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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

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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, 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

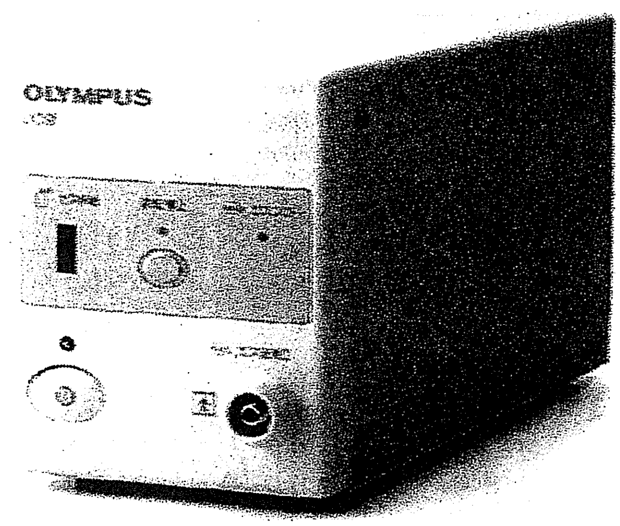

Fig. 1 UCR (CO_2 regulator). The UCR in upper gastrointestinal endoscopy has three levels of insufflation which can be controlled by using three types of connecting tubes. These amounts of insufflation are almost equivalent to the original three regulation levels of the EVIS LUCERA

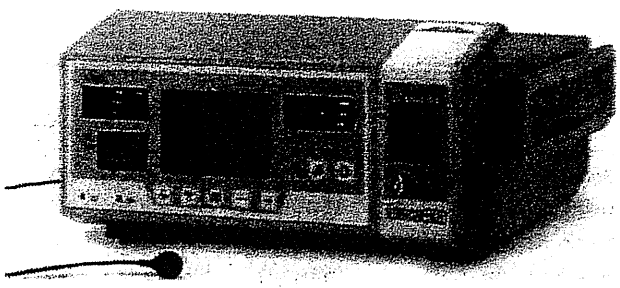

Fig. 2 The TOSCA measurement system and TOSCA 500 monitor, a noninvasive and continuous monitoring device for transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) that takes measurements using a sensor attached by a low-pressure clip to the patient's earlobe

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

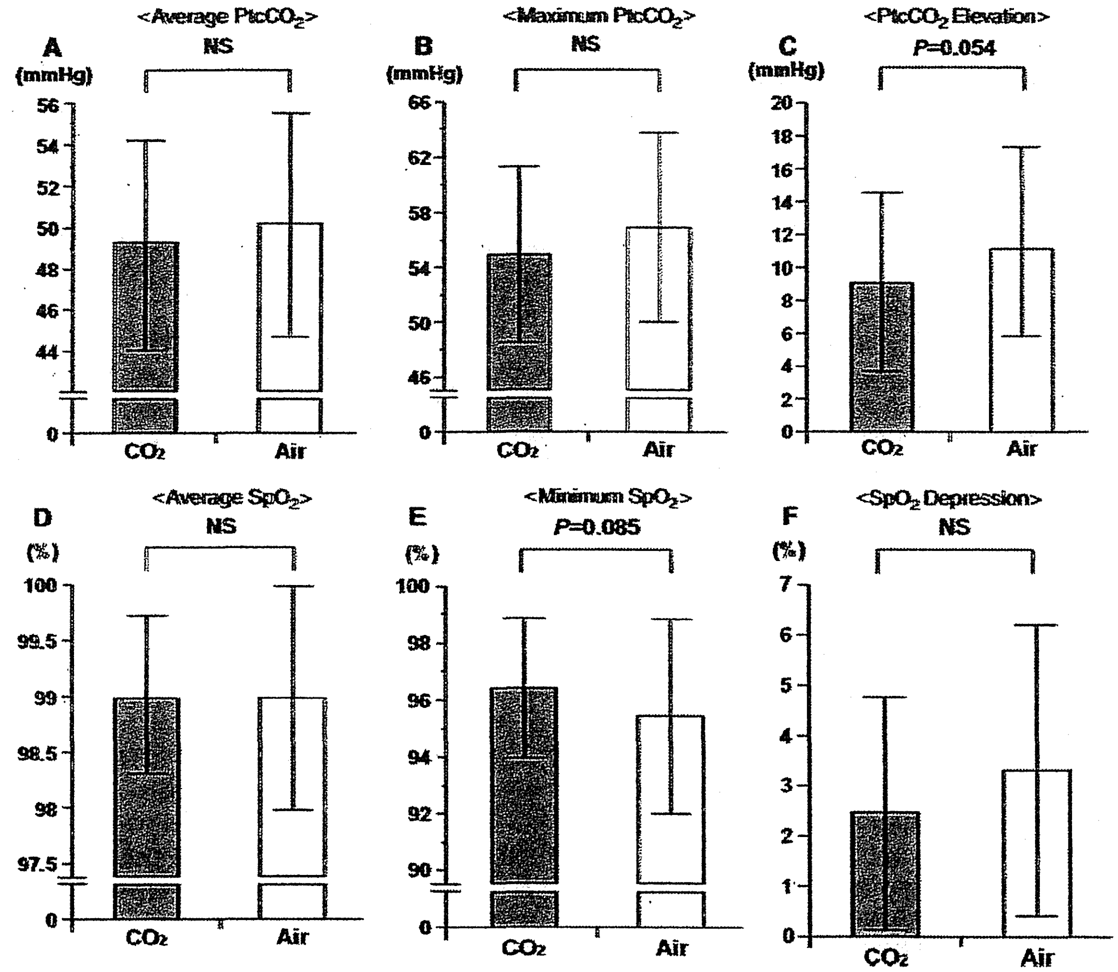

Fig. 3 Transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) and oxygen saturation (SpO_2) measurements. The $PtcCO_2$ and SpO_2 measurements were similar in the two groups, but the CO_2 group was better than the air group in $PtcCO_2$ elevation and minimum SpO_2

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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INDICATIONS FOR ENDOSCOPIC RESECTION OF COLORECTAL POLYPS AND SURVEILLANCE GUIDELINES

IMPACT OF NARROW-BAND IMAGING IN SCREENING COLONOSCOPY

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Narrow band-imaging (NBI) enhances mucosal visualization of the vascular network and surface structure and helps to increase the visibility of neoplasia by improving contrast. Studies on the detectability of colorectal neoplastic lesions using NBI have primarily been reported in Western countries, but the published opinions and conclusions remain controversial at the present time. Our earlier prospective pilot study demonstrated that NBI colonoscopy significantly improved detection of flat lesions, which are more likely to be missed, particularly on the right side of the colon. It is especially important that even examiners performing routine screening colonoscopies become sufficiently familiar with flat and depressed lesions and then take full advantage of the endoscopic systems and specific image enhancement functions currently available for improved detection of flat and diminutive lesions. Adequate bowel preparation is another important consideration.

Key words: detection, colonoscopy, narrow-band imaging (NBI), screening.

INTRODUCTION

Colonoscopy is the preferred screening method for colorectal cancer, but the number of missed colon polyps can be considerable. Back-to-back colonoscopies have found that the undetected rate for adenomatous polyps is approximately 25%[1,2] and even adenomas greater than 1 cm have been missed on occasion. Several techniques including chromoendoscopy,[3] cap-fitted colonoscopy,[4] retroflexion of the colonoscope[5] and wide-angle colonoscopy[6] have been used to improve the polyp detection rate and the newly developed Third Eye Retroscope system is expected to further increase overall detection.[7]

Narrow band-imaging (NBI) is based on modifying the bandwidth transmittance of spectral features using various optical filters to enhance visualization of the mucosal vascular network and surface structure.[8,9] This relatively new endoscopic technology has recently become available worldwide for use in the detection of colorectal neoplastic lesions, so greater attention is now being paid to whether NBI can be effective in adenoma detection.

This review focuses on the present status of the role of NBI, taking into account various other screening modalities, this promising technology's future prospects and the need for its further refinement.

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NARROW-BAND IMAGING

The center wavelengths of the dedicated trichromatic optical filters are shifted to shorter wavelengths of 500 nm, 445 nm and 415 nm with each having a bandwidth of 30 nm.[9] The NBI system is a relatively simple device in which two filters, a standard filter and an NBI filter, are built into one light source. NBI provides unique views especially of the mucosal vascular network and surface structure and helps in the visualization of neoplasia by improving contrast. One of the system's advantages is that the conventional view can be switched instantaneously to the NBI view and vice versa by pressing a single electronic button on the control handle of the colonoscope. NBI could potentially improve both polyp detection and differentiation of neoplastic from non-neoplastic polyps thereby serving a dual purpose in screening colonoscopy.

NBI in differentiating neoplastic from non-neoplastic colorectal polyps

Machida, Sano and their colleagues first reported that the NBI system improved endoscopic visualization without the need for any dye solution (high-contrast endoscopy).[10] In addition, their research examined the usefulness of NBI with magnification for the differential diagnosis of neoplastic from non-neoplastic lesions and determined that diagnostic accuracy using NBI was higher than that of conventional colonoscopy (93.4% *vs* 79.1%) and equal to that of chromoendoscopy using indigo-carmine dye spraying. Subsequently, the effectiveness of NBI in the differential diagnosis of colorectal polyps has clearly been demonstrated in several prospective studies[11–13] indicative of a growing consensus on the subject.

NBI for improving colorectal adenoma detection

Results from the first American randomized study on detectability using NBI were quite negative,[14] but a subsequent British comparative study on NBI was more positive particularly with respect to the detection of flat lesions.[15] Table 1 shows the results of our prospective pilot study.[16] Compared to conventional colonoscopy, the total number of adenomas detected by NBI was significantly higher. Based on the macroscopic type, flat lesions were detected significantly more often with NBI than with conventional colonoscopy. In terms of location, lesions on the right side of the colon were identified with NBI significantly more often compared to conventional colonoscopy. A number of NBI reports published primarily in Western countries, including the studies mentioned above, are characterized as being either positive or negative in Table 2,[17–21] but the opinions and conclusions are still controversial.

RECOMMENDATIONS

Comparing NBI systems and lack of reported information on function settings

In our review of the published reports on the detectability of colorectal adenomas using NBI, we noticed that two different Olympus (Tokyo, Japan) endoscopic video systems, either the sequential LUCERA series or the simultaneous EXERA-II series (also known as the 'color chip system') were used in all of the studies as both Olympus systems are now in service in different parts of the world. Nearly all of the positive studies used the LUCERA system while all of the negative studies relied on the EXERA-II system. Accordingly, the LUCERA system may be preferable to the EXERA-II system for polyp detection. Unfortunately, the specific NBI system image enhancement settings (i.e. surface structure and adaptive index of hemoglobin [IHb] color enhancement settings) were not indicated in any of the other reports so a truly accurate comparative analysis is even more problematic.

Table 1. Comparison of detected adenomas – total number, lesion size, macroscopic type and location

		CC	NBI	*P*-Value
Total number of detected adenomas		58	72	0.04
Lesion Size	<5 mm	48	57	0.15
	5–9 mm	58	68	0.06
	≥10 mm	10	9	0.61
Macroscopic type	Flat	58	72	0.04
	Polypoid	58	62	0.45
Location	Right Colon	72	87	0.02
	Left Colon	31	36	0.45
	Rectum	13	11	>0.99

CC, conventional colonoscopy; NBI, narrow-band imaging.

Table 2. Clinical outcomes of studies comparing adenoma detectability using narrow-band imaging and conventional colonoscopy

	Negative Studies	Olympus Endoscopic Video System
Rex DK, *et al.*[14]	2007, USA	EXERA-II
Kaltenbach T, *et al.*[17]	2008, USA	EXERA-II
Alder A, *et al.*[18]	2009, Germany	EXERA-II
Paggi S, *et al.*[19]	2009, Italy	EXERA-II
	Positive Studies	**Olympus Endoscopic Video System**
East JE, *et al.*[15]	2008, UK	LUCERA
Rastogi, *et al.*[20]	2008, USA	EXERA-II
Inoue, *et al.*[21]	2008, Japan	LUCERA
Our Study[16]	2008, Japan	LUCERA

Appropriate system function settings and other important considerations

We believe that appropriate NBI system function settings are essential in order to properly assess the detectability of adenomas using NBI.[22] Use of both enhancement functions previously mentioned markedly improves the contrast of NBI system images. The surface structure enhancement function includes six different image settings that provide increased definition of mucosal and microcirculatory structure. The adaptive IHb color enhancement function with its three separate level settings automatically calculates the average hemoglobin concentration in formulating the NBI view of the surrounding tissue in combination with the enhanced image features. The A-5 image setting of the surface structure enhancement function together with the level 3 adaptive IHb color enhancement setting seem to be the most suitable for detection of colorectal adenomas based on our experience.

Selection of an appropriate colonoscope is another important consideration. A high-definition colonoscope should be used for polyp detection, but a standard definition colonoscope is unsuitable for such a purpose (Fig. 1). In contrast, use of a high-definition colonoscope is not necessary for the differential diagnosis of polyps with magnification. In addition, the importance of adequate bowel preparation is even more pronounced with NBI compared to conventional colonoscopy. Lastly, it is increasingly important that screening colonoscopy examiners be sufficiently familiar with flat and depressed lesions in order to ensure a thorough colorectal screening examination.

NBI FUTURE PROSPECTS AND REFINEMENTS

A multicenter randomized controlled trial utilizing appropriate NBI system settings is currently being conducted in Japan to evaluate the efficacy of screening and surveillance colonoscopies. More precise NBI system settings for screening colonoscopy could increase the detection rate for flat adenomatous lesions and reduce variations in diagnostic performance. Finally, we recommend further refinement of the NBI system itself with practical improvements such as a more powerful light source to extend the NBI view in the colon and better enhancement of lesion margins, which would be most helpful in the detection of adenomas.

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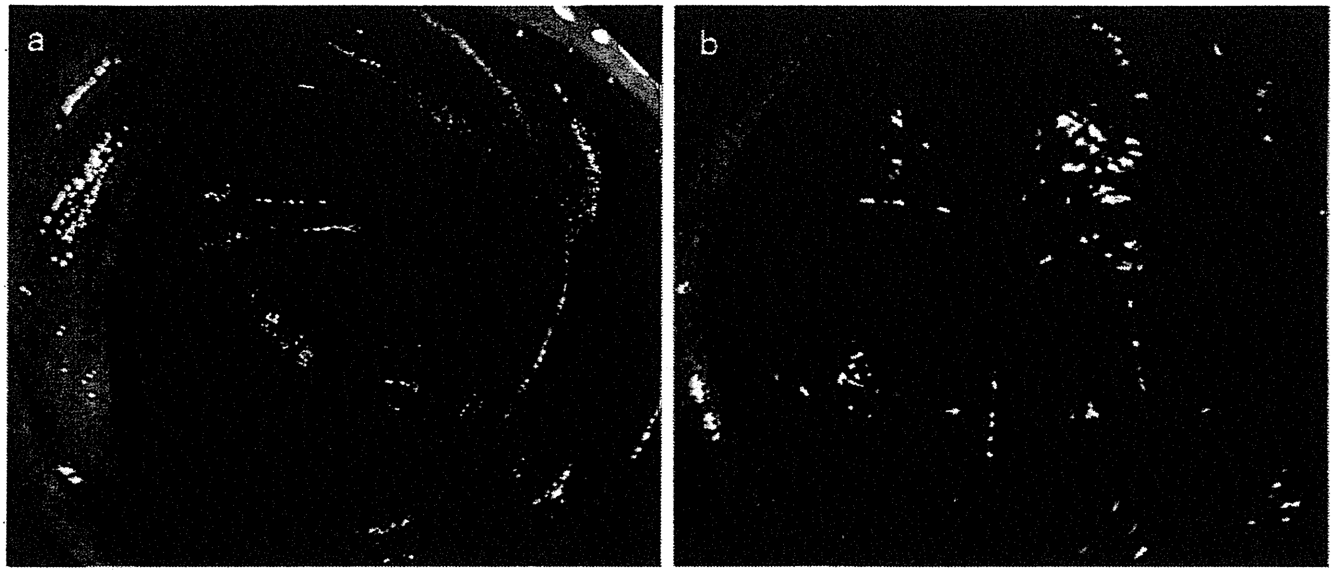

Fig. 1. Comparison of narrow-band images from different colonoscopes. (A) High-definition colonoscopy view with CF-H260AZI (Olympus, Tokyo, Japan). (B) Standard-definition colonoscopy view with PCF-240ZI (Olympus).

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特集：内視鏡・内視鏡外科治療最前線

下部消化管

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内視鏡治療の進歩　消化器領域

下部消化管

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Recent progress in endoscopic treatment for colorectal tumors

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Abstract

Background: Endoscopic mucosal resection (EMR) is indicated for the treatment of superficial, early-stage colorectal cancer because of its minimal invasiveness and excellent results in terms of clinical outcomes. Conventional EMR techniques currently used for the resection of laterally spreading tumors (LSTs), however, are inadequate for the en-bloc resection of flat lesions≧20 mm because both incomplete removal and local recurrence have been observed and reported on occasion. Endoscopic submucosal dissection (ESD) is widespread as a minimally invasive treatment for early gastric cancer, however, it is not as widely used in the colorectum because of its technical difficulty and complication risk.

Indications for colorectal ESD: Based on clinicopathological analyses of LSTs, the indication for colorectal ESD is an LST non-granular type (LST-NG) >20 mm. LST granular type (LST-G) >30 mm or 40 mm are possible candidates for ESD because they have a higher submucosal (SM) invasion rate and are difficult to treat even by endoscopic piecemeal mucosal resection (EPMR).

ESD procedures: ESD procedures were performed using a ball-tip bipolar needle knife (B-knife) and an insulation-tip knife (IT knife) with carbon dioxide (CO_2) insufflation. Glycerol and 0.4 % hyaluronic acid were used as an SM injection solution in order to provide longer lasting SM elevation.

Conclusion: ESD is an effective technique for treating colorectal LST-NGs >20 mm and LST-Gs >30 mm providing a higher en-bloc resection rate as well as being less invasive than surgery.

Key words: endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic piecemeal mucosal resection (EPMR), colorectum, laterally spreading tumor (LST)

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はじめに

早期大腸癌に対する内視鏡治療は1971年，Deyhleら[1]が高周波電流によるポリペクトミーの方法論を開発し，新谷らが大腸に臨床応用したことでその端緒が開かれた.

本法の治療学的な意義はMorsonらの提唱したポリープ癌化説(polyp cancer sequence)によって支持され，長い間，大腸癌における早期診断・早期治療の中心的役割を担ってきた．しかし，我が国では工藤らの診断努力によって陥凹型早期大腸癌がまれならず存在することが明らかとなり，現在では従来のポリープとは全く様相を異にする表面型大腸腫瘍の診断と治療が大きな課題となっている[2,3].

この表面型腫瘍に対する切除法は平坦な病変であるため，通常のポリペクトミーの手技では切除を困難としていた．このため，粘膜下層に生理食塩液を注入切除する内視鏡的粘膜切除術(EMR)が適用されるようになった[4]．またEMR手技の進歩により20mm以上の表面型腫瘍に対してもEMRの適応が拡大されるようになったが，通常のEMRでは分割切除(EPMR)となることが多い．EPMRにおいては，遺残・再発率が一括切除と比較して多く[5]，詳細な病理学的検索が困難となる場合があるといった点から，一括切除を目的とした内視鏡的粘膜下層剥離術(ESD)[6]が大腸においても行われるようになった．早期胃癌および食道癌に対する内視鏡治療としては，EMRより高額に保険収載され，ここ数年で急速に普及し，それに伴い大腸ESD[7,8]を施行する施設も増えている.

1. EMRの適応の現状

EMRの適応に関しては，根治的治療がなしうることが絶対条件であり，必然的に深達度の限界が問題となる．Morsonは，大腸の粘膜内腫瘍は，転移の報告がなく局所切除で根治可能であるとしている．したがって粘膜内病変に関しては，大きさや部位などの条件から技術的困難性などが適応の限界点になる．一方，大腸SM癌に関しては，10％程度のリンパ節転移が認められる．2005年7月に大腸癌治療ガイドライン2005年度版が出版され，更に2009年の改訂版において内視鏡的摘除後の追加治療の適応基準[9]として推奨カテゴリーB(低いレベルのエビデンスに基づき，ガイドライン作成委員の意見が一致している)として以下の基準が示された.

‘垂直断端陽性の場合は外科的切除が望ましい.

摘除標本の組織学的検索で以下の一因子でも認めれば，追加治療としてリンパ節郭清を伴う腸切除を考慮する.

(1) SM浸潤度1,000μm以上 (2) 脈管侵襲陽性 (3) 低分化腺癌，印環細胞癌，粘液癌 (4) 浸潤先進部の簇出(budding) grade 2/3’

以上の因子のうち治療前に臨床的に推測可能なものは壁深達度のみであり，治療方針の決定には拡大内視鏡や超音波内視鏡などに基づいた深達度診断が重要となってくる．当院では，通常内視鏡診断に加え[10]，‘工藤・鶴田分類’をもとに3群に分けた藤井らの臨床分類を使用し，腫瘍性病変が内視鏡治療が適切(non-invasive pattern)か，それとも外科手術が妥当(invasive pattern)かを判断している[3,11].

2. 内視鏡治療の種類

病変の大きさ，形に応じて，内視鏡治療の方法を使い分ける必要がある.

a. Hot biopsy(図1-a)

主に6mm程度までの腺腫性ポリープに対して施行する．鉗子でポリープを把持し粘膜面から持ち上げた状態で通電することで，ポリープと正常粘膜間の最も薄くなった部分が切除される．それ以上の大きさのポリープや，早期癌，陥凹性病変に対しては通常，適用しない.

b. ポリペクトミー(図1-b)

スネアでポリープの基部正常粘膜部を把持し通電切除する方法であり[1]，主にIpなどの隆起型病変に対して施行される．スネアの最大径が3cm程度であるため大きさの限界がある.

c. EMR(図1-c)

表面型腫瘍や粘膜内癌に対して施行される.

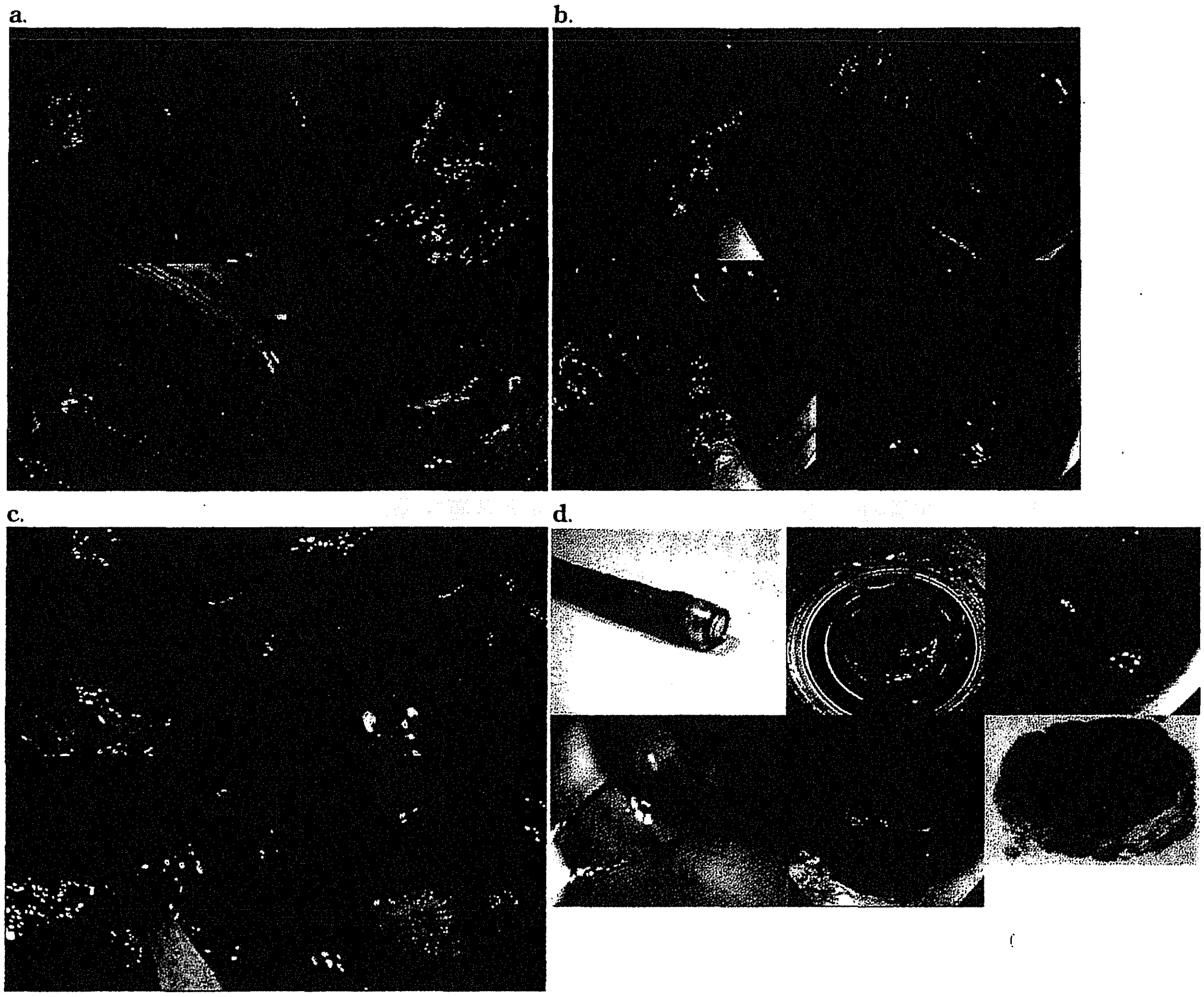

図1　内視鏡治療法

a: hot biopsy
主に6mm程度までの腺腫性ポリープに対して施行する．鉗子でポリープを把持し粘膜面から持ち上げた状態で通電することで，ポリープと正常粘膜間の最も薄くなった部分が切除される．
b: ポリペクトミー
スネアでポリープの基部正常粘膜部を把持し通電切除する方法であり，主にIpなどの隆起型病変に対して施行される．スネアの最大径が3cm程度であるため大きさの限界がある．
c: EMR
表面型腫瘍や粘膜内癌に対して施行される．生理食塩液などを粘膜下層に局注して表面型病変をポリープ状に隆起させたうえで切除する．
d: ESMR-L(endoscopic submucosal resection with a ligation device)

ポリペクトミーと同様スネアで切除するが，生理食塩液などを粘膜下層に局注して表面型病変をポリープ状に隆起させたうえで切除する[4]．EMRにおいてはいかに適切な粘膜下膨隆を形成できるかが，手技の成否にかかわってくる．最近は，生理食塩液の代わりに，グリセオール®[12]やヒアルロン酸製剤(ムコアップ®)[7]が粘膜下局注剤として使用されるようになり，粘膜下膨隆の持続時間も長くなり，また形の良い膨隆が容易に形成できるようになっている．

d. Endoscopic submucosal resection with a ligation device(ESMR-L)(図1-d)

キャプ法(EMR-C法)とともに，食道では多用されてきたが大腸では穿孔の危険性からあまり使用されない．手技は簡便であり，短時間で施行でき，粘膜下層をしっかり切除できるため

直腸カルチノイドの治療に非常に有用である.

3. 大きさからみたEMRの適応の限界

大きさからみた通常EMRによる内視鏡的一括切除術の限界は,スネアの大きさに規定される.大腸癌治療ガイドラインの2009年度版において,内視鏡的摘除の適応基準に関し,‘(1)粘膜内癌,粘膜下層への軽度浸潤癌.(2)最大径2cm未満.(3)肉眼型は問わない.’としている.またコメントで,‘ポリペクトミーやスネアEMRで無理なく一括切除できる限界は2cmである.’としている.

陥凹型(IIa+IIc, IIc)および表面型(非顆粒型LST: LST-NG)病変に関しては,腺腫癌化説とは異なる発育進展系(de-novo様進展)が考えられ一括切除が望まれるため,2cmまでの粘膜内癌と診断される病変がEMRの適応となる.

4. 内視鏡的分割切除(EPMR)

2cmを越える病変でも,顆粒型LST(LST-G)などは腺腫あるいは腺腫内癌であって,そのほとんどが腺腫であれば分割切除(EPMR)が許容されると考えられ[13],EMRが普及してからは,多くの施設でEPMRが施行され始めている[14].注意すべきは,癌部あるいはSM浸潤部などを絶対にスネアで分断しないことである.正確な病理組織診断,深達度診断や脈管侵襲の評価ができなくなる可能性があり,その場合,適切な追加外科手術が選択できなくなる危険性がある.

LST-Gは,顆粒均一型では,腫瘍径が大きくなってもそのほとんどが腺腫あるいは腺腫内癌であり,EPMRの良い適応と考えられる[13,14].一方,粗大結節を含む結節混在型においては,腫瘍径とともにSM浸潤率も上昇することから3-4cmまでをEPMRの適応としている[13].

LST-Gでは,粗大結節部か陥凹部でSM浸潤をきたすことが多いが,結節部においては拡大内視鏡を用いてもinvasive patternを呈さない場合がある.したがって,invasive patternを呈さないLST-Gでは最初に,粗大結節を含む部位をできるかぎり大きく切除し,残りの顆粒均一部に関してはpiecemeal resectionで対応する計画的分割切除術を行う必要がある[13,14].

5. 内視鏡的粘膜下層剥離術(ESD)

EMRの腫瘍径の限界,EPMRの局所遺残の問題点を克服することを可能とした画期的方法がESDである.元々は平尾らのendoscopic resection with local injection of HSE solution (ERHSE)法を改良し,細川ら[6]・小野らが開発したITナイフを使用して早期胃癌の一括切除を目的としていた.その後,Yamamotoら[7],矢作らが先駆者となり,深部結腸においても局注液やナイフに工夫をし,ESDを積極的に行うようになった.しかしながら,大腸では腸管壁の薄さからくる穿孔の危険性や,管腔が狭いことから内視鏡の操作性が悪いといった技術的困難性から,いまだESDは一般化していない.また胃癌と異なり,EMRの適応となるいわゆる側方発育型腫瘍(LST)ではその多くが腺腫内癌であり,分割切除でも十分に対応できている[14]ことも,大腸におけるESDが広まらない理由の一つと考えられる.

しかしながら,LSTの中でもLST-NGにおいては,k-ras, p-53などの遺伝子の検討からも陥凹型腫瘍に近い性質を有していることが示唆されている[15].またSM浸潤率やSM浸潤様式の点からもLST-NGに関しては一括切除が必要であるという認識はある程度統一した見解となっている[13].そこで,大腸ESDを安全に行うための工夫が必要となり,以下に示すように様々な工夫,機器の改良が行われている.

a. 局注液(図2-d)

十分な粘膜下膨隆を長時間維持する目的でグリセオール®の有用性が報告されている[12].しかしながら大腸においてESDを行うにはグリセオール®だけでは十分でなく,更に粘稠度の高い局注液が必要となりムコアップ®[7]が必須となっている.また200ccのグリセオール®に1-2ccのインジゴカルミン®,および1ccのボスミン®を混合し,粘膜下層の視認性を高め,止血効果をも期待している.最近では,メチルセルロースなどの更に粘稠度の高い局注液も研究されており,今後の臨床応用が期待される.

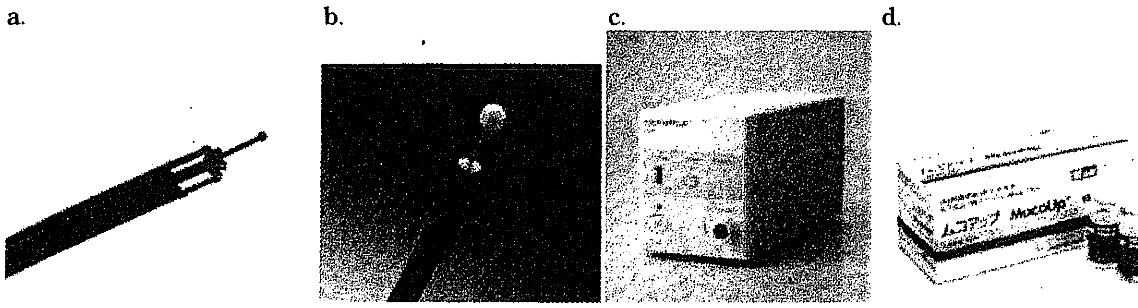

図2 国立がんセンター中央病院における大腸ESDのデバイス
a: ボールチップ型Bナイフ, b: ITナイフ, c: CO_2送気装置, d: 局注剤ムコアップ®.

b. ナイフ・メス(図2-a, b)

1) 針状メス

Yamamotoら[7]によりERCP用のプリカッティングナイフが大腸ESDでも使用されている. シャープな切開・剥離が可能で, ねらった部位を確実に切開できる利点がある反面, 筋層に向かって通電すると容易に穿孔をきたす危険性がある.

2) ITナイフ

ITナイフは針状メスの先端に絶縁セラミックチップを取り付けることにより穿孔の危険性を減らしている[6]. 一度に切開できる面が多いために切開speedが早いことが特徴である. 欠点として, 横方向(短軸方向)の切開に弱い点があげられるが, 粘膜が薄く, また粘膜下層の組織のまばらな大腸においては, 横方向の切開においても十分にテンションをかけて切れば, 粘膜切開も可能である. しかしながら粘膜・粘膜下層の薄い大腸においては絶縁チップの大きさがやや大きく, また新しく開発されたITナイフ2は筋層への思わぬ損傷を引き起こす危険性がある. そこで著者らはチップを小型化し安全性・操作性を高めた大腸専用ITナイフの開発を行っている.

3) フックナイフ

小山らが考案し, 主に食道ESDで使用されているデバイスである. 特に線維化の強い部位の剥離においてはSTフード®などを装着して粘膜下層に潜り込み, フックナイフでその線維化部分を少しずつ剥離する方法が選択される.

4) フレックスナイフ

シースもナイフの部分も柔らかく, 多少押しつけても穿孔の危険が少ないとされる. またシース先端の太りがストッパーとなるため, このストッパーを視認しながら切開・剥離することで安全な大腸ESDが可能である. しかしながら, 穿孔の危険が少ないものの構造上はモノポーラーナイフであり, 筋層に垂直に当たっている場合はわずかの通電でも穿孔をきたしうる.

5) Dual knife

フレックスナイフの後継品である. ナイフ長を固定し, 助手のナイフ長調整の手間を省いた. ナイフ先端がdisk状となっており, 安全性が増している. またナイフを収納した状態で止血やマーキングが可能である. 以上はすべてオリンパス社製である.

6) Bナイフ

Bナイフはバイポーラーシステムという構造上, 針状ナイフとシース先端の電極間のみに電流が流れナイフ先端から病変に対して電流が流れず, 穿孔の危険性が極めて少なく, また組織への凝固の影響も少ない[16]. またナイフ長が調整可能であり, ナイフが病変と垂直にしか当たらない場合はナイフ長を1mm程度に短く調整することで安全にESDを行うことが可能である. 最近, 著者らは, 先端にボールチップを擁したボールチップ型Bナイフを開発した. 先端が鈍であり穿孔の危険性が更に減じられており, また先端のボールチップで組織をフックした切開剥離が可能である. 周囲切開から粘膜下層剥離まで1本のナイフでESDが可能であり, 安全性および手技の容易さから大腸ESDの初心者には特にお勧めのナイフである.

7) フラッシュナイフ

豊永らが開発した送水機能(局注も可能)付きの針状メスである．針の長さも1-3mmまでのラインアップを擁している．フレックスナイフやBナイフと同様，周囲切開から粘膜下層剥離までESDのすべての工程をこの1本で完結することが可能である．生理食塩液の局注が可能ではあるが，グリセオール®やヒアルロン酸の局注は難しいようである．

8) その他

他各社から，幾つかのナイフが発売されている．

c. 止血デバイス

1) コアグラスパー®

出血に対する凝固は主にオリンパス社製のコアグラスパー®が使用され，soft凝固の70-80Wで止血する．大腸では壁が薄いので，過度な通電は穿孔の危険性があるため，慎重を要する．また太い血管は切開前に，あらかじめ止血しておくことが望ましい．

2) ヘモスタットY®

ペンタックス社製のヘモスタットY®はバイポーラーの止血鉗子である．大腸ESD時の出血に対しては，筋層への熱焼灼の影響も少なく安全に使用できる．

d. 内視鏡

大腸ESDにおける反転操作は，ESDを安全にかつspeedyに施行するために必須であると考える．反転操作が難しい症例においては，特にITナイフを用いた粘膜下層の剥離は困難となる．そこで著者らは，大腸のいかなる部位においても反転操作を行えるよう細径スコープであるオリンパス社製PCF-240Z®あるいはwater jet機能付きの大腸ESD専用細径スコープ(PCF260WJ®)を主に使用している．また肝彎曲付近でスコープの固定が難しい病変に対し，矢野らは，大腸ESD専用のダブルバルーン内視鏡を開発し有効性を報告している．更にはまた直腸や左半結腸の病変においては，操作性の点から上部用スコープを使用することも一案である．

e. 先端アタッチメント

胃のESDにおいてはITナイフによるESDでは先端アタッチメントを使用する場面は少ないが，大腸ESDでは先端アタッチメントは必須である．

1) 先端アタッチメント

通常オリンパス社製あるいはトップ社製のソフト先端アタッチメントが汎用されている．胃のESDと比較し，先端を長めに装着することがポイントである．

2) 先端細径フード(STフード®)

STフード®は線維化の影響などで粘膜下層に潜り込めないときには非常に有用である[7]．欠点として視野が若干不良で，またナイフ用のレールが装着されていることからITナイフなどを使用するとレールに絶縁チップが引っ掛かってしまう不具合があった．したがって線維化以外のESDを最初から最後までSTフード®で完遂することはあまりないと考える．そこで著者らは，それらの欠点を改良したshort STフードの開発を行っている．

f. 送気

大腸ESDにおいては，腫瘍径の大きな病変を対象にしているため治療時間は長くなる傾向にあり，腸管内に多量の空気が注入されると被検者の苦痛は大きい．これらの問題を解決するため2004年10月より大腸ESDにおいて送気にCO_2を用いている[17](図2-c)．現在まで400例以上に実施したが数例で軽度嘔気の訴えがあったのみで問題となるような偶発症は経験していない．意識下鎮静法で行っているため，CO_2 retentionの危険性は少ないが念のため経皮的にCO_2濃度をモニターしている．慢性閉塞性肺疾患，重度心疾患のある患者に対しては使用を控える必要がある．最近は大腸ESDのみでなくdeep sedationを必要とする食道ESDでの安全性も報告している[18]．

g. 偶発症対策

大腸ESDにおける主な偶発症は穿孔と出血である．

1) 穿孔

穿孔に関しては，大腸の穿孔は腹膜炎を併発

する危険性から外科手術が必要であるという考えが一般的であった．しかしながら最近では，内視鏡的にクリップ縫縮することで保存的な経過観察の可能性も報告されている[19]．これにはニフレック®やマグコロール®などで腸管内洗浄が完全に行われるようになったこと，またESDにおける穿孔は通常EMRによる穿孔と比べて小さな穿孔であることが多くクリップ縫縮が容易であることなどが要因となっていると思われるが，現時点では胃の穿孔と同じには考えず慎重に対応するべきである．

したがって穿孔を起こさない心構えが大前提ではあるが，万一の穿孔に備え前処置の強化が重要となる．当院では更に第2世代セフェムの静注を，治療当日に予防的に行っている．また腸液の腸管外への漏出を予防する目的で，ESD前に余分な腸液の吸引および腸液が病変と反体側に移動するよう被検者の体位変換をしている．この体位変換は病変の重力を利用したESDにも有用である．万一穿孔した場合は，可及的速やかにクリップ縫縮を行うが，その際その後のESDの邪魔にならないよう，ある程度剥離を進めてからクリップ縫縮することがポイントである．保存的に経過観察する場合でも外科医と緊密な連携を取り，緊急手術のタイミングを逃さないことが重要である．

2）出　血

出血は術中出血と後出血に分けられる．術中出血に関しては，細い血管を視認した場合は凝固モードでゆっくりと切開することで対応可能である．太い血管は前述のようにあらかじめ凝固してから剥離に入ることがポイントである．後出血の頻度は多くないものの，便器が真っ赤になる程度の下血を認めた場合は内視鏡的な止血が必要となる．術中止血はその後の剥離の妨げにならぬよう凝固止血を主に使用するが，後出血の際はクリップにて露出血管を処理する場合もある．

6. ESDを安全に行う工夫

a. Traction法

大腸ESDの良い適応であるLST-NGは粘膜内病変であっても，non-lifting signを呈する症例では粘膜下層の剥離に難渋することがある．そこで粘膜下層を直視する工夫として，sinker法を開発した．病変の剥離された辺縁に，sinker(錘)の装填されたクリップを装着し，患者の体位を適切な方向に変換することで，病変にsinkerの重さのトラクションがかかり，切除すべき粘膜下層が展開する．粘膜下層を直視しながらESDを進め，最後にsinkerシステムと切除標本を同時に回収する．ほかに，坂本らはSOクリップを用いて，浦岡らはダブルスコープを用いてそれぞれ切除された粘膜にトラクションをかける工夫を報告している．ESDでは外科手術における外科医の左手にあたるトラクションをいかに効果的にかけるかがポイントとなる．

7. 国立がんセンターにおける大腸ESDの実際(図3-a～f)

a. 適応の診断

肉眼型からESD適応であるか否かを判断し，粘膜内病変であることを通常内視鏡・拡大内視鏡などを駆使して診断する．

b. 周囲切開

大腸病変に関して基本的に病変境界は明瞭であり，病変周囲のマーキングは必要ないが，治療前にはインジゴカルミン®を撒布し側方への進展を観察する(**図3-a**)．周囲切開からボールチップ型Bナイフ(effect 3, endocut 50W)にて，病変口側から約1/4-半周の切開を開始するが，切開の割合は病変の大きさに応じて調整する(**図3-b**)．

c. 粘膜下層の剥離

粘膜下層の剥離も主にボールチップ型Bナイフで行っている．凝固モード(effect 3, forced 40W)で剥離するため出血が少なく，細い血管であればゆっくりBナイフを動かすことで出血を予防することが可能である．

粘膜下層の剥離が十分進んだ後に，スコープの反転を解除し(**図3-c**)，病変肛門側の周囲切開および粘膜下層の剥離を開始する．病変の剥離が進むと，被検者の体位変換により病変がそ

a. b.
c. d.
e. f.

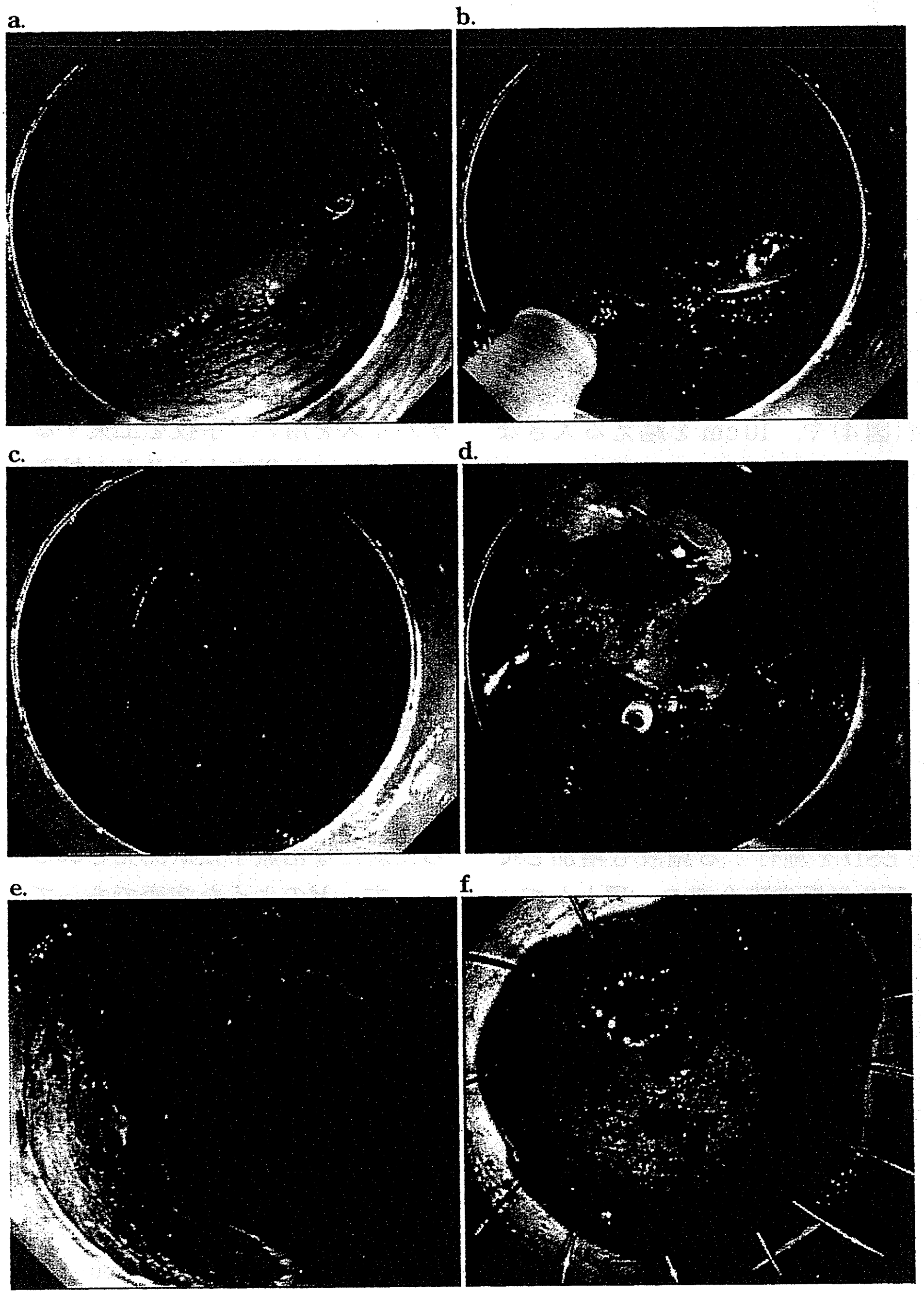

図3 大腸ESDの実際

a: 反転にて4cm大の非顆粒型LST(LST-NG)を口側から観察している. インジゴカルミン®撒布および先端アタッチメントの装着により病変境界は明瞭に観察可能である.

b: 同様に反転にて周囲切開からボールチップ型Bナイフ(effect 3, endocut 50 W)にて, 病変口側から約1/4–半周の切開を開始するが, 切開の割合は病変の大きさに応じて調整する.

c: 粘膜下層の剥離が十分進んだ後に, スコープの反転を解除し, 病変肛門側の周囲切開および粘膜下層の剥離を開始する.

d: 病変の剥離が進むと, 被検者の体位変換により病変がそれ自体の重さで重力方向に牽引される. そのような場面では, 粘膜下層を直視しながらITナイフで, 筋層に平行に剥離することで, 安全にかつspeedyに剥離可能である.

e: 一括切除後潰瘍面.

f: 切除検体.