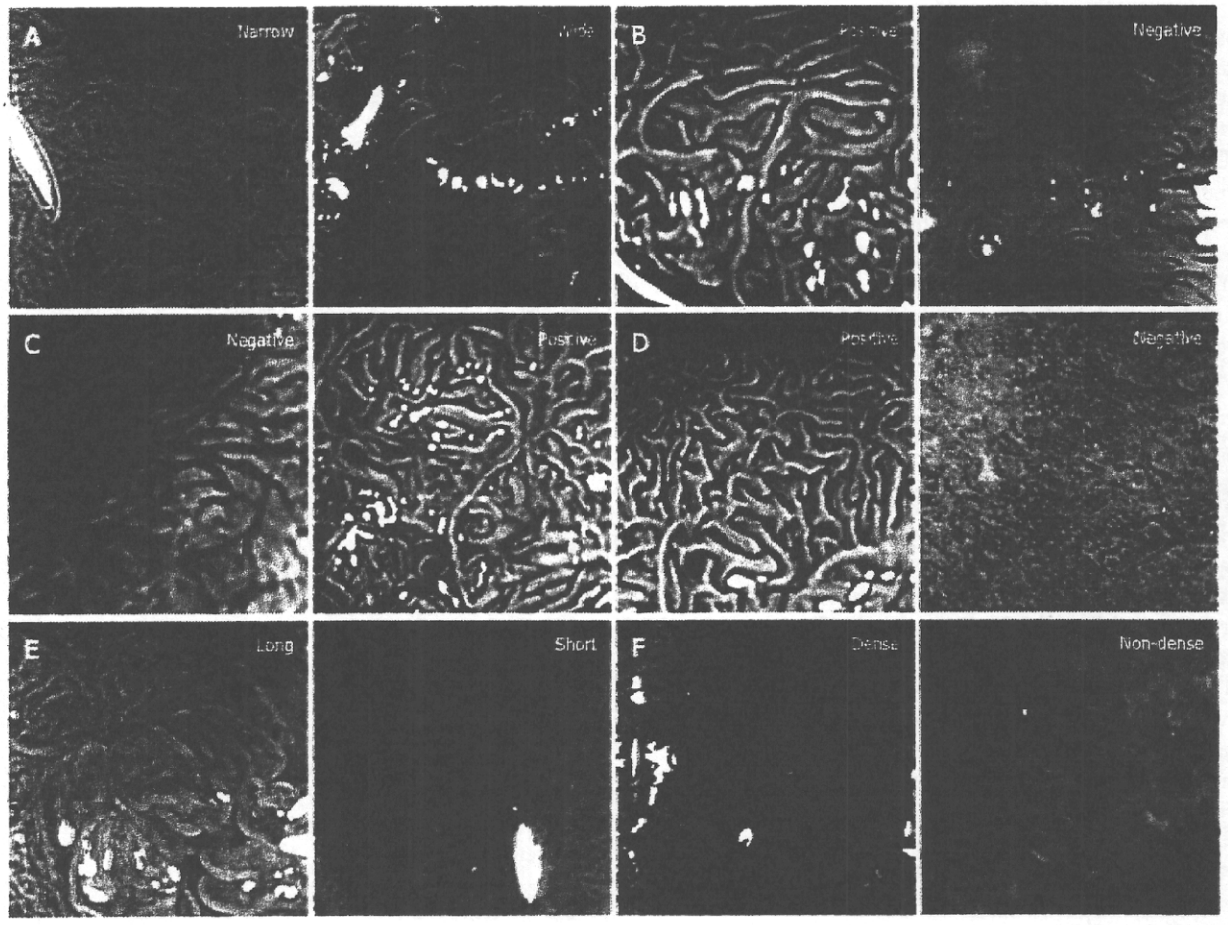

Figure 1 Microvascular architecture. A: Caliber, narrow: Capillaries are narrow diameter. Caliber, wide: Capillaries are wide diameter; B: Caliber regularity, positive: Capillaries are uniform thickness. Caliber regularity, negative: Capillaries are unequal thickness; C: Meandering, negative: Capillaries 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 and 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	12.4-13 133.1
	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-

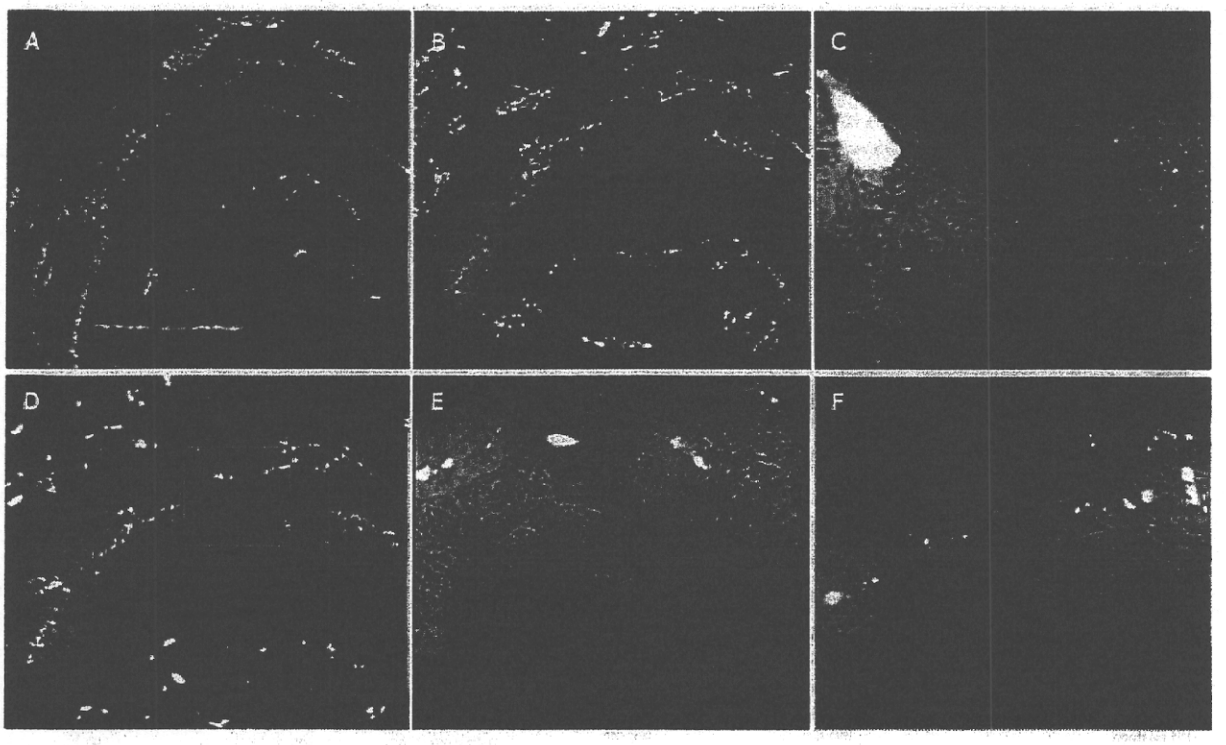

Figure 2 35 mm laterally spreading tumor, non-granular (LST-NG) type, located in the ascending colon. A: Conventional colonoscopy image; B: Conventional colonoscopy image following 0.4% IC dye spraying; C: Narrow-band imaging (NBI) with magnification image at center of the lesion enclosed by the red 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.

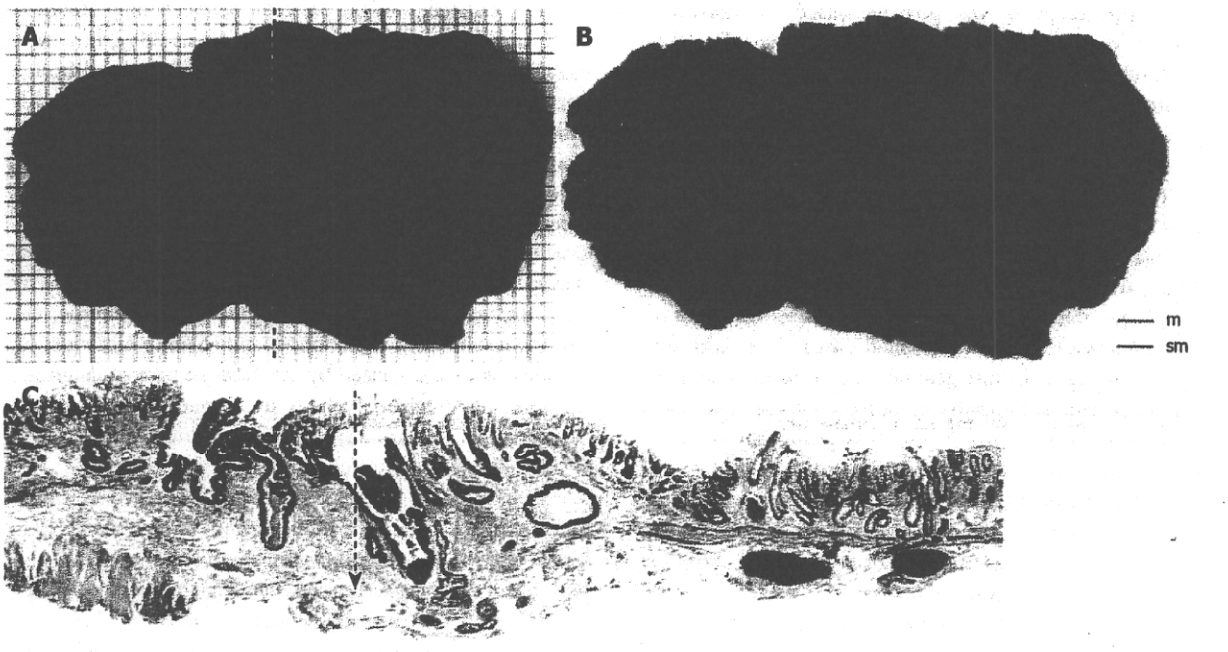

Figure 3 Stereomicroscopic view and histological images. A: Stereomicroscopic view; B: Red lines indicate submucosal penetration of the tumor; C: Histological diagnosis at dotted line in A was a well-differentiated adenocarcinoma and depth of invasion was sm (1300 mm) shown with the arrow. Invasion depth 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 and 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.

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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.

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GASTROENTEROLOGY

Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy

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Key words
colon cancer, colorectal cancer, depth diagnosis, magnifying endoscopy, submucosal cancer.

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Abbreviations:
CRC, colorectal cancer; EMR, endoscopic mucosal resection; s.m., submucosal; s.m.-s., submucosal slight; s.m.-d., submucosal deep; LST-G, laterally spreading tumor granular type.

Abstract

Background and Aims: Early colorectal cancer (CRC) with submucosal deep (s.m.-d.) invasion should not be treated with endoscopic mucosal resection due to the higher incidence of lymph-node metastasis. It is, therefore, clinically important to accurately diagnose s.m.-d. lesions before treatment.

Methods: We analyzed the endoscopic features, including pit patterns, of early CRC with s.m.-d. invasion observed using magnifying colonoscopy. We retrospectively investigated 379 cases of early CRC. Lesions were divided into three macroscopic subtypes (pedunculated type, sessile type and superficial type) based on endoscopic findings. Eight endoscopic factors were evaluated retrospectively for association with s.m. invasion and then compared to histopathological findings.

Results: The superficial type had a significantly higher frequency of s.m.-d. invasion (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], P-value < 0.05, respectively, for pedunculated and sessile types). Based on multivariate analysis, an independent risk factor for s.m.-d. invasion was the existence of an invasive pit pattern in sessile and superficial types (odds ratios of 52.74 and 209.67, respectively). Fullness was also an independent risk factor for s.m.-d. invasion in the superficial type (odds ratio = 9.25). There were no independent risk factors for s.m.-d. invasion in the pedunculated type.

Conclusion: High magnification pit pattern diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial types although it was not as helpful with the pedunculated type.

Introduction

The incidence of colorectal cancer (CRC) has recently been increasing in Japan. Early CRC that consist of intramucosal cancers or submucosal (s.m.) cancers that only superficially invade the s.m. layer (s.m.-s.) can be removed by endoscopic mucosal resection (EMR).[1] Endoscopic treatment for early CRC is considered appropriate when the following conditions have been satisfied: a lesion is determined histopathologically to be well differentiated; invasion of the s.m. layer is < 1000 μm (s.m.-s.); and the lesion is negative for both lymphovascular invasion and sprouting.[2] Early CRC with s.m. deep (s.m.-d.) invasion should not be treated with EMR due to an increased risk of lymph-node (LN) metastasis, which has been reported to range from 6.9% to 22.2%.[2] Consequently, it is clinically important to accurately diagnose the depth of invasion before treatment.

A role for magnifying endoscopy in the colon has previously been indicated for the diagnosis of flat and depressed lesions, identification of dysplasia in ulcerative colitis, discrimination among polyp types and assessing the completeness of EMR.[3–5] Pit pattern classification for colonic lesions has also been well documented in the past. We have already reported that pit pattern analysis using magnification colonoscopy was useful in the diagnosis of invasive depth in early CRC, particularly flat and depressed lesions.[6–9] No studies have been reported as yet, however, that focused on the diagnosis of s.m. invasion in pedunculated and sessile type lesions.

The aim of this study was to analyze the endoscopic features (including pit patterns) of early CRC with s.m.-d. invasion from a large number of early CRC including pedunculated and sessile types using magnifying colonoscopy in order to determine the appropriate therapeutic strategy.

Methods

A total of 844 early CRC were resected endoscopically or surgically at the National Cancer Center Hospital in Tokyo between October 1998 and September 2005. In this series, 687 lesions were removed by endoscopic resection and 157 underwent surgical treatment. All lesions were examined using magnifying colonoscopy before treatment. Among them, 232 tumors were positive for s.m. invasion (612 intramucosal cancer lesions, 52 s.m.-s. lesions

and 180 s.m.-d. lesions). We also investigated the 256 consecutive intramucosal early CRC that were resected between January 2004 and September 2005 as our control group (EMR, 253 lesions; and surgery, three lesions) to help ascertain and evaluate differences between intramucosal and s.m. invasive cancers. From this total of 488 early colorectal lesions, 68 (13.9%) were excluded because the quality of their magnifying colonoscopy pictures was too poor for an accurate assessment either because of mucous or the pictures were out of focus leaving 420 (86.1%) lesions with suitable pictures for s.m. invasion diagnostic purposes. In addition, granular type laterally spreading tumors (LST-G) consist of several different shapes. For example, some LST-G have a flat elevated component surrounding a large nodule. It is therefore difficult to categorize such lesions as being either the protruded or flat type.[10,11] Accordingly, 41 LST-G were excluded from this study. Eventually, a total of 379 lesions were analyzed retrospectively (179 intramucosal lesions, 40 s.m.-s. lesions and 160 s.m.-d. lesions). These lesions were then divided into three subtypes according to the Paris classification: pedunculated type (type 0-Ip), sessile type (type 0-Is) and superficial type, which included slightly elevated (0-IIa), completely flat (0-IIb) and slightly depressed lesions without ulcer (0-IIc).[13]

Endoscopic examination

In our medical facility, all colonoscopies are performed with magnification. When a lesion was detected by conventional endoscopic examination, surface mucin was washed away with lukewarm water containing pronase (Pronase MS, Kaken Pharmaceutical, Tokyo, Japan) and then 0.4% indigo-carmine dye was sprayed over the lesion in order to enhance its surface detail. High magnification colonoscopes (CF-240ZI, PCF-240ZI and CF-200Z, Olympus Optical, Tokyo, Japan) were also used in this study. When a high magnification observation with indigo-carmine dye was not enough to determine the surface structure (pit pattern analysis), staining was added with 0.05% crystal violet.[14] The additional time usually needed to complete the magnification observation was less than 10 min including 30 s to one minute to wash the lesion, one minute for crystal violet staining and one to five minutes for the actual observation.

The depth of tumor invasion was classified as intramucosal, s.m.-s. (invasion < 1000 μm from the muscularis mucosa) and s.m.-d. (invasion ≥ 1000 μm from the muscularis mucosa). In order to elucidate the possible association between s.m.-d. invasion and various endoscopic findings, we selected eight endoscopic factors related to s.m. deep invasion from previously published literature[10-12] and then those eight endoscopic factors were investigated retrospectively.

1 Tumor Size—receiver operating characteristic (ROC) curves were used to determine the relationship between tumor size cut-offs and diagnostic accuracy. Based on these ROC curves, we chose tumor size cut-offs for pedunculated (20 mm), sessile (15 mm) and superficial (10 mm) tumors. The size for en bloc resected specimens was estimated by histopathological examination and for piecemeal resected specimens by reviewing endoscopic photographs.
2 Loss of Lobulation—with or without a loss of lobulation (Fig. 1).

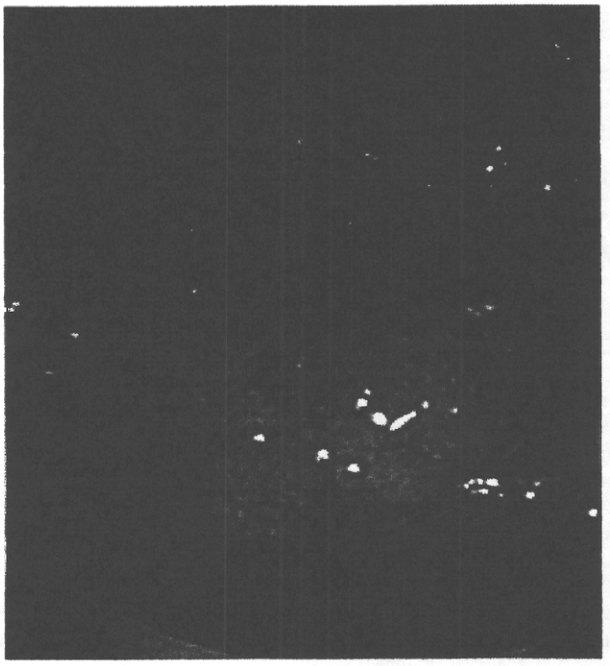

Figure 1 Loss of lobulation.

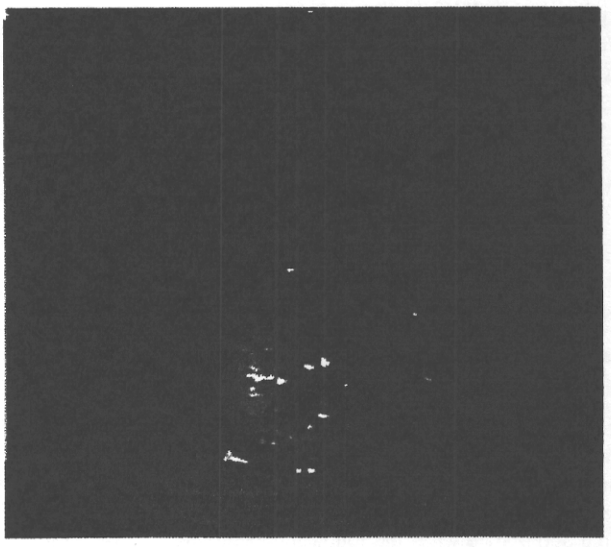

Figure 2 Excavation.

3 Excavation—a crumbled, damaged area of the tumor that prevents observation of the surface structure (Fig. 2).
4 Demarcated Depressed Area—with or without such a demarcation (Fig. 3).
5 Stalk Swelling—a thickened and expanded stalk (Fig. 4).
6 Fullness—a bursting appearance due to expansive growth of the tumor (Fig. 5).
7 Fold Convergency—a fold convergency towards the tumor (Fig. 6).

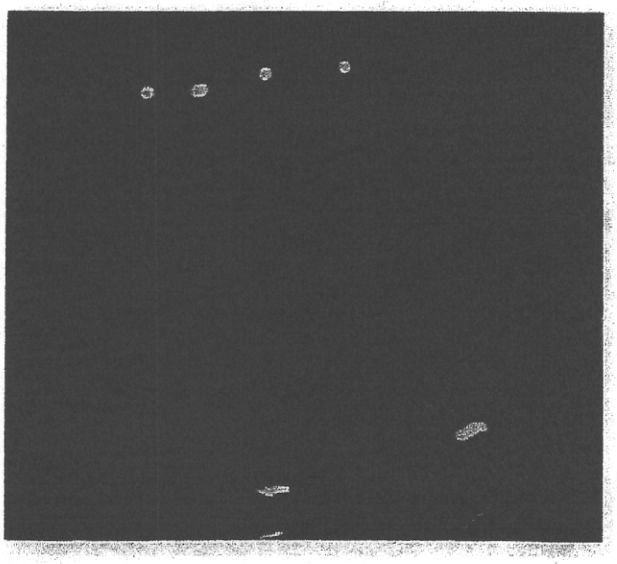

Figure 3 Demarcated depressed area.

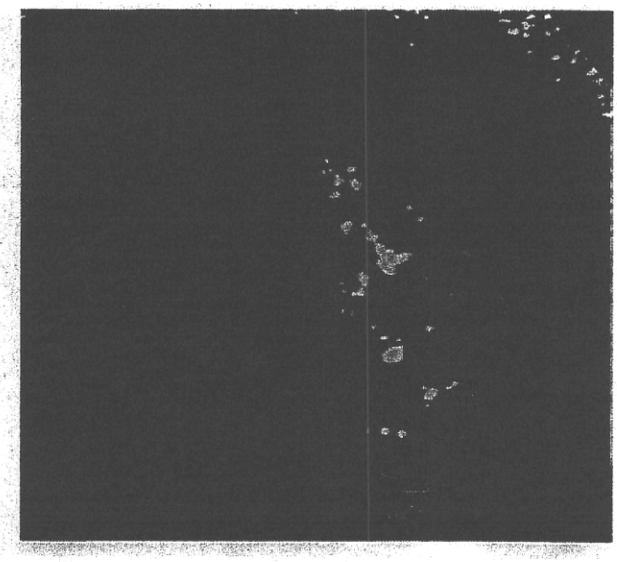

Figure 5 Fullness.

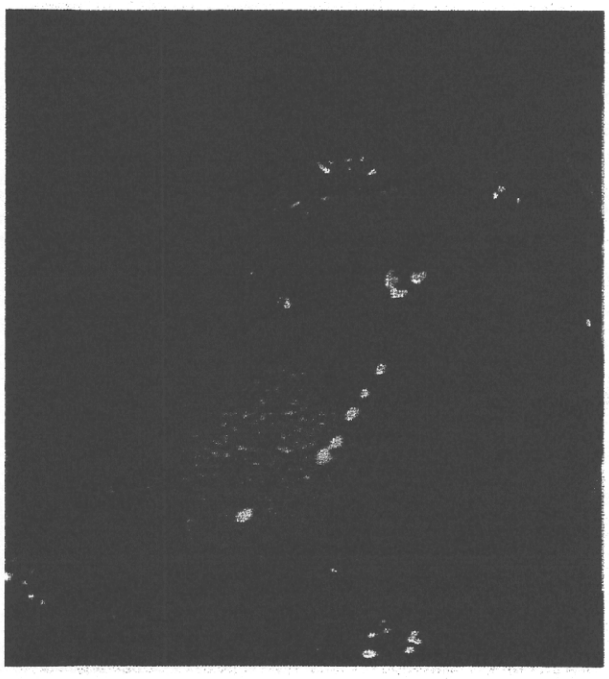

Figure 4 Stalk swelling.

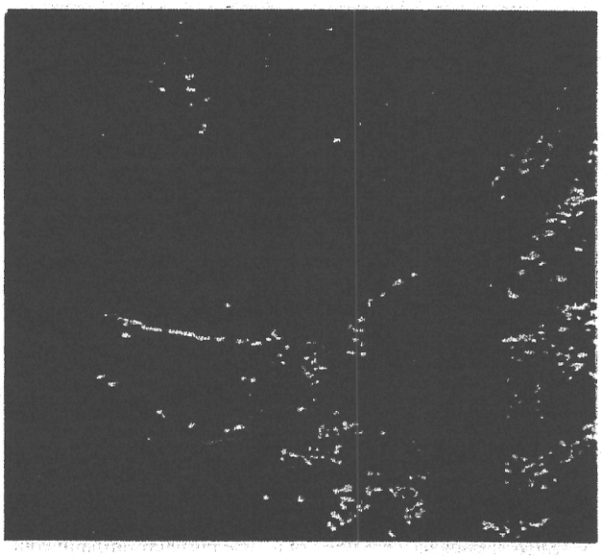

Figure 6 Fold convergency.

8 Pit Pattern—'Invasive pattern' or 'Non-invasive pattern' with the 'Invasive pattern' characterized by irregular and distorted epithelial crests observed in a demarcated area suggesting s.m.-d. invasion $\geq 1000\,\mu m$ while the 'Non-invasive pattern' did not have those two findings that suggested intramucosal neoplasia or s.m.-s. invasion $< 1000\,\mu m$ (Fig. 7a,b).[2,3,15]

Different endoscopic factors were assessed for each type. 'Stalk Swelling' was assessed for only the pedunculated type; 'Loss of Lobulation' and 'Excavation' were assessed for the pedunculated and sessile types; 'Fullness' and 'Fold Convergency' were assessed for the superficial type; and 'Size', 'Demarcated Depressed Area' and 'Pit Pattern' were assessed for all three types.

All endoscopic factors were determined retrospectively by three highly experienced endoscopists (H. I., Y. S. and T. M.) each of whom had previously performed over 1000 colonoscopies each year for more than five years. Final determination of endoscopic findings was decided by agreement of at least two of the three endoscopists. The relationships between the various endoscopic factors and the extent of s.m.-d. invasion were analyzed histopathologically in those lesions with s.m.-d. invasion.

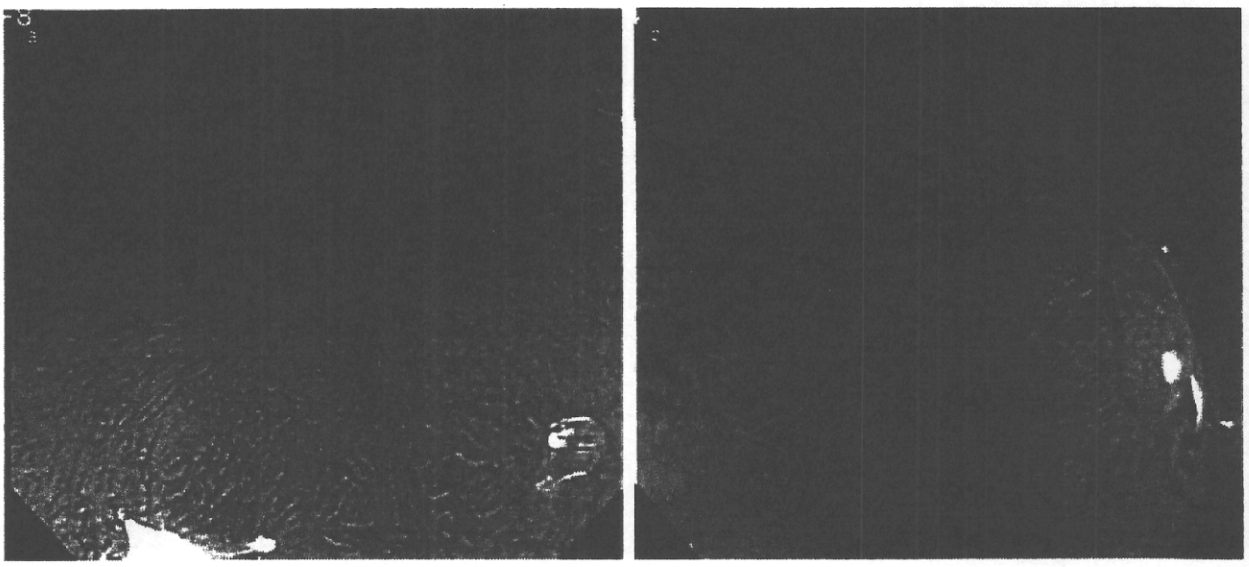

Figure 7 (a) Non-invasive pattern. (b) Invasive pattern.

Table 1 Clinicopathological characteristics of lesions

	Pedunculated type	Sessile type	Superficial type
Number of lesions	57	175	147
Tumor size (mean ± SD)	17.2 ± 6.5 mm	16.5 ± 8.5 mm	16.3 ± 8.6 mm
Histopathological diagnosis			
Intramucosal cancer	37	98	44
s.m.-s. (< 1000 μm)	6	8	26
s.m.-d. (≥ 1000 μm)	14 (24.6%)	69 (39.4%)	77 (52.4%)
Distribution			
Right colon	9 (15.8%)	43 (24.6%)	58 (39.5%)
Left colon	44 (77.2%)	60 (34.3%)	41 (27.9%)
Rectum	4 (7.0%)	72 (41.1%)	48 (32.6%)

SD, standard deviation; s.m.-d., submucosal deep invasion; s.m.-s., submucosal superficial invasion.

Histopathology

Resected specimens were fixed in a 10% buffered formalin solution, embedded on paraffin and then cut into 2–3 mm slices. Each section was stained with hematoxylin–eosin and then histopathologically diagnosed by a highly experienced pathologist. Histopathological diagnosis was based on the Vienna classification.[16] A microscope with a built-in ruler was used to determine the depth of s.m. invasion.

Statistical analysis

Among the three macroscopic subtypes, the proportion of s.m. invasion was compared using the χ^2-test. When characteristics showed a significant difference, we performed logistic regression including all such characteristics as part of the model. Statistical analyses were done with the SPSS 11.0 for Windows software package (SPSS, Chicago, IL, USA). Each test was two-sided and a P-value < 0.05 was defined as being statistically significant.

Results

Clinicopathological characteristics

Table 1 shows the clinicopathological characteristics of the early CRC examined in this study. The superficial type had a significantly higher frequency of s.m.-d. invasion compared to the pedunculated and sessile types (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], respectively). The pedunculated type was most commonly diagnosed in the left colon (77.2% [44/57]) in contrast to the sessile and superficial types, which were most commonly diagnosed in the rectum (41.1% [72/175]) and the right colon (39.5% [58/147]), respectively.

Endoscopic factors for submucosal deep invasion

In the pedunculated type, a larger tumor size (≥ 20 mm), loss of lobulation, excavation, the presence of an invasive pit pattern and

Table 2 Relationship between endoscopic factors and submucosal deep invasion in 57 pedunculated type lesions

		s.m.-d. ca./*n*	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 20 mm	10/22	< 0.01	1.49	0.22–10.31	0.69
	< 20 mm	4/35				
Loss of lobulation	Present	12/28	< 0.01	3.15	0.47–21.01	0.24
	Absent	2/29				
Excavation	Present	7/11	< 0.001	2.52	0.36–17.47	0.35
	Absent	7/46				
Demarcated depressed area	Present	2/4	0.25	ND	ND	ND
	Absent	12/53				
Pit pattern	Invasive	7/9	< 0.0001	4.62	0.50–42.98	0.18
	Non-invasive	7/48				
Stalk swelling	Present	9/19	< 0.01	2.00	0.40–10.10	0.40
	Absent	5/38				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

Table 3 Relationship between endoscopic factors and submucosal deep invasion in 175 sessile type lesions

		s.m.-d. ca./*n*	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 15 mm	53/96	< 0.0001	1.86	0.61–5.66	0.28
	< 15 mm	16/79				
Loss of lobulation	Present	63/92	< 0.0001	5.99	1.76–20.42	< 0.01
	Absent	6/83				
Excavation	Present	42/57	< 0.0001	1.51	0.45–5.05	0.50
	Absent	27/118				
Demarcated depressed area	Present	19/29	< 0.01	0.20	0.03–1.44	0.11
	Absent	50/146				
Pit pattern	Invasive	55/61	< 0.0001	52.74	10.89–255.33	< 0.0001
	Non-invasive	14/114				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

swelling of the stalk were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, however, there was no independent risk factor for s.m.-d. invasion (Table 2).

In the sessile type, the presence of a larger tumor size (≥ 15 mm), loss of lobulation, excavation, a demarcated depressed area and an invasive pit pattern were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were loss of lobulation and the existence of an invasive pit pattern ($P < 0.01$, odds ratio = 5.99; and $P < 0.0001$, odds ratio = 52.74, respectively) (Table 3).

In the superficial type, fullness, fold convergency, a demarcated depressed area and an invasive pit pattern were significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were the existence of fullness and an invasive pit pattern ($P < 0.01$, odds ratio = 9.25; and $P < 0.0001$, odds ratio = 209.67, respectively) (Table 4).

Pit pattern analysis

The clinical classification of pit patterns has proven to be effective in differentiating intramucosal or s.m.-s. invasion < 1000 μm from s.m.-d. invasion (≥ 1000 μm). The calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy are shown in Table 5. The overall accuracy for differentiating intramucosal or s.m.-s. invasion from s.m.-d. invasion was 84.2% in the pedunculated type, 88.6% in the sessile type and 92.5% in the superficial type. The diagnostic accuracy of the invasive pit pattern was lower for pedunculated type lesions than for the other two macroscopic subtypes.

Number of endoscopic factors analysis

Diagnostic accuracy based on the number of positive endoscopic factors observed during conventional endoscopy performed without magnification is shown in Table 6. When a particular lesion included four or more such endoscopic factors, overall accuracy was highest for the pedunculated type (86.0%). As for both the sessile and superficial types, however, overall accuracies of 81.1% and 80.3%, respectively, were highest when a particular lesion included two or more of the endoscopic factors.

Table 4 Relationship between endoscopic factors and submucosal deep invasion in 147 superficial type lesions

		s.m.-d. ca./n	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 10 mm	68/123	0.11	ND	ND	ND
	< 10 mm	9/24				
Fullness	Present	66/86	< 0.0001	9.25	2.14–40.00	< 0.01
	Absent	11/61				
Fold convergency	Present	38/50	< 0.0001	1.99	0.50–7.97	0.33
	Absent	39/97				
Demarcated depressed area	Present	52/68	< 0.0001	1.92	0.45–8.15	0.37
	Absent	25/79				
Pit pattern	Invasive	76/86	< 0.0001	209.67	23.05–1907.48	< 0.0001
	Non-invasive	1/61				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

Table 5 Diagnostic analysis of invasive pit pattern by macroscopic type

	Macroscopic type		
	Pedunculated type	Sessile type	Superficial type
Sensitivity	50.0%	79.7%	98.7%
Specificity	95.3%	94.3%	85.7%
PPV	77.8%	90.2%	88.4%
NPV	85.4%	87.7%	98.4%
Overall Accuracy	84.2%	88.6%	92.5%

The χ^2-test evaluates differences in sensitivity and there were significant differences among all three groups ($P < 0.05$).
NPV, negative predictive value; PPV, positive predictive value.

Discussion

Diagnosis of submucosal deep invasive cancer

We investigated various endoscopic factors including high magnification diagnosis of pit patterns in order to evaluate the predictive factors for s.m.-d. invasion in three macroscopic subtypes of early CRC. A higher incidence of s.m.-d. invasion in the superficial type and a difference in the diagnostic accuracy for predicting s.m.-d. invasion between the pedunculated type and the other two macroscopic types were found in our study.

In the superficial type, fullness and existence of the invasive pit pattern were independent risk factors for s.m.-d. invasion. Yokota *et al.* reported that conventional endoscopic findings were subjective,[12] however, fullness may not be a universal factor for determining s.m.-d. deep invasion. In the sessile type, multivariate analysis showed that loss of lobulation and existence of the invasive pit pattern were each independent risk factors for s.m.-d. invasion. A total of 68 lesions were excluded because of the poor quality of their magnifying colonoscopy pictures, however, so there could very well be a bias towards better pit pattern diagnostic analysis results in this study for both the superficial and sessile types.

In the pedunculated type, we were unable to demonstrate any independent endoscopic factors despite using pit pattern analysis. In addition, a combination of factors in pedunculated type lesions examined without magnification indicated that size and stalk swelling together had the same degree of overall diagnostic accuracy as produced by an analysis of invasive pit pattern using magnification. These results indicated that it is difficult to estimate the depth of tumor invasion in pedunculated type lesions using current magnification methods.

Endoscopic diagnosis versus non-lifting sign

In previous studies, Uno *et al.* reported the clinical usefulness of the non-lifting sign to predict the depth of invasion prior to EMR for early CRC.[17] In addition, Ishiguro *et al.* classified s.m. extension of early colorectal cancer as s.m.1 (infiltration into the upper third of the s.m. layer), s.m.2 (middle third) or s.m.3 (lower third) according to the vertical level of s.m. invasion. They reported that the non-lifting sign indicated s.m.3 invasion had a sensitivity of 100% and a specificity of 83% although only 30.4% of s.m.2 cancers were non-lifting sign positive in their study.[18]

Our group reported that the sensitivity, specificity and accuracy of the non-lifting sign (61.5%, 98.4% and 94.8%, respectively) were insufficient in comparison with endoscopic diagnosis of invasion depth (84.6%, 98.8% and 97.4%, respectively).[19] Given these results, magnifying colonoscopy can be considered more effective than the non-lifting sign in distinguishing s.m.-d. invasive cancer based on the techniques and methods used in this study.

Magnifying colonoscopy versus endoscopic ultrasonography

We previously reported that high magnification colonoscopy was superior to endoscopic ultrasonography (EUS) for the determination of invasion depth in early CRC.[13] In contrast, Hurlstone *et al.* demonstrated the superiority of EUS mini-probe staging over magnification colonoscopy.[20] At the present time, it is unclear whether magnification colonoscopy or EUS is superior for staging purposes. There is a learning curve associated with both modalities so the results can be influenced by the skill and experience of the endoscopist performing the procedure.

Magnifying endoscopy

We routinely use magnifying colonoscopy because a magnifying endoscope enables standard conventional observations, but can

Table 6 Diagnostic analysis according to number of positive endoscopic factors

		Number of positive endoscopic factors				
		≥ 1	≥ 2	≥ 3	≥ 4	≥ 5
Pedunculated type	Sensitivity	92.7%	71.4%	64.3%	42.7%	14.3%
	Specificity	44.2%	67.4%	86.1%	100%	100%
	PPV	35.1%	41.7%	60.0%	100%	100%
	NPV	95.0%	87.9%	88.1%	84.3%	78.2%
	Overall accuracy	56.1%	68.4%	80.7%	86.0%	79.0%
Sessile type	Sensitivity	97.1%	87.0%	52.2%	13.0%	ND
	Specificity	46.2%	77.4%	90.6%	99.1%	ND
	PPV	54.0%	71.4%	78.3%	90.0%	ND
	NPV	96.1%	90.1%	74.4%	63.4%	ND
	Overall accuracy	66.3%	81.1%	75.4%	65.1%	ND
Superficial type	Sensitivity	100%	87.0%	45.5%	1.3%	ND
	Specificity	34.3%	72.9%	91.4%	100%	ND
	PPV	62.6%	77.9%	85.4%	100%	ND
	NPV	100%	83.6%	60.4%	48.0%	ND
	Overall accuracy	68.7%	80.3%	67.4%	48.3%	ND

ND, no data; NPV, negative predictive value; PPV, positive predictive value.

also provide images from low to high magnification using a one-touch operational system. It is possible to distinguish between non-neoplastic and neoplastic lesions and estimate depth of tumor invasion in less than 10 minutes. The insertion technique and manipulation of the magnifying endoscope also are similar to those of a conventional endoscope during colonoscopy.[21,22]

Treatment strategy

In considering therapeutic strategies, EMR should be the first-line treatment for intramucosal and s.m.-s. early CRC because it is less invasive. LN metastasis is more frequently present in s.m.-d. invasive cancer,[23,24] however, so we should avoid EMR for s.m.-d. invasive cancer because histopathological assessment is more difficult. In addition, incomplete EMR is thought to cause accelerated growth of any residual cancer and is also considered to be a positive risk factor for distant metastasis.[25,26] Recognizing the importance of reported endoscopic factors for predicting s.m.-d. invasion therefore is essential in determining the proper treatment choice in any given case.

For sessile and superficial type lesions endoscopically diagnosed as having an invasive pit pattern, a high percentage of cases revealed invasive cancer, particularly s.m.-d. cancer, so surgical resection is undoubtedly the appropriate treatment. Those lesions endoscopically diagnosed as having a non-invasive pattern, however, were mostly limited to the intramucosal layer, which makes EMR feasible. It is also technically possible now to remove large superficial lesions using the more recently developed endoscopic submucosal dissection procedure.[27–30]

In the pedunculated type, it is difficult to accurately estimate the depth of s.m.-d. invasion prior to endoscopic treatment, but the endoscopic resection of a pedunculated polyp is relatively easy from a technical point of view. It is recommended therefore that a pedunculated type lesion first be removed endoscopically followed by a histopathological determination of the depth of invasion. A surgical resection should then be performed when stalk invasion or lymph-vessel involvement has been revealed histopathologically.

Limitations

This was a retrospective study conducted in a single center so the results need to be confirmed in a prospective multi-center trial. In addition, only pedunculated, sessile and superficial lesion macroscopic subtypes were included in this study.

Conclusion

Pit pattern high magnification diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial type lesions, although it was not helpful with the pedunculated type. Consequently, diagnostic endoscopic treatment is advisable for pedunculated early CRC.

Acknowledgment

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Safety of carbon dioxide insufflation for upper gastrointestinal tract endoscopic treatment of patients under deep sedation

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Abstract
Background It is well known that carbon dioxide (CO_2) is absorbed faster in the body than air and also that it is rapidly excreted through respiration. This study aimed to investigate the safety of CO_2 insufflation used for esophageal and gastric endoscopic submucosal dissection (ESD) in patients under deep sedation.
Methods Patients with either early gastric or esophageal cancers that could be resected by ESD were enrolled in this study from March 2007 to July 2008 and randomly assigned to undergo ESD procedures with CO_2 insufflation (CO_2 group) or air insufflation (air group). A TOSCA measurement system and TOSCA 500 monitor were used to measure and monitor both transcutaneous partial pressure of CO_2 ($PtcCO_2$) and oxygen saturation (SpO_2).
Results The study enrolled 89 patients and randomly assigned them to a CO_2 group (45 patients) or an air group (44 patients). The mean CO_2 group versus air group measurements were as follows: $PtcCO_2$ (49.1 ± 5.0 vs. 50.1 ± 5.3 mmHg; nonsignificant difference [NS]), maximum $PtcCO_2$ (55.1 ± 6.5 vs. 56.8 ± 7.0 mmHg; NS), $PtcCO_2$ elevation (9.1 ± 5.4 vs. 11.4 ± 5.6 mmHg; $p = 0.054$), SpO_2 (99.0 ± 0.7% vs. 99.0 ± 1.0%; NS), minimum SpO_2 (96.5 ± 2.4% vs. 95.4 ± 3.3%; $p = 0.085$), and SpO_2 depression (2.4 ± 2.3% vs. 3.3 ± 2.9%; NS). The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but the CO_2 group was better than the air group in $PtcCO_2$ elevation and minimum SpO_2.
Conclusions The findings demonstrated CO_2 insufflation to be as safe as air insufflation for upper gastrointestinal tract ESDs performed for patients under deep sedation without evidencing any adverse effects.

Keywords Carbon dioxide insufflation · Deep sedation · Endoscopic submucosal dissection · Transcutaneous partial pressure of carbon dioxide · Upper gastrointestinal tract

Several recent studies investigating colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) have reported that carbon dioxide (CO_2) insufflation reduces abdominal pain and discomfort caused by bowel hyperextension and can be used as safely as air insufflation [1–6]. It is well known that CO_2 is absorbed faster in the body than air and that it also is rapidly excreted through respiration unless some type of pulmonary dysfunction exists [1, 2]. To date, almost all endoscopic procedures have been performed using air insufflation, although it has led to some problems of abdominal pain and discomfort in routine examinations and perforation-related subcutaneous or mediastinal emphysema and pneumoperitoneum in endoscopic treatments [7, 8].

With the relatively recent development and increasingly widespread use of endoscopic submucosal dissection (ESD) as a minimally invasive treatment, performance of ESD for early gastrointestinal (GI) neoplasm in the esophagus, stomach, and colorectum has increased dramatically [9–16]. Quite naturally, the number of complications also has increased as a direct result, including perforations that occur during the technically difficult ESD procedure itself and the delayed bleeding experienced afterward [7, 8, 14, 17, 18]. In fact, the reported ESD perforation rate is 7% for cases involving the esophagus,

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4% for cases involving the stomach, and 5% for cases involving the colorectum [10, 14, 15]. Perforation can cause peritonitis and mediastinitis, and possibly also thromboembolism due to blood flow congestion (compartment syndrome) when significant pneumatic leakage results in excess internal pressure [19–24]. It is anticipated that such associated problems will be minimized by further use of CO_2 insufflation.

Colonoscopy with conscious sedation and the use of CO_2 insufflation has become more generally accepted since the demonstration of the safety and effectiveness of CO_2 insufflation in a previously published reported [5]. We previously conducted a case–control study that showed CO_2 insufflation to be both safe and effective for colorectal ESD with conscious sedation [25]. However, the safety of CO_2 insufflation has not been established for upper GI tract endoscopic treatment such as ESD with deep sedation in which CO_2 retention and decreased oxygenation are more important factors than in colonoscopy performed with conscious sedation.

This study aimed to investigate the safety of CO_2 insufflation for esophageal and gastric ESDs with deep sedation. Both operations are lengthy procedures.

Materials and methods

Patients

We prospectively assessed the safety of CO_2 insufflation for upper GI tract ESDs performed with the patient under deep sedation compared with air insufflation from March 2007 to July 2008 at the National Cancer Center Hospital (NCCH) in Tokyo, Japan. The study enrolled 89 patients with either early gastric or esophageal cancer that could be resected by ESD and randomly assigned them to undergo ESD procedures with CO_2 insufflation (CO_2 group) or air insufflation (air group).

The study excluded patients with severe pulmonary disease including either chronic obstructive pulmonary disease (COPD) or disease resulting in less than 80% of vital capacity (%VC) or less than 70% of the forced expiratory volume in 1 s as a percentage of the forced vital capacity (FEV1%), patients with severe cardiovascular disease including NYHA III or IV heart failure or arrhythmia with any treatment history, patients with hepatic or renal dysfunction, and patients with a change in insufflation methods from CO_2 to air or from air to CO_2 for any reason during their ESDs.

Endoscopic procedures

All ESD procedures were performed with Olympus video endoscopes and a standard videoendoscope system (EVIS LUCERA; Olympus Optical Co., Ltd., Tokyo, Japan). For ESD procedures, an insulation-tipped diathermic knife (IT-knife; Olympus) was used from March to October 2007 and an improved IT-knife (IT-knife 2; Olympus) from November 2007 to July 2008 [11, 26, 27].

First, marking dots were made around the lesion using a needleknife (Olympus). This was followed by injection of diluted epinephrine with normal saline (1:200,000) to lift the submucosal layer and allow the tip of the IT-knife or IT-knife 2 to be inserted into the submucosal layer. A small initial incision then was made by a needleknife, and a complete circumferential mucosal incision around the periphery of the marking dots was performed with the IT-knife or IT-knife 2. After an additional submucosal injection, the submucosal layer beneath the lesion was directly dissected using the same IT-knife or IT-knife 2.

Although all ESDs were generally performed in this manner, we sometimes used not only other devices such as an argon plasma coagulation probe for the marking dots and a bipolar needleknife (B-knife; XEMEX Co., Tokyo, Japan) for the initial incision and submucosal dissection [15, 28], but also another injection solution, sodium hyaluronate (MucoUp; Johnson & Johnson Co., Ltd., Tokyo, Japan) diluted with normal saline (1:1), especially for esophageal ESDs [12, 29–31]. The final objective was to achieve successful en bloc resections for precise pathologic evaluations.

Patients received midazolam, propofol, or both for deep sedation, and oxygen (O_2) was administered nasally (2 l/min) during ESD. Initially, 3–5 mg of midazolam was used for induction of venous anesthesia, with an additional 1–3 mg given repeatedly as necessary based on the judgment of the individual endoscopist. Propofol was administered initially at a dosage of 20 mg for induction, with another 0.1–0.5 mg/kg/h given continuously for maintenance depending on the condition of the patient.

CO_2 insufflation and transcutaneous measurements

A CO_2 regulator prototype (Olympus) connected to a CO_2 bottle was used for CO_2 insufflation until the Olympus UCR (Fig. 1) became commercially available in Japan in May 2008 [25]. During the procedure, CO_2 insufflation was set at a constant rate of 1.2 l/min, which is a moderate level. In upper GI endoscopy, the UCR has three insufflation levels, which can be controlled by the use of three types of connecting tubes. These insufflation amounts are almost equivalent to the original three regulation levels of the EVIS LUCERA (Olympus).

Measurement of the arterial partial pressure of CO_2 (partial pressure of carbon dioxide [PCO_2] and arterial partial pressure of carbon dioxide [$PaCO_2$]) is an invasive, intermittent, and unpleasant process widely used for

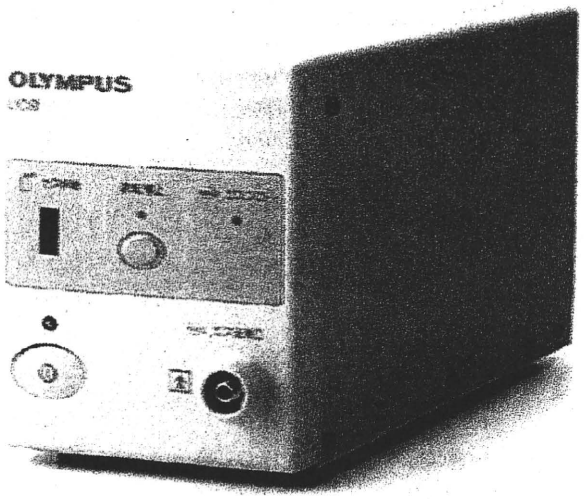

Fig. 1 UCR (CO_2 regulator). The UCR in upper gastrointestinal endoscopy has three levels of insufflation which can be controlled by using three types of connecting tubes. These amounts of insufflation are almost equivalent to the original three regulation levels of the EVIS LUCERA

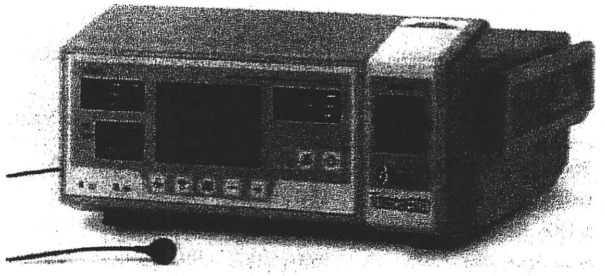

Fig. 2 The TOSCA measurement system and TOSCA 500 monitor, a noninvasive and continuous monitoring device for transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) that takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe

various patients as the gold standard, but determining the variation of $PaCO_2$ during ESD using CO_2 insufflation has proved to be quite difficult.

In this study, a TOSCA measurement system and TOSCA 500 monitor (Linde Medical Sensors, Basel, Switzerland) (Fig. 2) was used to measure and monitor both transcutaneous partial pressure of CO_2 ($PtcCO_2$) and oxygen saturation (SpO_2). This system, which takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe, is a noninvasive, continuous, trend-monitoring device for $PtcCO_2$ reported in several studies to provide general agreement between $PtcCO_2$ and $PaCO_2$ measurements [32–37]. We used a default temperature setting of 42°C for the earlobe sensor and recalibrated the TOSCA system to minimize the possibility of measurement error before each ESD. Procedure time was measured from endoscope insertion to its completed withdrawal after ESD, with $PtcCO_2$ and SpO_2 recorded every 3 s for both groups using the TOSCA system.

Statistical analysis

All variables in this study were described in terms of mean ± standard deviation as well as median and range. We used chi-square and *t*-tests to compare baseline characteristics and measurements between the two groups. All statistical analyses were performed using the SAS Statistical Package (SAS Institute, Tokyo, Japan), and a p value less than 0.05 was considered statistically significant.

Ethics

The ethics committee at NCCH approved the study protocol, and written informed consent was obtained from all patients before they were enrolled in the study.

Results

No significant differences in patient characteristics between the two groups were observed (Table 1). The CO_2 group study consisted of 45 patients (39 men and 6 women) with 52 lesions. These 45 patients (involving 15 esophageal and 30 gastric ESD cases) had a mean age of 68.5 ± 8.8 years (range, 50–84 years). The air group consisted of 44 patients (38 men and 6 women) with 51 lesions. These 44 patients (involving 12 esophageal and 32 gastric ESD cases) had a mean age of 67.6 ± 8.0 years (range, 43–84 years).

The macroscopic types of tumors included 13 elevated lesions, 32 flat and depressed lesions, 6 combined lesions, and 1 residual lesion in the CO_2 group and 11 elevated lesions, 34 flat and depressed lesions, 5 combined lesions, and 1 residual lesion in the air group (nonsignificant difference [NS]). In the CO_2 group, the median size of the tumors, determined histopathologically, was 13 mm (range, 5–60 mm), and the 35 adenocarcinomas included 2 Barrett's carcinomas, 15 squamous cell carcinomas (SCCs), and 2 adenomas. The median size of the tumors in the air group was 19 mm (range, 5–55 mm), and the 37 adenocarcinomas included 2 Barrett's carcinomas, 13 SCCs, and 1 adenoma. The difference between the two groups was not significant. The median specimen size was 35 mm (range, 20–75 mm) in the CO_2 group and 35 mm (range, 20–68 mm) in the air group (NS). The median procedure time was 115 min (range, 30–575 min) in the CO_2 group and 96 min (range, 38–309) in the air group (NS). Midazolam was received by 30 patients at a median

Table 1 Patient characteristics

	CO_2 (*n*)	Air (*n*)	*p* Value
Patients/lesions	45/52	44/51	
Mean age (years)	68.5 ± 8.8	67.6 ± 8.0	NS
Male/female	39/6	38/6	NS
Esophagus/stomach	15/30	12/32	NS
Macroscopic type			
Elevated	13	11	
Flat and depressed	32	34	
Combined	6	5	
Residual	1	1	NS
Histopathologic type			
SCC	15	13	
Adenocarcinoma	35	37	
Adenoma	2	1	NS
Median tumor size: mm (range)	13 (5–60)	19 (5–55)	NS
Median specimen size: mm (range)	35 (20–75)	35 (20–68)	NS
Median procedure time: min (range)	115 (30–575)	90 (38–309)	NS
Perforations	3	0	NS
Patients receiving midazolam	30	31	NS
Patients receiving propofol	15	13	NS
Dosage of midazolam: mg (range)	12 (5–20)	12 (4–23)	NS
Dosage of propofol: mg (range)	640 (130–2460)	370 (180–1116)	NS

CO_2 carbon dioxide, *NS* not significant, *SCC* squamous cell carcinoma

dosage of 12 mg (range, 5–20 mg) in the CO_2 group and by 31 patients at a median dosage of 12 mg (range, 4–23 mg) in the air group (NS), and propofol was received by 15 patients at a median dosage of 640 mg (range, 130–2,460 mg) in the CO_2 group and by 13 patients at a median dosage of 370 mg (range, 180–1,116) in the air group (NS).

All the tumors were resected en bloc by ESD except in one esophageal case in the air group, In this case, the patient's main lesion was resected en bloc by ESD, whereas another smaller synchronous lesion was treated by using endoscopic mucosal resection (EMR) with a cap-fitted panendoscope, resulting in a piecemeal resection [38].

Measurements of $PtcCO_2$ and SpO_2

The mean CO_2 group versus air group measurements were as follows: $PtcCO_2$ (49.1 ± 5.0 vs. 50.1 ± 5.3 mmHg; NS), maximum $PtcCO_2$ (55.1 ± 6.5 vs. 56.8 ± 7.0 mmHg; NS), $PtcCO_2$ elevation (9.1 ± 5.4 vs. 11.4 ± 5.6 mmHg; $p = 0.054$), SpO_2 (99.0 ± 0.7% vs. 99.0 ± 1.0%; NS), minimum SpO_2 (96.5 ± 2.4% vs. 95.4 ± 3.3%; $p = 0.085$), and SpO_2 depression (2.4 ± 2.3% vs. 3.3 ± 2.9%; NS) (Table 2; Fig. 3A–F). The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but in $PtcCO_2$ elevation and minimum SpO_2, the CO_2 group was better than the air group.

The patient characteristics did not differ significantly between the two groups when esophageal and gastric ESD cases were considered separately, nor did the $PtcCO_2$ and SpO_2 measurements differ significantly between the two groups when only esophageal ESD cases were considered. The CO_2 group versus air group measurements in gastric ESD cases were as follows: $PtcCO_2$ elevation (8.0 ± 5.2 vs. 10.8 ± 5.7 mmHg; $p = 0.049$) and SpO_2 depression (1.9 ± 1.8% vs. 2.8 ± 2.5%; $p = 0.087$). Although the $PtcCO_2$ and SpO_2 measurements again were similar for the two groups, when only gastric ESD cases were considered, the CO_2 group was better than the air group in $PtcCO_2$ elevation and SpO_2 depression.

Table 2 Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and oxygen saturation (SpO_2) measurements

	CO_2	Air	*p* Value
Mean $PtcCO_2$ (mmHg)	49.1 ± 5.0	50.1 ± 5.3	NS
Maximum $PtcCO_2$ (mmHg)	55.1 ± 6.5	56.8 ± 7.0	NS
$PtcCO_2$ elevation (mmHg)	9.1 ± 5.4	11.4 ± 5.6	0.054
Mean SpO_2 (%)	99.0 ± 0.7	99.0 ± 1.0	NS
Minimum SpO_2 (%)	96.5 ± 2.4	95.4 ± 3.3	0.085
SpO_2 depression (%)	2.4 ± 2.3	3.3 ± 2.9	NS

NS not significant

Five CO_2 group patients and five air group patients experienced a maximum $PtcCO_2$ exceeding 60 mmHg that continued for more than 5 min (NS). The median duration time was 12 min (range, 6–166 min) for the CO_2 group and 35 min (range, 10–148 min) for the air group (NS). The

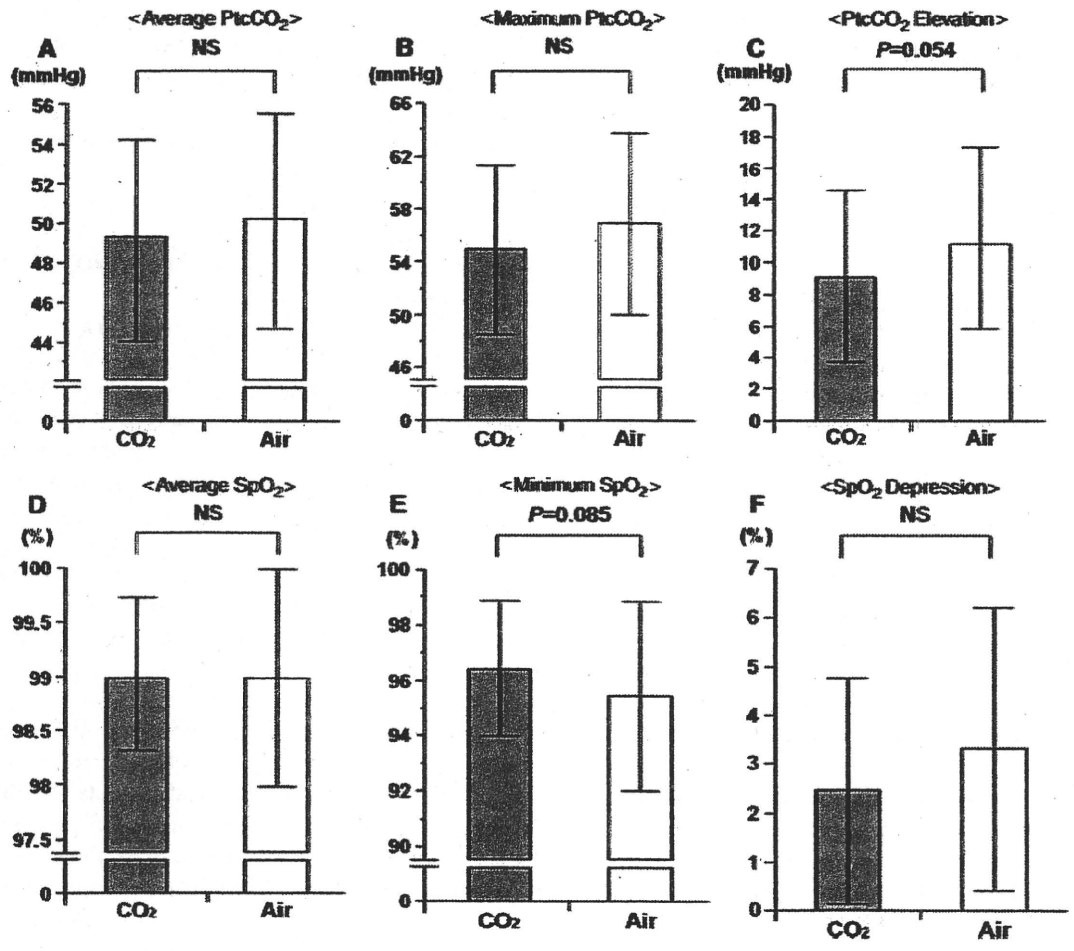

Fig. 3 Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and oxygen saturation (SpO_2) measurements. The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but the CO_2 group was better than the air group in $PtcCO_2$ elevation and minimum SpO_2

maximum $PtcCO_2$ was 72 mmHg in the CO_2 group and 74 mmHg in the air group (NS) (Table 3). None of the cases in either group involved an SpO_2 level lower than 90% that continued for more than 1 min, and no harmful oxygenation effects occurred. Temporary SpO_2 depression lower than 90% for less than 1 min resulted from the aspiration of two patients in the air group, but the condition subsequently improved and did not impair treatment (Table 3).

Table 3 Maximum transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and minimum oxygen saturation (SpO_2)

	CO_2 ($n = 45$)	Air ($n = 44$)	p Value
Maximum $PtcCO_2$ >60 mmHg[a]	5	5	NS
Median duration: min (range)	12 (6–166)	35 (10–148)	NS
Maximum $PtcCO_2$ (mmHg)	72	74	–
Minimum SpO_2 <90%[b]	0	0	NS
Median duration: min (range)	–	–	–
Minimum SpO_2 (%)	91	88	–

[a] >5-min duration

[b] >1-min duration

No adverse effects were caused by CO_2 insufflation in the CO_2 group. Perforations involving CO_2 insufflation occurred in three cases including two esophageal ESD cases and one gastric ESD case, but x-rays did not show any subcutaneous or mediastinal emphysema or pneumoperitoneum. As for the three patients in the CO_2 group with perforations, histopathologic examinations of the one gastric ESD patient showed a well-differentiated intramucosal adenocarcinoma located in the cardia, and the two esophageal ESD patients had SCCs within the lamina propria mucosae located in either the middle or lower thoracic esophagus. Antibiotics were administrated for all three patients over 3 to 5 days. Oral diet intake was started on either postoperative day 2 or 4, and each patient was discharged on postoperative day 6

without any invasive intervention, as is the usual course for gastric and esophageal ESD patients at our hospital. All the CO_2 group procedures were completed without delays, and none of the 45 CO_2 insufflation patients required extended hospitalization.

Discussion

To the best of our knowledge, this is the first study to investigate the safety of CO_2 insufflation in lengthy upper GI tract ESD procedures for patients under deep sedation. The results of our study indicate that CO_2 insufflation can be used as safely as air insufflation without any adverse effects by continuous monitoring of $PtcCO_2$ and SpO_2 during both esophageal and gastric ESDs.

Bretthauer et al. [4, 6] reported no significant observed difference in $PtcCO_2$ elevation between air and CO_2 insufflation groups during ERCP with deep sedation, and no significant increase in end-tidal CO_2 levels was demonstrated between the two groups in colonoscopy examinations without sedation, although patient abdominal discomfort was significantly less in the CO_2 group. In our study, midazolam and propofol were used, so it was difficult to measure patient discomfort levels using a visual analog scale after ESD because of considerable differences in the rate of recovery between those two sedatives.

The PCO_2 level basically depends on ventilation, so PCO_2 elevation can be regarded generally as caused by depression of both the ventilation rate and the tidal volume. Nelson et al. [39] reported $PtcCO_2$ elevation exceeding 40 mmHg and a maximum $PtcCO_2$ greater than 100 mmHg in ERCP using air insufflation, although there were no evident adverse effects.

In our results, the maximum $PtcCO_2$ per duration time, with $PtcCO_2$ exceeding 60 mmHg, was 72 mmHg for 166 min in the CO_2 group and 74 mmHg for 148 min in the air group, but with no adverse events in either group. No harmful oxygenation effects resulted from using CO_2 insufflation during ESDs because all the patients received O_2 nasally. These results suggest that $PtcCO_2$ elevation, which registered a maximum value of 74 mmHg without SpO_2 depression, did not represent a clinical problem, and no actual correlation was found between the two measurements in any of the cases. We believe that $PtcCO_2$ elevation was not caused solely by CO_2 insufflation but that other important factors were involved, including sedation levels and respiratory status, because the air group showed even higher $PtcCO_2$ values than the CO_2 group (Table 2; Fig. 3A–C) [5, 40].

Concerning the observation of differences between the two groups in $PtcCO_2$ elevation and minimum SpO_2 in all cases as well as $PtcCO_2$ elevation and SpO_2 depression in only the gastric ESD cases, we considered that ventilation rate and tidal volume were difficult to decrease because abdominal distension and diaphragm elevation were reduced to relieve bowel hyperextension. Accordingly, it also can be speculated that CO_2 insufflation may stimulate the respiratory center, leading theoretically to hyperventilation. Except for patients with COPD, who were excluded from this study, $PtcCO_2$ elevation may have been caused by hypoactivity of the respiratory center resulting from deep sedation rather than CO_2 insufflation or oxygen administration.

In the upper GI tract, especially the esophagus, the most serious complications are arrhythmia, cardiac collapse, thromboembolism produced by blood flow congestion resulting from a perforation (compartment syndrome), and pneumothorax [19–24]. We also considered why no subcutaneous or mediastinal emphysema or pneumoperitoneum appeared, and we suspected that leaked CO_2 in the three patients who experienced perforations probably was absorbed rapidly into the surrounding tissue [1, 2]. It can be expected that CO_2 insufflation will reduce all such complications. Because CO_2 insufflation was demonstrated to be safe in this study, it is recommended that to avoid any unexpected developments during treatment in the upper GI tract, particularly in the esophagus, ESD should be performed from the start using CO_2 insufflation. In addition, CO_2 insufflation is recommended for endoscopists with limited ESD experience, who likely will need more time to complete the procedure and may have a greater possibility of a perforation occurring because of their relative inexperience.

It generally is considered that a severe acidosis condition leads to arrhythmia, cardiac collapse, or hyperkalemia. If CO_2 retention does occur, the CO_2 can serve as a factor in decreasing the pH balance, although no clinical problem is involved if the pH balance is preserved within normal limits by other factors. Based on our findings, it appears that no adverse events may result if normal oxygenation is maintained even when a $PtcCO_2$ exceeding 60 mmHg persists for some time. Although CO_2 insufflation is not recommended for patients with severe pulmonary or cardiovascular disease, it is associated with no clinical disadvantage compared with air insufflation. We currently recommend, however, that $PtcCO_2$ be measured for enhanced safety during upper GI ESDs.

Several studies have shown a close correlation between $PtcCO_2$ and $PaCO_2$, so $PtcCO_2$ currently is regarded as a reliable and accurate measurement, although it is known that a discrepancy can exist between the two under certain body temperature and skin conditions [41]. No blood gas samples were taken in this study, so we have no data on actual patient pH levels and $PaCO_2$ values during the ESD procedures.

We were able to perform continuous measurement of the $PtcCO_2$ level and monitoring of its elevation during upper

GI tract endoscopic treatments, neither of which had previously been completely certain. Although more than 2,000 upper GI tract ESDs have been performed for patients at NCCH [42], very few major respiratory-related problems with the use of air insufflation have occurred despite the lack of certainty about previous $PtcCO_2$ levels. The advantage of having precise $PtcCO_2$ data is avoidance of additional sedatives resulting in excessively deep sedation that may cause respiratory dysfunction because PCO_2 elevation suggests depression of the ventilation rate and tidal volume. This also prevents tracheal intubation due to pulmonary arrest.

Use of a bispectral index (BIS) monitor that indicates a patient's sedation level by monitoring brain waves has been reported recently, so it is conceivable that the combined use of CO_2 insufflation with continuous $PtcCO_2$ measurement and the BIS monitor could result in safer upper GI tract endoscopic treatment procedures in the future [43, 44].

Conclusions

This study demonstrated CO_2 insufflation to be as safe as air insufflation for upper GI tract ESDs performed for patients under deep sedation without evidencing any adverse effects. We believe that CO_2 insufflation may be particularly effective for esophageal cases in which severe subcutaneous or mediastinal emphysema can be caused by perforations that may occur during the ESD procedure.

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Disclosures Satoru Nonaka, Yutaka Saito, Hajime Takisawa, Yongmin Kim, Tsuyoshi Kikuchi, and Ichiro Oda have no conflict of interests or financial ties to disclose.

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