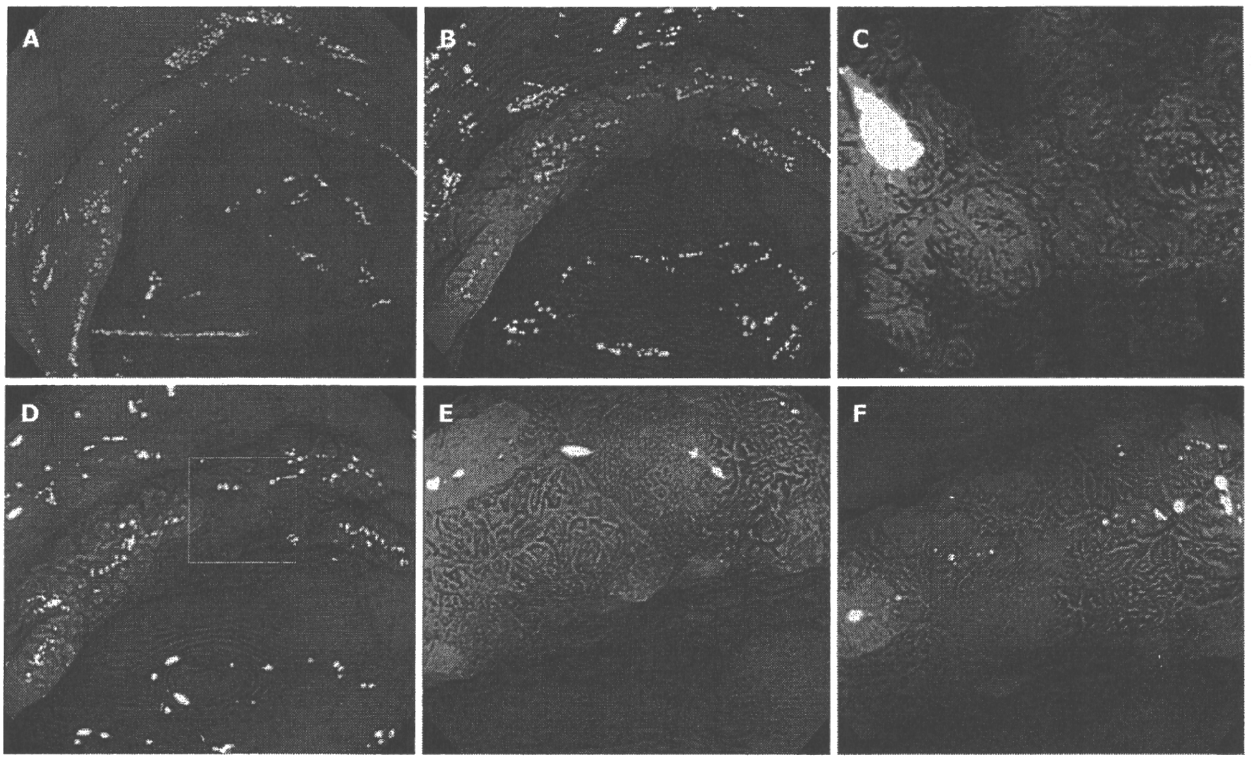

Figure 2 35 mm laterally spreading tumor, non-granular (LST-NG) type, located in the ascending colon. A: Conventional colonoscopy image; B: Conventional colonoscopy image following 0.4% IC dye spraying; C: Narrow-band imaging (NBI) with magnification image at center of the lesion enclosed by the red box in A. Microvascular architecture consisted of non-dense vessel density and negative vessel regularity; D: Crystal violet staining image; E: Magnification view of the portion enclosed by the red box in D revealed a noninvasive pattern; F: Magnification view of the portion enclosed by the yellow box in D also revealed a noninvasive pattern, such the estimated depth was intramucosal and this LST-NG lesion was treated by endoscopic submucosal dissection.

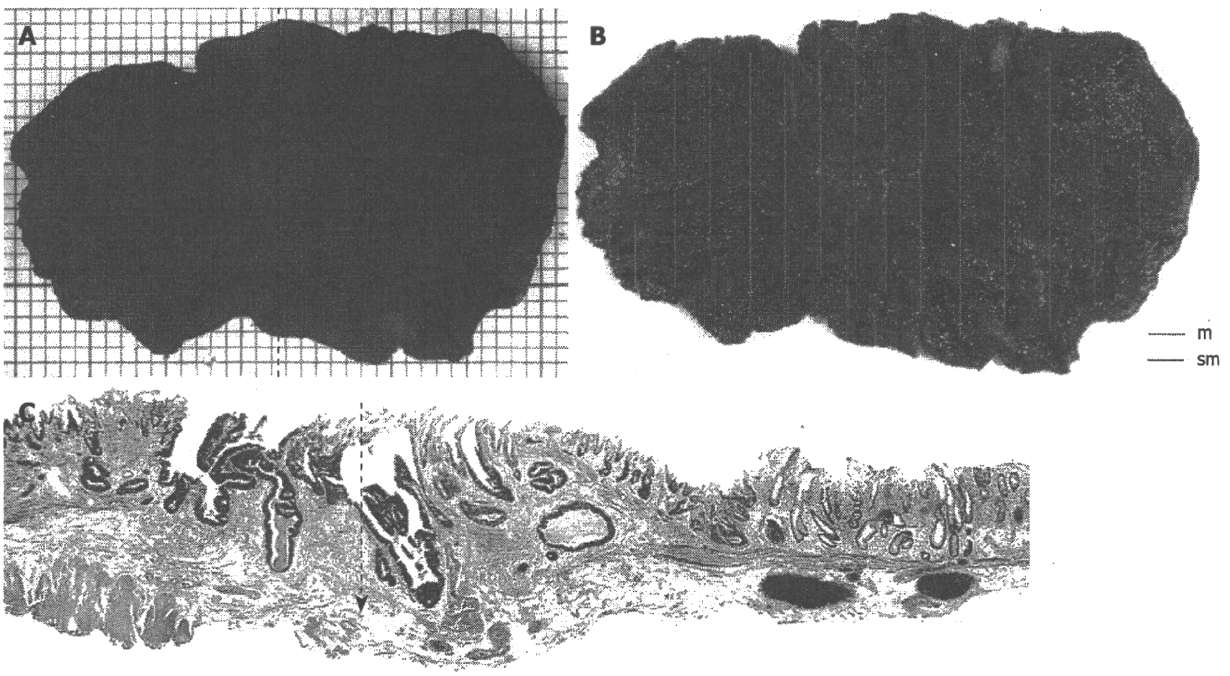

Figure 3 Stereomicroscopic view and histological images. A: Stereomicroscopic view; B: Red lines indicate submucosal penetration of the tumor; C: Histological diagnosis at dotted line in A was a well-differentiated adenocarcinoma and depth of invasion was sm (1300 mm) shown with the arrow. Invasion depth diagnosis using NBI with magnification was correct, based on findings of non-dense vessels and negative vessel regularity, but pit pattern diagnosis of this lesion was inaccurate.

nifying endoscopy. In cancerous lesions, characteristic changes of the intrapapillary capillary loops can be seen in the superficial mucosa according to the depth of tumor invasion. There have been few studies to assess invasion depth in cancerous lesions from microvascular architecture. However, the NBI system enabled observation of

Table 3 Assessment of the carcinomatous invasion depth based on microvascular architecture

Microvascular architecture	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (%)
Vessel density	33/43	68/69	0.97 (0.85-0.99)	0.87 (0.78-0.94)	90.2
Non-dense	0.77 (0.61-0.88)	0.99 (0.92-0.99)			
Vessel regularity	38/43	61/69	0.83 (0.69-0.92)	0.92 (0.83-0.97)	88.4
Negative	0.88 (0.75-0.96)	0.88 (0.78-0.95)			
Caliber regularity	42/43	25/69	0.49 (0.38-0.60)	0.96 (0.80-0.99)	59.8
Negative	0.98 (0.88-0.99)	0.36 (0.25-0.49)			
Vessel length	37/43	49/69	0.65 (0.51-0.77)	0.89 (0.78-0.96)	76.8
Short	0.86 (0.84-0.99)	0.71 (0.59-0.81)			
Meandering	41/43	20/69	0.46 (0.35-0.56)	0.91 (0.71-0.99)	54.5
Positive	0.95 (0.84-0.99)	0.29 (0.19-0.41)			
Caliber	41/43	7/69	0.40 (0.30-0.50)	0.78 (0.40-0.97)	42.9
Wide	0.95 (0.84-0.99)	0.10 (0.04-0.20)			

PPV: Positive predictive value; NPV: Negative predictive value.

Table 4 Assessment of the carcinomatous invasion depth: comparison between microvascular architecture & pit pattern analysis

Microvascular architecture	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (%)
Non-dense vessel density	38/43	60/69	0.81 (0.67-0.91)	0.92 (0.83-0.97)	87.5
and/or negative vessel regularity	0.88 (0.75-0.96)	0.87 (0.77-0.94)			
Non-dense vessel density	35/43	69/69	1.00 (0.90-1.00)	0.90 (0.81-0.95)	92.9
and negative vessel regularity	0.81 (0.67-0.92)	1.00 (0.95-1.00)			
Pit pattern	37/43	68/69	0.97 (0.86-0.99)	0.92 (0.83-0.97)	93.8
(Invasive pattern)	0.86 (0.72-0.95)	0.99 (0.92-0.99)			

microvascular architecture of the tumor surface in the GI tract. In a similar fashion, we used NBI with magnification to investigate whether or not quantitative ECC invasion depth diagnosis was possible based on analysis of capillary vessel patterns instead of pit patterns. Based on our results, it appeared that non-dense vessel density and negative vessel regularity, as observed by NBI with magnification, could be diagnostic indicators of sm-d invasion, as effectively as pit pattern analysis.

Regular hexagonal or honeycomb-like capillary patterns are formed around the crypts of normal colorectal mucosa. In contrast, it has been reported that these capillaries are larger in tumor adenomas, whereas vascular disruption, caliber irregularity and dense vessels have been observed in severe atypical cases[37]. In addition, vascular changes do not generally occur in non-neoplastic lesions such as hyperplastic polyps, with the exception of inflammatory polyps[38]. The NBI technique provides clearer observation of microvascular architectural characteristics, therefore, it has been reported that differentiation of neoplastic from non-neoplastic lesions on the basis of different vascular patterns is equally possible using NBI or chromoendoscopy[21-30], and pit pattern diagnosis has likewise been explored using NBI[21,24,27,28]. Previous studies have shown that the accuracy of pit pattern diagnosis of invasion depth by magnification endoscopy was 98.8%[8], whereas such diagnostic accuracy in this study was 93.8%.

The area surrounding crypts in the superficial layer of the mucosa is covered with capillaries and has previously been recognized as a pit using the NBI technique. Machida *et al*[21] have reported that NBI pit pattern diagnosis is significantly more useful ($P < 0.001$) than conventional observation, but inferior to chromoendoscopy ($P < 0.05$). Hirata *et al*[24] have reported that overall diagnostic consistency in pit patterns between magnification NBI and dye-spraying observations was 84%, but even higher for types Ⅱ, Ⅲ, Ⅳ and V_N pit patterns, although somewhat lower at 78%, for the type V_I pit pattern. In addition, Tischendorf *et al*[27] have reported that there is no significant difference in the PPV for neoplastic lesions as determined by pit pattern and vascular findings using NBI. There was a discrepancy, however, between two endoscopists in their NBI pit pattern diagnosis of types Ⅲ-Ⅴ neoplastic lesions[27]. This may have been because the actual pit structure was not observed using the NBI technique, unlike the results from the contrast and staining methods; or, it could have been caused by the NBI pit pattern diagnosis of types Ⅲ-Ⅴ lesions, which are considered particularly important in determining the most suitable method of treatment, not having been performed accurately.

More recently, Katagiri *et al*[30] have reported that capillary patterns observed by NBI with magnification are highly accurate in distinguishing between low-grade and high-grade dysplasia/invasive cancer, and thus could be used to predict the histopathological features of colorectal neoplasia. In addition, Hirata *et al*[25] have reported vascular findings of significant sm-d invasion based on their NBI observation of thick blood vessels with irregularity on the surface of tumors. This differs somewhat from the results of our investigation, but the difference could be caused by a number of factors, such as variations in our respective definitions of vascular findings, and the macroscopic types of lesions involved in the two studies.

Magnification observation with dye spraying and staining, in particular crystal violet staining, however, can be time-consuming. Patient symptoms including abdominal discomfort and peristalsis are more likely to appear in longer duration colonoscopy examinations, which may render detailed observation more problematic. In contrast, the press of a single button on the handle of the endoscope with the NBI system can almost immediately change from NBI to the conventional view and back again, thereby shorting examination times and reducing the burden on patients and endoscopists alike. A mucous attachment on the endoscope can also interfere with diagnosis, and washing the surface of a lesion with pronase solution takes additional time during pit pattern diagnosis by magnification colonoscopy with IC dye spraying or crystal violet staining. Hirata *et al*[24] have further reported that NBI observation results in more accurate pit pattern diagnosis than dye spraying observation in cases with mucous attachment.

Our study suffered from some limitations. First, the NBI assessments were made on still images by three endoscopists, whereas the pit pattern diagnosis was done in real time after initial inspection with NBI, which could account for some further bias. Second, the different NBI features of the microvasculature are not independent: the endoscopist is not blinded to one feature if he scores the other. In addition, lesions that were diagnosed histologically as cancer had a diameter of at least 10 mm, thus lesions < 10 mm in diameter were not assessed in this study. Accordingly, future prospective studies will require that relevant data be accumulated and analyzed on a more objective basis.

In conclusion, the results of this study indicated that two microvascular architectural characteristics, non-dense vessel density and negative vessel regularity, observed using NBI with magnification during colonoscopy examinations could be reliable indicators of ECC sm-d invasion.

ACKNOWLEDGMENTS

The authors wish to thank Christopher Dix for his assistance in helping to edit this manuscript.

COMMENTS

Background

The intra-papillary capillary loops can be seen in the normal esophageal mucosa by magnifying endoscopy. In cancerous lesions, characteristic changes of the intrapapillary capillary loops can be seen in the superficial mucosa according to the depth of tumor invasion. Narrow-band imaging (NBI) enables detailed observation of microvascular architecture of the tumor surface.

Research frontiers

NBI provides clearer observation of microvascular architectural characteristics, and it has been reported that differentiation of neoplastic from non-neoplastic lesions on the basis of different vascular patterns is equally possible using NBI or chromoendoscopy. However, there have been only a few reports concerning invasion depth diagnosis using NBI with magnification in a large series of cases. This study clarifies the efficiency of NBI with magnification colonoscopy for invasion depth diagnosis of early colorectal cancer (ECC).

Innovations and breakthroughs

Some studies have already reported the clinical usefulness of pit pattern diagnosis using magnifying chromoendoscopy for predicting the depth of invasion of ECC. The authors' results indicate that NBI with magnification findings were comparable to pit pattern diagnosis results.

Applications

Magnification observation with dye spraying and staining, in particular crystal violet staining, however, can be time-consuming. In contrast, the press of a single button on the handle of the endoscope with the NBI system can almost immediately change from NBI to the conventional view and back again, thereby shortening examination times and reducing the burden on patients and endoscopists alike.

Peer review

The authors present a trial analyzing the impact of NBI colonoscopy on assessing the invasion depth in ECC. Overall, 112 patients were included; additionally pit pattern analysis was performed in 64 patients. The study investigated interesting questions.

REFERENCES

1 **Kudo S**, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, Himori M, Yagyuu A. Colorectal tumours and pit pattern. *J Clin Pathol* 1994; **47**: 880-885
2 **Fu KI**, Sano Y, Kato S, Fujii T, Nagashima F, Yoshino T, Okuno T, Yoshida S, Fujimori T. Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. *Endoscopy* 2004; **36**: 1089-1093
3 **Kato S**, Fu KI, Sano Y, Fujii T, Saito Y, Matsuda T, Koba I, Yoshida S, Fujimori T. Magnifying colonoscopy as a non-biopsy technique for differential diagnosis of non-neoplastic and neoplastic lesions. *World J Gastroenterol* 2006; **12**: 1416-1420
4 **Sano Y**, Saito Y, Fu KI, Matsuda T, Uraoka T, Kobayashi N, Ito H, Machida H, Iwasaki J, Emura F, Hanafusa H, Yoshino T, Kato S, Fujii T. Efficacy of Magnifying Chromoendoscopy for the Differential Diagnosis of Colorectal Lesions. *Digestive Endoscopy* 2005; **17**: 105-116
5 **Trecca A**, Gai F, Di Lorenzo GP, Hreniuc H, Pasciuto A, Antonellis F, Sperone M. [Conventional colonoscopy versus chromoendoscopy and magnifying endoscopy for the diagnosis of colorectal lesions: a comparative prospective study in 995 patients] *Chir Ital* 2004; **56**: 31-36
6 **Kudo S**, Tamura S, Nakajima T, Yamano H, Kusaka H, Watanabe H. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc* 1996; **44**: 8-14
7 **Fujii T**, Hasegawa RT, Saitoh Y, Fleischer D, Saito Y, Sano Y, Kato S. Chromoscopy during colonoscopy. *Endoscopy* 2001; **33**: 1036-1041
8 **Matsuda T**, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N, Ikehara H, Ikematsu H, Fu KI, Emura F, Ono A, Sano Y, Shimoda T, Fujimori T. Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. *Am J Gastroenterol* 2008; **103**: 2700-2706
9 **Nagata S**, Tanaka S, Haruma K, Yoshihara M, Sumii K, Kajiyama G, Shimamoto F. Pit pattern diagnosis of early colorectal carcinoma by magnifying colonoscopy: clinical and histological implications. *Int J Oncol* 2000; **16**: 927-934
10 **Kumagai Y**, Inoue H, Kawano T. Magnifying endoscopic observation of superficial esophageal carcinoma. *Dig Endosc* 2004; **16**: 277-281
11 **Kumagai Y**, Inoue H, Nagai K, Kawano T, Iwai T. Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial esophageal carcinoma. *Endoscopy* 2002; **34**: 369-375
12 **Otsuka Y**, Niwa Y, Ohmiya N, Ando N, Ohashi A, Hirooka Y, Goto H. Usefulness of magnifying endoscopy in the diagnosis of early gastric cancer. *Endoscopy* 2004; **36**: 165-169
13 **Gono K**, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of en-