Chapter 12

Therapeutic and Diagnostic Approaches in Colonoscopy

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http://dx.doi.org/10.5772/52733

1. Introduction

Colorectal cancer is a common gastrointestinal malignancy in the USA, Europe, and Japan. Most colorectal cancers are thought to arise from preexisting adenomas based on the concept of the adenoma-carcinoma sequence [1]. Chromoendoscopy, using Kudo and Tsuruta's pit pattern classification, is an efficient tool for the differential diagnosis of colorectal polyps [2-4]. Recently, image-enhanced endoscopy (IEE) has been used for diagnosing gastrointestinal tumors [5-7]. Endoscopic therapy, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is used worldwide to treat adenoma and early colorectal cancer [8-10]. In this chapter, we demonstrated the effectiveness of IEE and discuss strategies of therapeutic endoscopy including EMR and ESD.

2. Image-enhanced endoscopy

Colonoscopy is accepted as an efficient examination for the detection of neoplastic colorectal lesions. However, the diagnostic capability of white-light endoscopy (WL) for the differentiation of neoplastic and non-neoplastic polyps shows low sensitivity (38–76%) and variable specificity (66–97%) [11-13]. On the other hand, chromoendoscopy has demonstrated high sensitivity (96.3–97.0%) and specificity (93.5–100%) for the differentiation of neoplastic and non-neoplastic polyps [10,11]. However, chromoendoscopy is time-consuming. Now, image-enhanced endoscopy (IEE) is used to diagnose gastrointestinal tumors. This method is a change from conventional WL endoscopy, and requires no dye. It only requires the push of a button. IEE such as narrow band imaging (NBI), flexible spectral imaging color enhancement (FICE), and autofluorescence imaging (AFI) offer many advantages for diagnosis of neoplastic tumors, evaluation of invasion depth of cancerous lesions, and detection of neoplastic lesions. We

demonstrated the efficacy of IEE for diagnosis of colorectal tumors in view of endoscopic treatment options.

3. NBI, FICE, and AFI systems

With the NBI system (Olympus Medical Co., Tokyo, Japan), optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are mechanically inserted between a xenon lamp and a red/green/blue rotation filter [12-15]. Narrow vessels at the mucosal surface can be seen most clearly at 415 nm, which is the wavelength that corresponds to the hemoglobin absorption band, while thick vessels in the deep layer of the mucosa can be detected at 540 nm. Thus, NBI can enhance vascular patterns [Figure 1]. Moreover, NBI can detect pit like structures, which have been recognized as surface patterns by a Japanese consensus symposium [16].

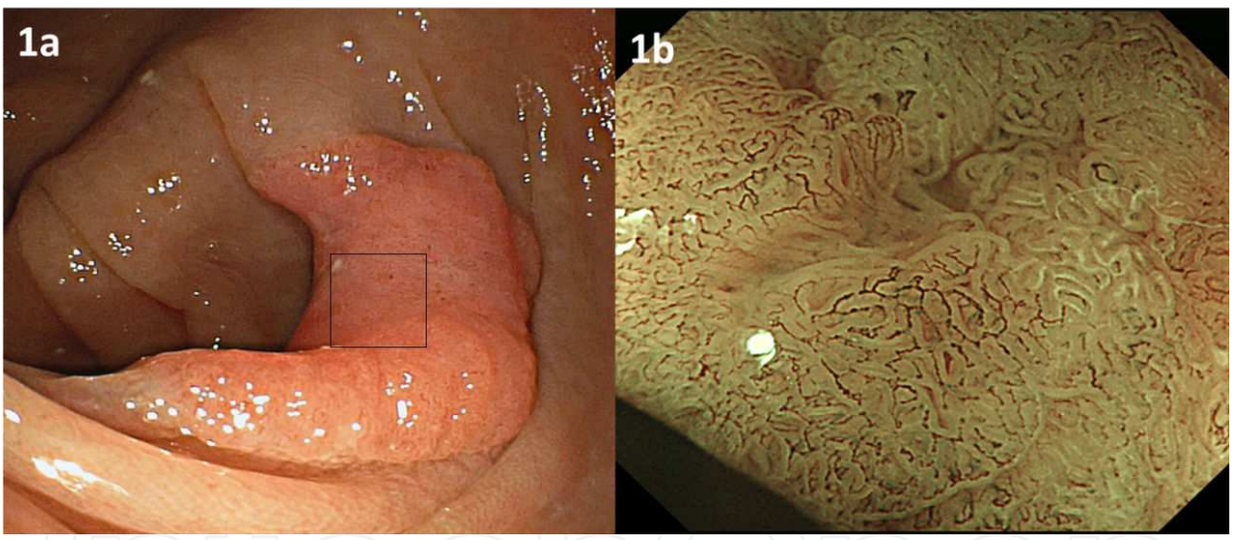

Figure 1. NBI with magnification. 1a: 0-IIa polyp, 20 mm in diameter. White-light endoscopy image. 1b: Mucosal capillary and irregular surface pattern were detected by NBI with magnification. The polyp was diagnosed as a neoplastic polyp.

The FICE system (Fujifilm Medical Co., Tokyo, Japan) is another type of IEE, but is unlike NBI. FICE was formerly known as Fuji Intelligent Color Endoscopy, but this definition has recently changed. FICE depends on optical filters and spectral-estimation technology to reconstruct images at different wavelengths based on WL images [17,18]. The suitable RGB wavelength settings and contrast levels for FICE to evaluate colorectal polyps are 540 (1) nm, 460 (4) nm, and 460 (4) nm, respectively [19,20]. FICE can display color images in real time with RGB components that have been assigned selected spectra. FICE can enhance vascular and surface patterns (Figure 2)[19-23]. AFI videoendosco-

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py (Olympus Medical Co., Tokyo, Japan) is comprised of a blue light to provoke emissions and a green light for hemoglobin absorption [24-26]. Neoplastic areas involve a thickening of the mucosal layer and increased hemoglobin, and so are expected to exhibit weaker autofluorescence compared to non-neoplastic areas (Figure 3).

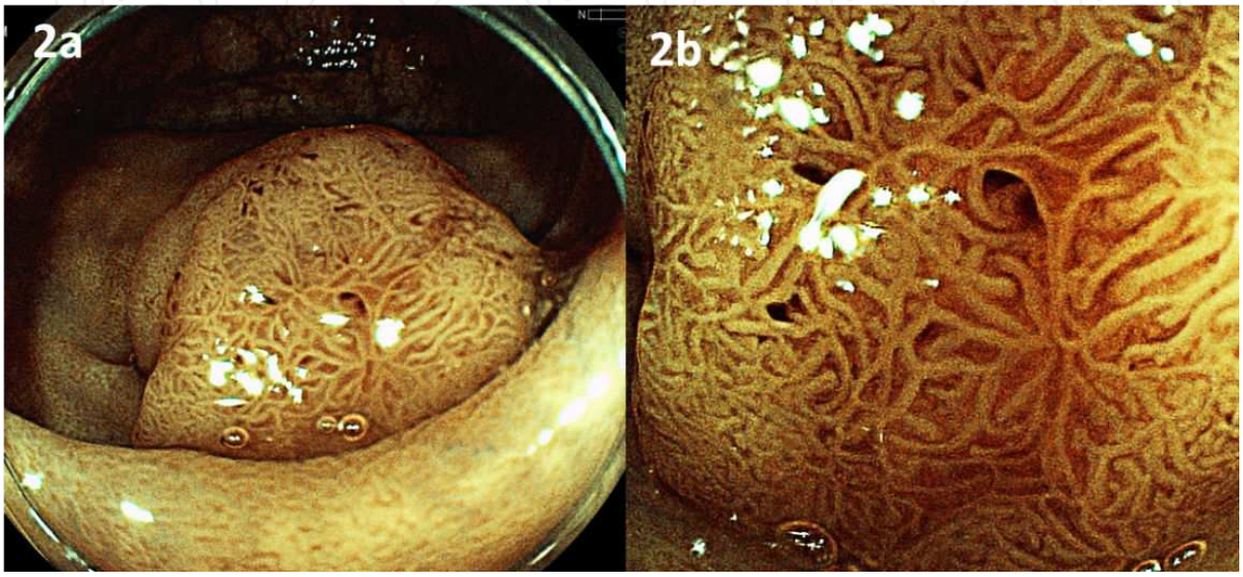

Figure 2. FICE with magnification. 2a: 0-Isp polyp 12 mm in diameter. White-light endoscopy image. 2b: Mucosal capillary and surface pattern were detected with FICE with magnification. The polyp was diagnosed as a neoplastic polyp.

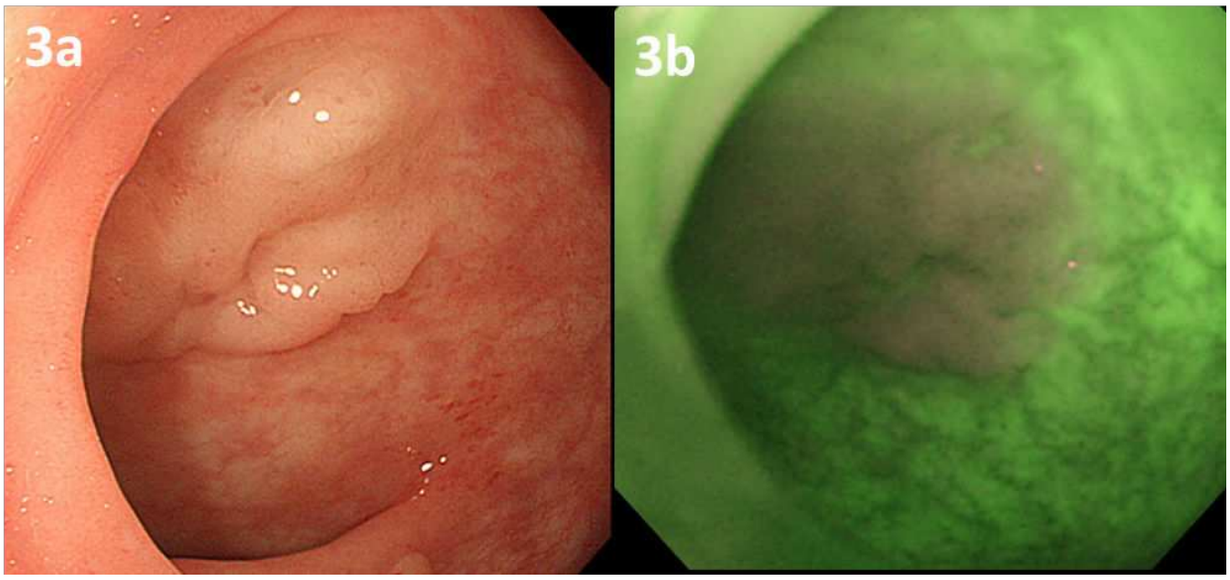

Figure 3. AFI. 3a. 0-IIa polyp 20 mm in diameter. White-light endoscoy image. 3b. In AFI, the normal mucosa is detected by green color and the neoplastic polyp was detected by magenta color.

4. Clinical advantages of NBI and FICE

Magnifying endoscopy (ME) is uncommon in the USA and Europe. Therefore, accurate diagnosis of colorectal polyps through endoscopy without magnification is required. In NBI, high-definition colonoscopy without magnification has been able to predict whether a colorectal polyp is neoplastic or non-neoplastic [26, 27]. A meshed capillary network is one of the important endoscopic features of neoplastic polyps in NBI without magnification, as described by Sano et al. [5] (Figure 4). Rex [28] adopted a surface pattern including pit and vascular pattern for neoplastic features in NBI, and Rastogi et al. used 5 different surface patterns (including mucosal, pit, and vascular patterns) to differentiate neoplastic polyps from non-neoplastic polyps [11]. In various studies, NBI without magnification had an accuracy of 89–92.7%, sensitivity of 87.9–95.7%, and specificity of 87–90.5% (Table 1) [26-30].

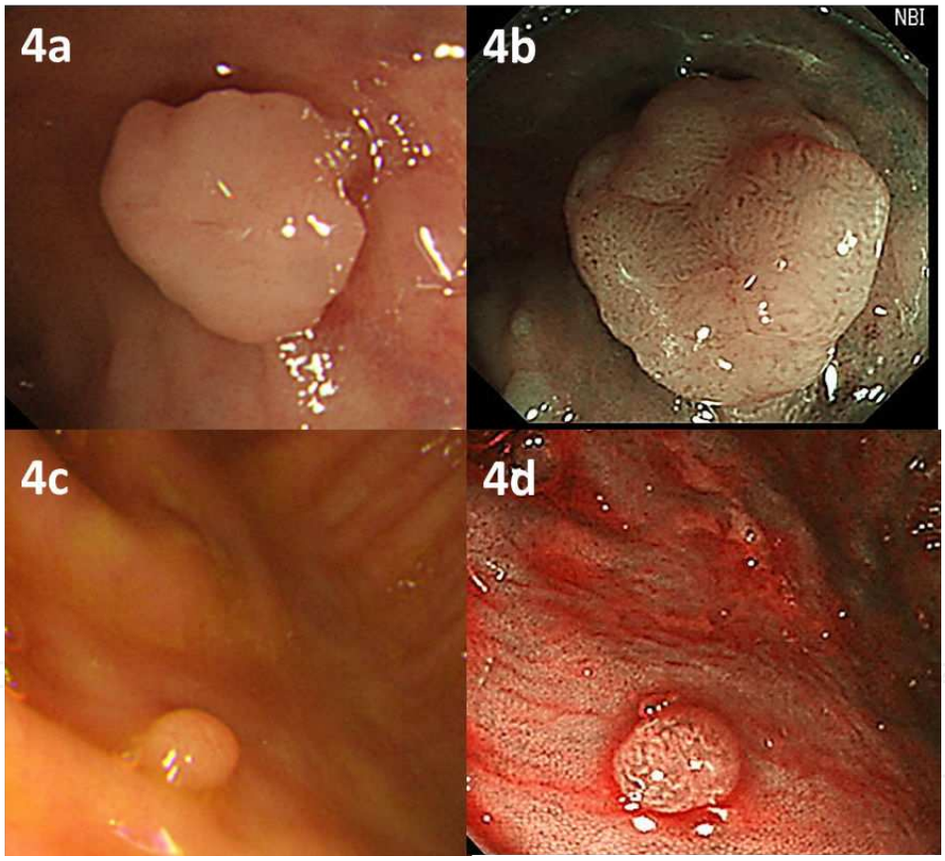

Figure 4. NBI without magnification. 4a: 0-Isp polyp 6 mm in diameter. White-light endoscopy image. 2b: Meshed capillary pattern was detected with NBI without magnification. The polyp was diagnosed as a neoplastic polyp. 4c: 0-Is polyp 3 mm in diameter. White-light endoscopy image. 4d: Meshed capillary pattern was detected with NBI without magnification. The polyp was diagnosed as a neoplastic polyp.

FICE without magnification is also reported to be useful for differentiation between neoplastic and non-neoplastic polyps. The detection of surface patterns by FICE is a reliable method to determine whether a polyp is neoplastic or non-neoplastic, and evaluation of vascular pattern

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has also been described (Figure 5) [19]. In various studies, FICE without magnification has demonstrated an accuracy of 84.4–89.4%, sensitivity of 89.4–93.2%, and specificity of 81.2–88%, similar to the findings for NBI (Table 1) [19,30].

Author	System	No. of cases	Accuracy (%)	Sensitivity (%)	Specificity (%)
Henry ZH et al	NBI	126	90.0	93.0	88.0
Su MY et al	NBI	110	92.7	95.7	87.5
Tischendorf JJW et al	NBI	100	89.0	87.9	90.5
Rex DK	NBI	451	89.0	92.0	87.0
Lonqcroft-Wheaton GR	FICE	232	88.0	-	-
Pohl J et al	FICE	321	84.4	93.2	61.2
Yoshida N et al	FICE	151	89.4	89.4	88.0
Sato R et al	AFI	358	91.9	92.7	92.9

NBI: narrow-band imaging, FICE: flexible spectral imaging color enhancement

Table 1. Reports of image-enhanced endoscopy without magnification for the differentiation of neoplastic and non-neoplastic polyps

When polyp size is considered, the accuracy of NBI without magnification for Polyps 10mm or greater in diameter (accuracy: 96.0%) were greater than those for polyps 5 mm or less in diameter (accuracy: 90.0%) [27]. In FICE without magnification, the accuracy, sensitivity, and specificity for polyps 6 mm or greater in diameter (97.1%, 95.2%, 90%, respectively) are greater than those for polyps 5 mm or less in diameter (82.7%, 78.0%, 87.5%) [18,32]. Diagnosis of small polyps is important for the prevention of colorectal cancer. A procedural decision to avoid resection of non-neoplastic polyps would spare patients the cost and risk of a polypectomy that serves no useful purpose.

Recently, an international cooperative group, the Colon Tumor NBI Interest Group, was formed. The group consists of members from Japan, the USA, and Europe, and it has developed the NBI international colorectal endoscopic (NICE) classification, which classifies colorectal tumors into types 1–3 and is even applicable to colorectal tumors closely observed without magnification (Table 2) [16]. NICE types 1 and 3 are mainly observed in hyperplastic polyps and massively invasive submucosal cancer, respectively. NICE Type2 is observed in various histopathological types such as adenoma, intramucosal cancer, and less invasive submucosal cancer. The NICE classification with or without magnification is considered valid in the USA, Europe, and Japan for differentiating neoplastic and non-neoplastic polyps [33].

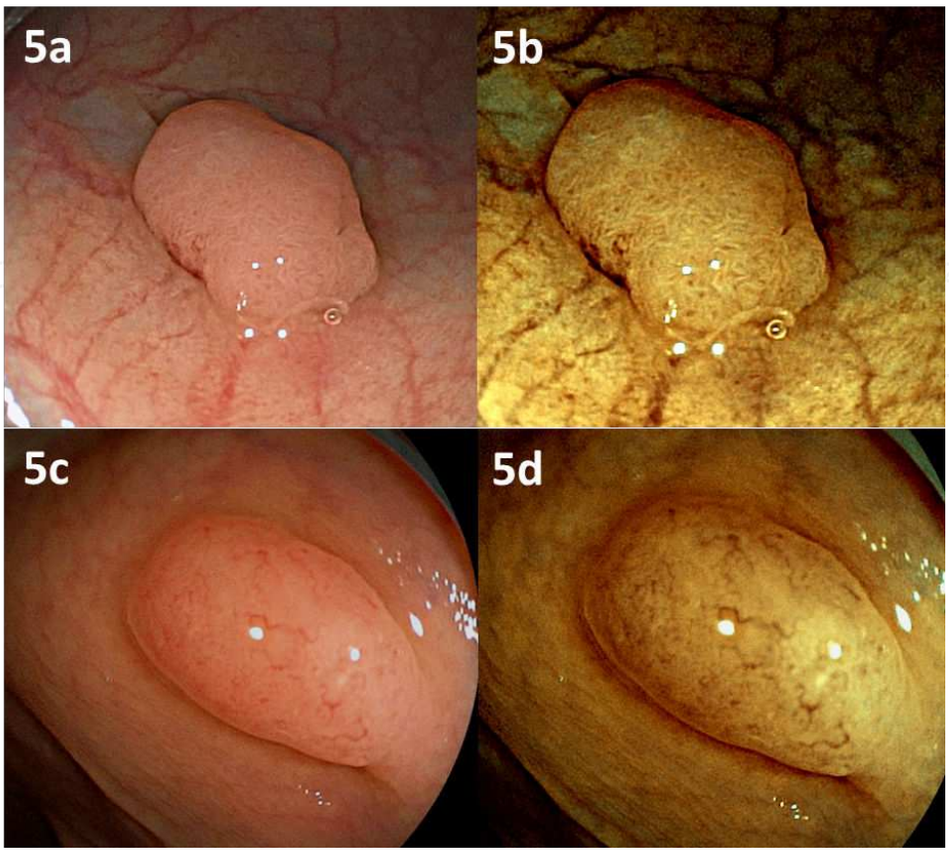

Figure 5. FICE without magnification. 5a: 0-Isp polyp 5 mm in diameter. 5b: Image of FICE without magnification. Tubular and oval pits were identified as neoplastic surface patterns. Vascular patterns were detected. 5c: 0-Is polyp 3 mm in diameter. 5d: Image of FICE without magnification. Round pits were identified as non-neoplastic surface patterns.

	Type 1	**Type 2**	**Type 3**
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vascular pattern	None, or isolated lacy vessels may be present coursing across the lesion	Thick brown vessels surrounding white structures	Has area(s) with markedly distorted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogenous absence of pattern	Oval, tubular or branched white structures surrounded by brown vessels	Areas of distortion or absence of pattern

Table 2. NICE classification

Regarding of IEE-ME techniques, there have been many studies on both NBI-ME and FICE-ME [12, 13, 17, 23, 34-36]. These studies have reported accuracy of 93.4–98.9%, sensitivity of 90.9–100%, specificity of 75–98.9%, PPV of 91.2–97.3%, and NPV of 90–100% for the differentiation of neoplastic and non-neoplastic lesions (Table 3). There are 4 published classifications

of NBI-ME, including the Sano classification, the Hiroshima classification, the Showa Classification, and the Jikei Classification, and 1 published classification for FICE-ME [15, 16, 23, 34, 37]. In brief, the Sano classification, Showa classification, and Jikei classification are based only on vascular patterns, while the Hiroshima classification and FICE classification use surface and vascular patterns. The efficacy of surface pattern detection in NBI and FICE with magnification has been reported [16, 23].

Author	System	No. of cases	Accuracy (%)	Sensitivity (%)	Specificity (%)
Machida H et al	NBI	43	93.4	100.0	75.0
Sano Y et al	NBI	150	95.3	96.4	92.3
Wada Y et al	NBI	617	96.7	90.9	97.1
Tanaka S et al	NBI	289	98.9	100.0	98.9
Togashi K et al	FICE	107	87.0	93.0	70.0
Santos CE et al	FICE	111	92.8	97.8	79.3

NBI: narrow-band imaging, FICE: flexible spectral imaging color enhancement

Table 3. Reports of image-enhanced endoscopy with magnification for differentiation of neoplastic and non-neoplastic polyps

The accuracy, sensitivity, and specificity of each NBI and FICE classification for massively invasive submucosal cancer are described in Table 4 [15, 16, 23, 34, 37]. Accuracy of 87.7–98.3%, sensitivity of 63.8–100%, specificity of 88.7–100%, PPV of 71.8–100%, and NPV of 90–96.2% have been reported. NBI and FICE with magnification are thought to be useful for directing therapeutic strategies, including endoscopic resection by EMR, ESD, or surgery for colorectal tumors. However, the sensitivity (63.8%–100%) and specificity (88.7–100%) are not enough. Chromoendoscopy using the pit pattern classification should be performed when a lesion suspected as cancerous is detected with NBI and FICE or is diagnosed by NBI and FICE with low confidence. The following sections contain details of 2 of the published NBI classifications.

Author	System	No. of cases	Accuracy (%)	Sensitivity (%)	Specificity (%)
Wada Y et al	NBI	584	96.1	100.0	95.8
Tanaka S et al	NBI	97	94.1	63.8	100.0
Ikematsu H et al	NBI	130	87.7	84.8	88.7
Yoshida N et al	FICE	124	98.3	77.7	100.0
Saito S et al	NBI	291	88.7	95.6	77.3

NBI: narrow-band imaging, FICE: flexible spectral imaging color enhancement

Table 4. Reports of image-enhanced endoscopy with magnification for identification of massively invasive submucosal cancer

5. Sano classification (Figure 6) [5, 15]

This classification is based on the surface characteristics of the meshed capillaries. Capillary pattern (CP) type I indicates that there is no meshed capillary pattern visible, as in hyperplastic polyps. CP type II describes the regular small caliber capillaries observed in adenomatous polyps. CP type III is defined as an irregular and unarranged pattern in a mesh-like microvascular architecture that exhibits at least 1 of the following: irregular size, complicated branching, or disrupted irregular winding [35]. CP type III lesions are further classified into 2 groups, IIIA or IIIB, according to microvascular architecture and microvessel density with lack of uniformity and blind endings, branching and irregularly curtailed. CP type IIIA is observed mainly in adenoma, intramucosal cancer, and less invasive submucosal cancers. CP type IIIB was reported in 28% of intramucosal cancers and 72% of massively invasive submucosal cancers.

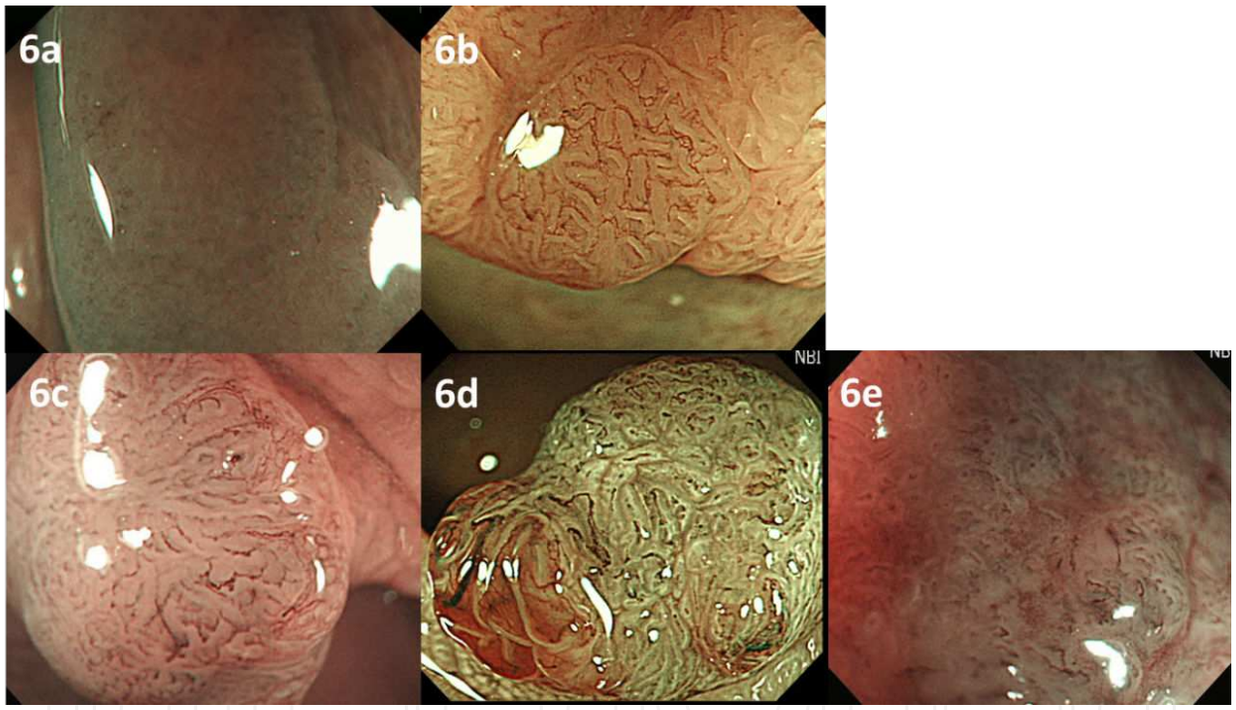

Figure 6. NBI classification. 6a. CP Type I in Sano classification. Type A in Hiroshima classification. 6b. CP Type II in Sano classification. Type B in Hiroshima classification. 6c. CP Type IIIA in Sano classification. Type C-1 in Hiroshima classification. 6d. CP Type IIIB in Sano classification. Type C-2 in Hiroshima classification. 6e. CP Type IIIB in Sano classification. Type C-3 in Hiroshima classification.

6. Hiroshima classification (Figure 6) [13]

The Hiroshima classification is based on vascular patterns and surface patterns, and includes type A, type B, or type C. Type A indicates that microvessels are not observed or are extremely opaque. In type B, fine microvessels are observed around surface patterns, and clear pits are

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observed via the nest of microvessels. In type C, the microvessels are irregular and the vessel diameter or distribution is heterogeneous. Type A is observed in hyperplastic polyps and type B is observed mainly in adenoma. Type C is divided into 3 subtypes (C1, C2, and C3), according to surface pattern's visibility, vessel diameter, irregularity, and distribution. In type C1, microvessels comprise an irregular network, surface patterns observed via the microvessels are slightly nondistinct, and vessel diameter or distribution is homogeneous. Type C1 has been reported in 46.7% of adenomas, 42.2% of intramucosal cancers, and 11.1% of massively invaded submucosal cancers. In type C2, microvessels comprise an irregular network, surface patterns observed via the microvessels are irregular, and vessel diameter or distribution is heterogeneous. Type C2 was observed in 45.5% of intramucosal cancers and 54.5% of massively invaded submucosal cancer. In type C3, surface patterns cannot be observed via the microvessels, irregular vessel diameter is thick, or the vessel distribution is heterogeneous, and avascular areas are seen. Type C3 is mainly found in massively invaded submucosal cancer.

7. Blue laser imaging by laser light source: A novel IEE

A newer endoscope system, "LASEREO," developed by Fujifilm, uses a semiconductor laser as a light source. It has narrow-bandwidth observation capability. The LASEREO system has 2 kinds of lasers. One laser provokes phosphor-illumination with a wavelength of 450 nm, similar to that of a xenon lamp. The combination of laser and fluorescent light provides an illumination that is almost equal to that of WL [Figure 7a]. The other laser is the "blue laser image (BLI)," which functions as a narrow-band light and has a wavelength of 410 nm [Figure 7b]. BLI is useful for acquiring mucosal surface information including surface blood vessel and structure patterns [Figure 7c]. By controlling the power of the 2 lasers, a BLI-bright mode is set by an appropriate combination of WL and BLI light. This mode is brighter than the BLI mode alone, and it is useful for tumor detection and observation of whole tumors.

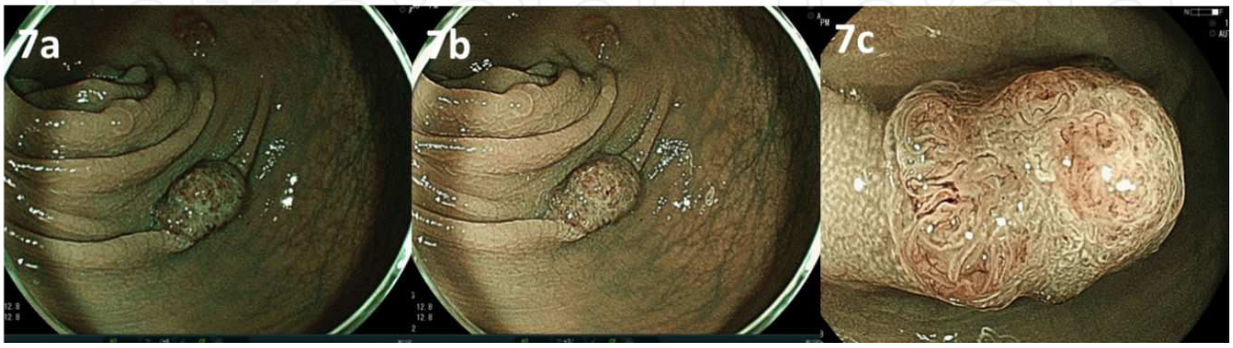

Figure 7. BLI. 7a. 0-Isp 12 mm with BLI. 7b. BLI-bright mode. 7c. Vascular pattern and surface pattern were detected clearly. CP type IIIB in Sano classification. Type C2 in the NBI classification (Hiroshima classification).

8. Adenoma detection rate

Colonoscopy is considered to be the standard examination against which the sensitivity of other colorectal cancer screening tests is compared [38,39]. A meta-analysis of 6 studies found that the missed polyp rate for polyps of any size was 22% [40]. The study also demonstrated that the missed adenoma rates were 2%, 13%, and 26% for polyp sizes of 10 mm <, 5–10 mm, and 1–5 mm respectively [41]. The reasons for missed polyps included the quality of bowel preparation, lesion characteristics (location, number, shape, and size), the endoscopist's experience, and the operator's insertion and withdrawal techniques [41-44]. Although many clinical studies, including randomized controlled trials (RCTs), have confirmed reduced missed rates in colonoscopy using NBI techniques [45-52], one recent meta-analysis revealed that there was no statistically significant difference in the rates of adenoma detection rate between NBI and WL [53], and a large-scale multicenter Japanese study did not show an improvement with NBI [54]. Moreover, another systematic review including 8 RCTs showed that NBI did not improve detection of colorectal polyps when compared to WL [55]. For FICE, 2 RCTs showed that any objective improvement of FICE was not correlated with the adenoma detection rate [56,57]. On the other hand, NBI and FICE systems have been improved recently and the recent combination of both systems and endoscopy employ high resolution and provide better contrast for vascular and surface patterns in ME than previous systems.

9. Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) is now performed worldwide for early colorectal cancers. The saline injection-assisted method was first described by Rosenberg, who identified it as a safe method for the removal of rectal and sigmoid polyps, and was reintroduced by Tada et al. in 1984 [58-59]. Most adenomas and intramucosal cancers can be resected by EMR, however, tumors greater than 20 mm in diameter are considered difficult candidates for en bloc resection [60-65], and the rate of en bloc resection by EMR of tumors >20 mm in diameter is especially low (Table 5)[60-65]. While the technical feasibility of EMR for en-bloc and extended resections must still be improved, most colorectal polyps removed by EMR are <20 mm in size. EMR achieves en-bloc and complete resection of these lesions at satisfactory rates, although even some smaller lesions are difficult to resect completely, especially for less-experienced endoscopists. Many injection solutions have been used to achieve sustained mucosal elevation, definitive en-bloc resection, and complete resection while preventing perforation during EMR. Hypertonic saline, glycerol, dextrose, fibrinogen, and succinylated gelatin provide better complete resection rates and longer-lasting mucosal elevation than does normal saline (NS) [65-69]. Yamamoto et al. first reported the efficacy of hyaluronic acid (HA) for novel endoscopic resection of a large colorectal polyp, and this procedure was subsequently termed endoscopic submucosal dissection (ESD) [68]. Hyaluronic acid (HA) has been shown to create higher and more sustainable mucosal elevation than NS [68,70-72]. We have previously reported that mucosal elevation with NS dissipates within 2 min from injection, which is the median time required for most endoscopists to perform an EMR [69]. Our same study found that the

viscosity of high-concentration HA can make snaring difficult. For this reason, and because HA is more expensive than NS, it is important to dilute HA prior to use. We have previously demonstrated that an HA concentration as low as 0.13% is effective for sustained mucosal elevation in resected porcine colon and in living minipig colon [69]. Moreover, we previously reported a prospective RCT concerning the efficacy of 0.13% HA in colorectal EMR that proved that using 0.13% HA instead of NS during EMR was more effective for complete resection and maintenance of mucosal elevation [73].

Author	Injection Solution	No. of cases	Rate of En bloc resection (%)	Rate of local recurrence (%)
Saito et al.	not described	228	33.0	14.0
Tanaka et al.	Glycerol	178	39.3	7.9
Tajika et al.		104	48.1	15.4
Iishi et al.	NS	56	25	not described
Kobayashi et al.		56	37.5	21.4
Uraoka et al.	NS Glycerol	44 39	20.5 23.1	18.6 15.2
Our data	HA	35	42.8	10.0

NS: normal saline, HA: hyaluronic acid

Table 5. Rates of en bloc resection and local recurrence of tumors larger than 20 mm in diameter treated by endoscopic mucosal resection (EMR)

Evaluation of en bloc resection is performed endoscopically, while complete resection is defined histopathologically based on the tumor-free lateral and vertical margins of the resected specimens. However some specimens resected by EMR have positive margins even after the tumor was grossly resected en bloc. Burning of the resected specimens may affect these results, and although most such tumors cause no local recurrence, some do recur locally. Therefore, endoscopists are obligated to perform EMR with tumor-free margins [74]. We describe a regular method of EMR to obtain complete resection of polyps. Firstly, polyp and margin are observed carefully and then injection is performed [Figure 8]. The recommended locus of injection is the proximal side of the polyp. If the injection is performed at the distal (anal) side of the polyp, the polyp may shift to a horizontal position to the endoscope. In this situation, the margin of the tumor cannot be confirmed. After injection, snaring is performed and polyp is resected with electrocau-

tery. After resection, endoscopic clipping is sometimes performed to prevent post-operative hemorrhage and perforation.

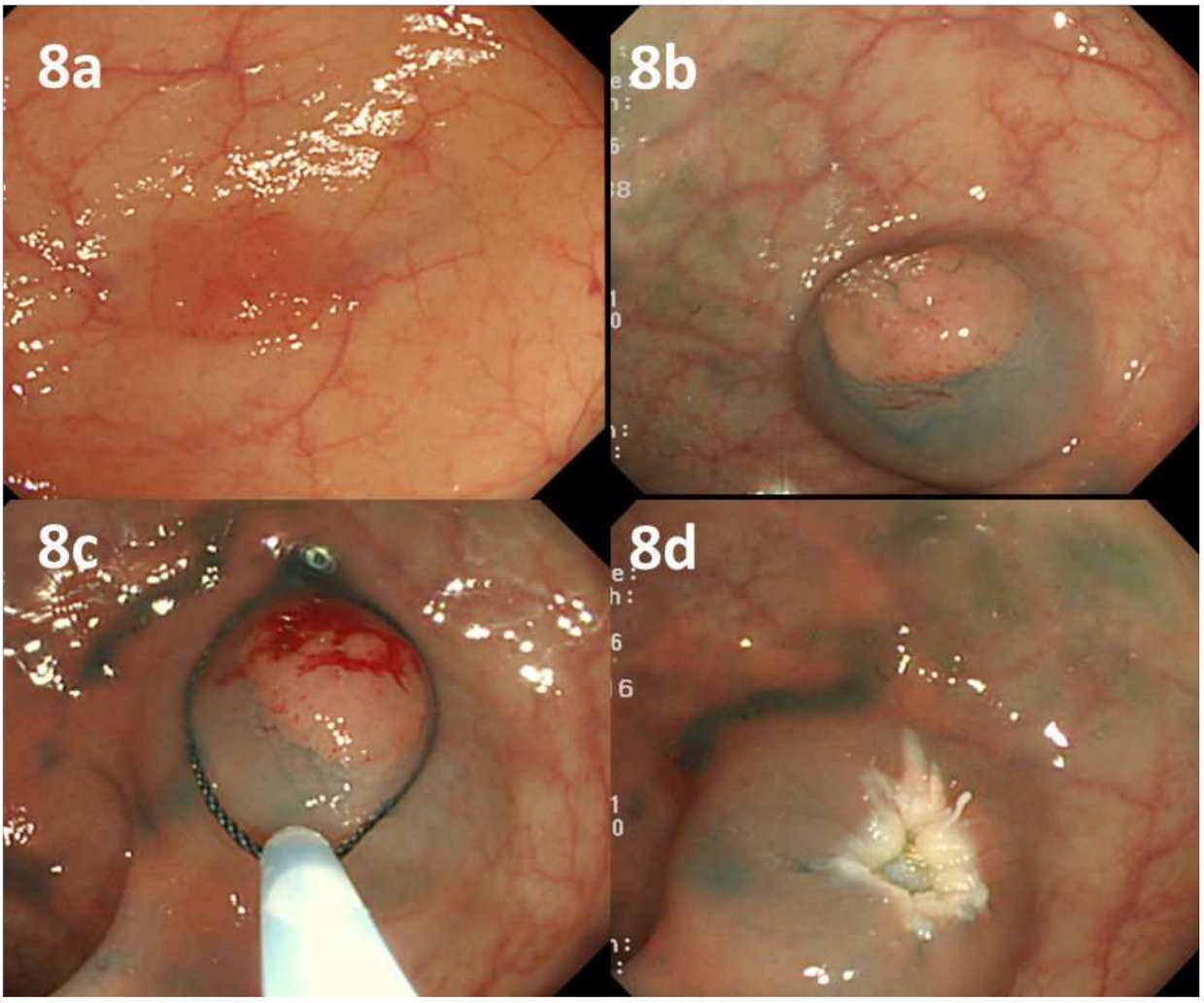

Figure 8. Strategy of EMR. 8a. Polyp and margin of it are observed carefully. 8b. Injection is performed at the oral (proximal) side of the polyp. 8c. Snaring is performed. 8d. Polyp is resected by electrocautery.

When en bloc resection of the tumor by EMR fails, piecemeal EMR is generally performed instead. Although piecemeal EMR enables the removal of large colorectal tumors, it has a high rate of local recurrence (7.9–21.4%)[60-65] (Table 5). Most recurrent adenomas, including partial intramucosal adenocarcinomas, can be cured by additional endoscopic therapy [74]. If possible, The use of piecemeal EMR should be examined carefully before endoscopic therapy by ME and IEE. In some cases, piecemeal EMR does not allow for precise histopathological evaluation. For example, partial submucosal invasion in submucosally invasive cancer can be missed in piecemeal-resected specimens. When the locus of submucosal invasion in submucosally invasive cancer is destroyed by burning, the tumor may be misdiagnosed as mucosal cancer, and when the positive vertical margin of submucosal or lymphatic-venous invasion is burned, the resection may misclassified as complete [74]. In these cases, the patient will not be

advised to undergo additional surgical resection, allowing recurrence a few years later. Recurrence may occur as lung, liver, and/or lymph node metastasis, and these patients are very difficult to cure.

10. Endoscopic submucosal dissection

In Japan and some other Western and Asian countries, endoscopic submucosal dissection (ESD) is reported to be an efficient treatment with a high rate of en bloc resection for large colorectal tumors and it is considered less invasive than laparoscopic colectomy (LAC) [75-83]. However, ESD can be a time-consuming procedure and carries a higher risk of perforation than EMR [81,82]. The use of ESD was initially proposed by the Japanese special ESD group [80]. Indications in detail are, first, large lesions >20 mm in diameter for which endoscopic therapy is indicated but for which en bloc resection by snare EMR would be difficult. Second, lesions that are suspected as invasive submucosal cancer should be resected en bloc by ESD. Thirdly, lesions other than these cases can be an indication for ESD, including mucosal lesions with fibrosis caused by prolapse due to biopsy or peristalsis of the lesions, local residual early cancer after endoscopic resection, and sporadic localized tumors in chronic inflammation such as ulcerative colitis. The rate of en bloc resection for large colorectal tumors by ESD has been reported to be 80–98.9%[75-83](Table 6). However, the procedure has not been standardized because of its associated technical difficulties. The colon is winding in nature and has many folds. Moreover, the wall of the colon is thinner than the gastric wall.

Author	No. of cases	Rate of En bloc resection (%)	Perforation rate (%)	Post-operative bleeding rate (%)
Saito et al.	1111	88.0	4.9	1.5
Toyonaga et al.	468	98.9	1.5	1.5
Isomoto et al.	292	90.1	8.2	0.7
Yoshida et al.	250	86.8	6.0	2.4
Fujishiro et al.	200	91.5	10.4	1.0
Zhou et al.	74	93.2	8.1	1.3
Tanaka et al.	70	80.0	10.0	1.4
Our recent data	410	92.6	4.1	1.9

Table 6. Rates of en bloc resection and complete resection by endoscopic submucosal dissection (ESD)

We describe standard ESD devices here. ESD is performed with a regular lower gastrointestinal endoscope with a single channel. In our institution, colonoscopes with single channels such as the EC 590 MP (Fujifilm Medical, Tokyo, Japan) or the PCF Q260AI (Olympus, Tokyo, Japan) are used. With regard to the choice of endoscope, an upper gastrointestinal endoscope is preferred in some institutions because it is slim and can be used in the retroflexed position [78]. ESD requires a high-frequency generator with an automatically controlled system. A transparent short hood (Olympus Medical Systems, Co. Ltd.) is fitted at the tip of the endoscope.

This helps the easy placement of endoscope during ESD. A mixture of 0.4% hyaluronic acid solution (Mucoup; Johnson & Johnson K.K., Tokyo, Japan and Seikagaku Corporation, Tokyo, Japan) is used as the injection liquid to induce a greater elevation of the submucosa and to lengthen the duration of the continuous elevation of the submucosa [77, 82].

Various knives are used in ESD for excising colorectal tumors (Figure 9). Among the obtuse short-tipped types are included the Flush knife (Fujifilm Medical, Tokyo, Japan), Dual knife (Olympus Optical Co, Tokyo, Japan), B-knife (Zeon Medical, Tokyo, Japan), and Splash needle (Pentax Co, Tokyo, Japan) [75, 82]. The Flush knife and Splash needle are capable of submucosal injections and they allow the endoscopist to omit switching between the knife and the injection needle [75, 83]. The Dual knife, B-knife, and Flush knife all have a ball disk at the tip of the knife, enabling the operator to hook the submucosa. The insulated tipped (IT) knife (Olympus Optical Co, Tokyo, Japan), whose efficacy has been reported to be satisfactory in ESD for gastric tumors, is being used in certain institutions [84]. The IT knife allows rapid dissection. A Hook knife (Olympus Optical Co, Tokyo, Japan) is particularly useful when the dissection of the submucosa is difficult due to poor elevation of the submucosa [80]. The B-knife is the only bipolar knife, and there is thought to be less burning of the muscularis propria layer with this knife than with other monopolar knives. The clutch cutter (Fujifilm medical, Tokyo, Japan) and SB knife (Sumitomo Bakelite Co., Tokyo, Japan) are grasping-type scissor forceps [85-86]. In our institution, the Flush knife is mainly used because it can effectively administer local injections, and the clutch cutter is used when the risk of perforation is high due to the poor elevation of the submucosa [74,85].

Following are the steps of the routine ESD procedure (Figure 10) [82,87]. Before ESD, residual feces and liquid are removed from the entire colon even if the tumor is located at the rectum. Residual feces prevent smooth submucosal dissection. Moreover, it is essential to remove residual feces in order to prevent the outflow of feces into the abdomen in the case of perforation. Firstly, the border of the tumor is carefully identified using indigo carmine dye. It is generally unnecessary to mark the borders by coagulation because in the majority of cases they are clearly visible. Injection for submucosal elevation is performed with a 25G needle (8B27A, TOP, Tokyo, Japan) after visualization of the border of the tumor, and mucosal incisions are made. A partial circumferential incision is made on the distal side of the tumor [77, 80]. If the size of the tumor exceeds 50 mm, the incision is performed at the proximal side of the tumor, because in large tumors it is sometimes difficult to resect residual mucosa on the proximal side in the presence of a partially resected tumor. Mucosal incisions are made only after adequate elevation of submucosa by mucosal injection is achieved, and then, simultaneously, an incision into the deep submucosa is made. Mucosal incisions are performed with the endocut mode (output 40 W, effect 2 in ICC200; or endocut I, effect 2, duration 2, interval 1 in VIO300D).

After mucosal and submucosal incisions are made at the anal side of the tumor, the submucosa below the tumor is resected from the distal side of the tumor. Dissection of the submucosa is performed using the endocut (output 40 W, effect 2 in ICC200; endocut I, effect 2, duration 2, interval 1 in VIO300D) or coagulation mode (forced coagulation, output 40 W in ICC200 or forced coagulation, output 40 W, effect 3 in VIO300D). To achieve submucosal elevation, additional injections are performed with the injection needle or flush knife, as appropriate.

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Then continuing to dissect while carefully avoiding perforation and hemorrhage, en bloc resection of the tumor is completed.

Figure 9. Various ESD knives.

The main complications of ESD are perforation and hemorrhage, similar to those of endoscopic mucosal resection (EMR). In particular, the rate of perforation is higher for ESD than for EMR (1.5–10.4%)(Table 6)[75-83]. Perforation of the colon can cause fatal peritonitis. Coagulation by knife is the most frequent cause of perforation [81]. Saito et al. showed that perforation risk was related to the number of ESD procedures, with higher risk when the endoscopist had performed fewer than 100 procedures [83]. Most cases of perforation are treated conservatively by endoscopic clipping, without need for urgent surgical intervention [40,41] (Figure 11). Carbon dioxide insufflations have been reported to be effective for the prevention of abdominal

fullness [88]. They also has been reported to be effective for prevention of perforation by decreasing pressure in the colorectum. On the other hand, the rates of postoperative hemorrhage are similar for ESD and EMR. When hemorrhage occurs, endoscopic therapy, including endoscopic clipping, is performed, and most cases, can be managed conservatively and without blood transfusion. A safe strategy, suitable knife, adoption of other equipment, and training in animal models are necessary in order to minimize the complications, including perforation, of ESD [42].

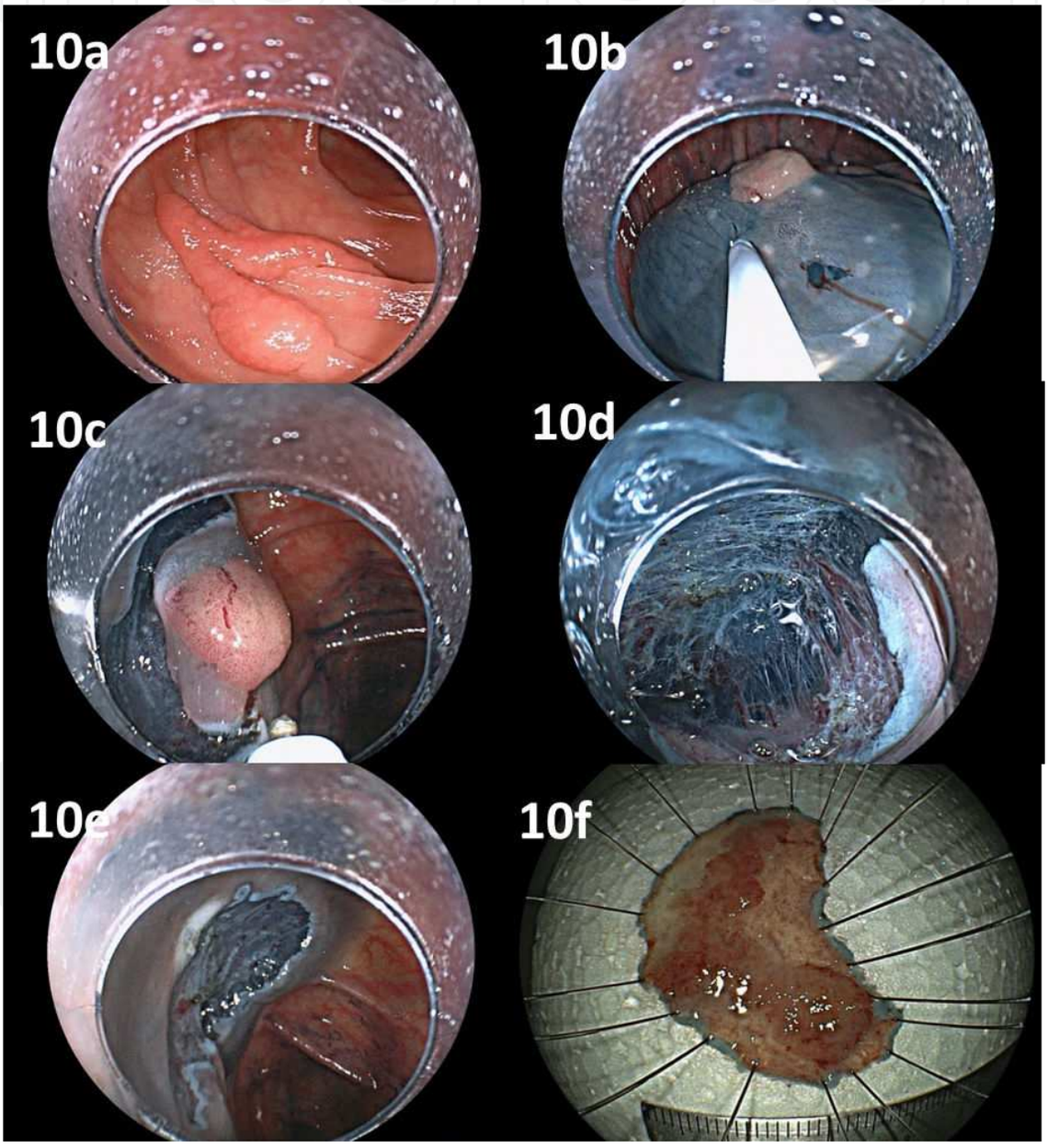

Figure 10. Strategy of ESD. 10a. 0–IIa 30 mm on the descending colon. Firstly, the tumor and margin of it are observed carefully. 10b. Injection is performed at the anal (distal) side of the tumor. 10c. A partial circumferential mucosal incision is made. 10d. Submucosal dissection is performed. 10e. The tumor is resected en-bloc. 10f. Resected specimen.

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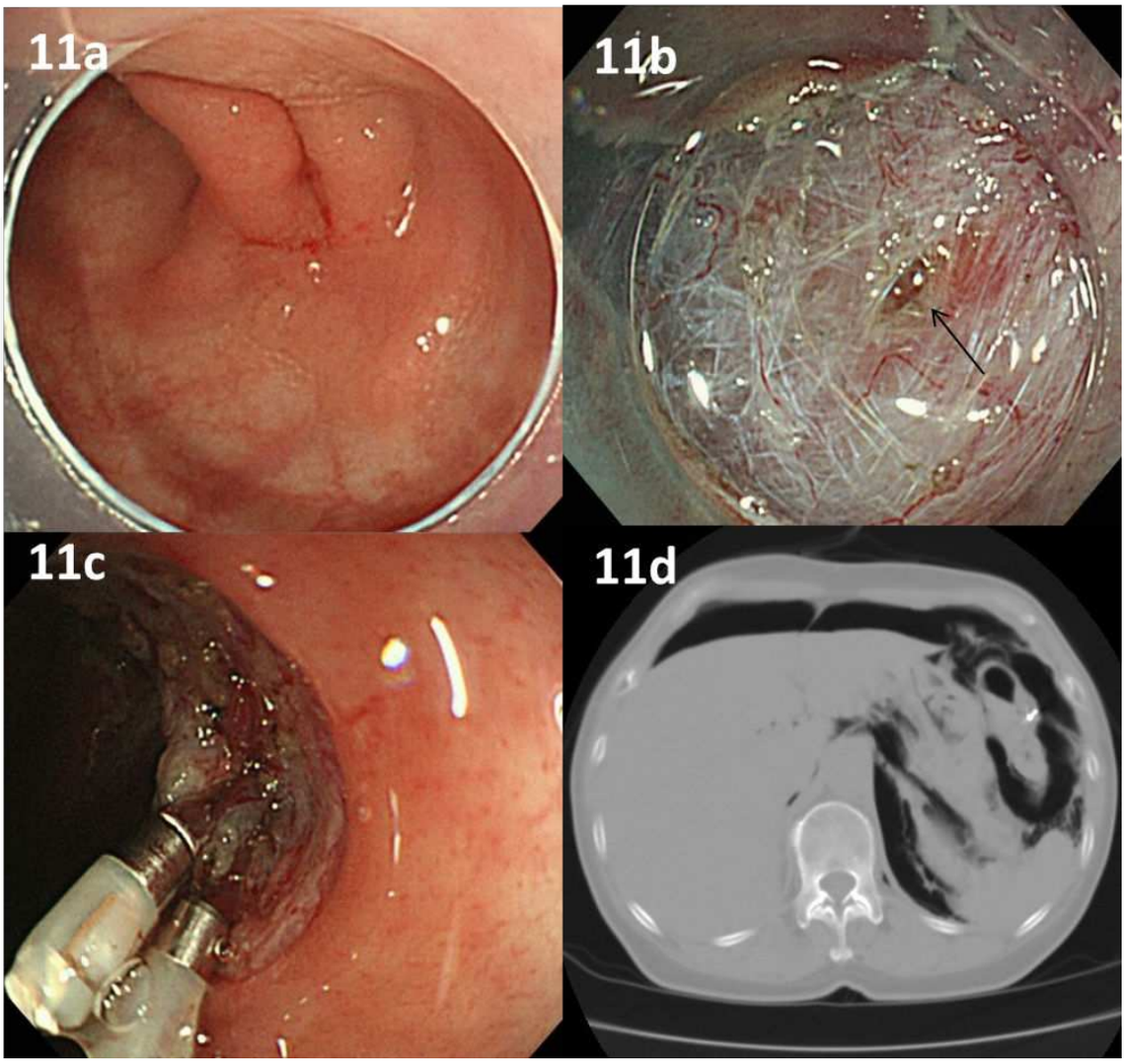

Figure 11. Perforation during ESD. 11a: 0–IIa 30 mm on the descending colon. 11b. Coagulation to submucosa during resection of submocosa below the tumor caused perforation (black arrow). 11c: The hole was closed by endoscopic clipping. 11d: CT revealed free air out side of the colorectum.

Submucosally invasive cancer can be resected by colorectal ESD. A multicenter study of 1111 colorectal ESDs showed that 213 submucosally invasive cancers (19.1%, 213/1111) were treated clinically by ESD [83]. The rate of submucosally invasive cancer in our institution is 10.2% (42/410), which is similar to the rates reported in other studies on colorectal ESD (range: 9.2%–25%)[78-80, 82]. Massively invaded submucosal cancer is not an indication for colorectal ESD and EMR, because of the possibility of lymph node metastasis. Endoscopic diagnosis of massively invasive submucosal cancer is limited even when ME for pit patterns, NBI, and FICE are available. The sensitivity of detail-magnifying observation for massively invasive submucosal cancer is only 63.8–100.0% [15, 16, 23, 34, 37] (Table 4). Therefore, some number of massively invasive submucosal cancers may be diagnosed as mucosal cancer or shallowly invaded submucosal cancer and scheduled for resection by ESD or EMR. In these cases, the probability of curative resection by ESD is influenced by various clinical features, including

histopathological vertical margin, lateral margin, and venous-lymphatic invasion. The characteristics of the submucosally invasive cancers treated at our institution are shown in Table 7 [74]. The average tumor size was 26.5 mm in the submucosal cancer (SM) group and 35.1 mm in the mucosal cancer (M) group ($P < 0.01$). The proportion of tumors in the rectum was higher in the SM group than in the adenoma (A) group ($P < 0.01$). The ratio of protruding tumors to superficial tumors was significantly higher in the SM group (14:19) than in the M group (32:112) or the A group (12:145) ($P < 0.01$). The rate of severe fibrosis was higher in the SM group (18.1%) than in the M group (5.5%) ($P < 0.05$). One cause of severe fibrosis is tumor invasion. However, mucosal cancers (5.5%) and adenomas (6.0%) also showed severe fibrosis in our study. Endoscopic biopsy sometimes leads to severe fibrosis. Matsumoto et al. showed that severe fibrosis complicated ESD and was associated with perforation [89]. The median operation time for the 7 cases in the SM group with severe fibrosis was 147 min, which was longer than the M group or the A group. Severe fibrosis is difficult to dissect, and it should be cautioned that perforation may occur during dissection of severe fibrosis. In our institution, the clutch cutter, which is a scissor-shaped knife, is used to dissect severe fibrosis with minimal risk of perforation, as it can grasp, coagulate, and cut a piece of tissue without perioperative hemorrhage [74].

	SM	M	A	P-value
Number of tumors	33	144	157	
Median age (range)	65.5 (46–83)	67.9 (48–87)	67.5 (39–87)	
M/F	21/12	86/58	81/76	NS
Tumor size (mm) (range)	26.5 (10–60)	35.1 (10–130)	27.0 (10–80)	<0.01
Location (Colon/Rectum)	18: 15	87: 57	124: 33	<0.01 SM:A
Morphology (protruding/superficial)	14: 19	32: 112	12: 145	<0.01
Operation time (min) (range)	109 (20–240)	118 (30–420)	92 (10–300)	NS
Severe Fibrosis (%)	18.1(7/33)	5.5(8/144)	6.3 10/157)	<0.05 SM:M
En bloc resection (%)	90.9	90.9	89.1	NS
Complete resection (%)	72.7	84.0	81.5	NS
Perforation (%)	6.0	7.6	1.9	NS
Postoperative hemorrhage (%)	0	6.2	1.2	NS

ESD: endoscopic submucosal dissection; SM: submucosal cancer; M: mucosal cancer; A: adenoma; NS: not significant

Table 7. Characteristics of colorectal tumors resected by ESD

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11. Training in EMR and ESD

Training in EMR and ESD is important for safe procedures. EMR of small polyps is considered easy and it is not rare that an inexperienced endoscopist will firstly perform EMR in these cases. Recently, animal models (Johnson & Johnson K.K., Tokyo, Japan) have become available for practicing EMR (Figure 12). Some animal model training for inexperienced endoscopists is used in our institution, and it has had positive impact on EMR in clinical cases. Colorectal ESD is difficult for less-experienced endoscopists. In general, endoscopists should acquire extensive experience with gastric ESD before performing colorectal ESD. However, different training for colorectal ESD is required when the number of patients with early gastric cancer is few, as in Western countries. In this situation, visiting ESD experts at other institutions and observing them at work are important components of training. Another expected component of ESD training is extensive practice using animal models [90-92]. Both *in vivo* animal models and *ex vivo* animal models using harvested organs have been used. Porcine and canine *in vivo* models have been reported to be useful systems for ESD training [90-92]. However, *in vivo* animal models are expensive and difficult to prepare. Hon et al. demonstrated the usefulness of a porcine colon *ex vivo* animal model for training in colorectal ESD [91]. However, training in endoscopic hemostasis is difficult in conventional *ex vivo* animal models. We have recently reported an *ex vivo* animal model with simulated blood flow (Johnson & Johnson K.K., Tokyo, Japan) [93](Figure 12). It can be made using the bovine cecum. The vessel around the cecum is detached, and red ink is injected. The mucosa shows "blood" flow after the red ink is injected (Figure 13), which can allow the endoscopist to gain whole ESD experience, including perioperative hemorrhage (Figure 14). A specific ESD training system has been implemented in some Japanese institutions, including ours. It is a step-by-step system starting with observing and assisting in ESD procedures performed by experts. Next, animal model training is performed to the extent possible. Finally, clinical practice is performed under the supervision of instructors. Generally, the clinical practice training proceeds according to the difficulty of the procedure, beginning with gastric ESD, then rectal ESD, and finally colonic ESD [93]. Regarding animal training in ESD, there are many reports on *ex vivo* animal models for gastric ESD [91, 94, 95]. There are also several reports on an *ex vivo* animal model for colorectal ESD [92, 93]. Repeated animal model training procedures have recently been proven to decrease procedure time [91-93]. For clinical colorectal ESD, Hotta et al. showed that approximately 40 procedures were sufficient to acquire skill in avoiding perforations, and the perforation rate in the first 40 cases was about 12.5% [96]. We believe that experience obtained by training on an animal model will also improve performance of clinical colorectal ESD, although the perforation rate did not decrease to zero even if the skill level improved greatly. Therefore, we believe the endoscopist must also obtain expertise in endoscopic closure. Small perforations can be closed by endoscopic clipping [81,97]. However, endoscopic clipping requires a high level of endoscopic skill and experience, and perforation is relatively rare in clinical medicine, making it difficult to gain experience in the endoscopic clipping technique in clinical practice. *Ex vivo* animal models for perforation are more useful for training in endoscopic closure than *in vivo* animal models [93] (Figure 15).

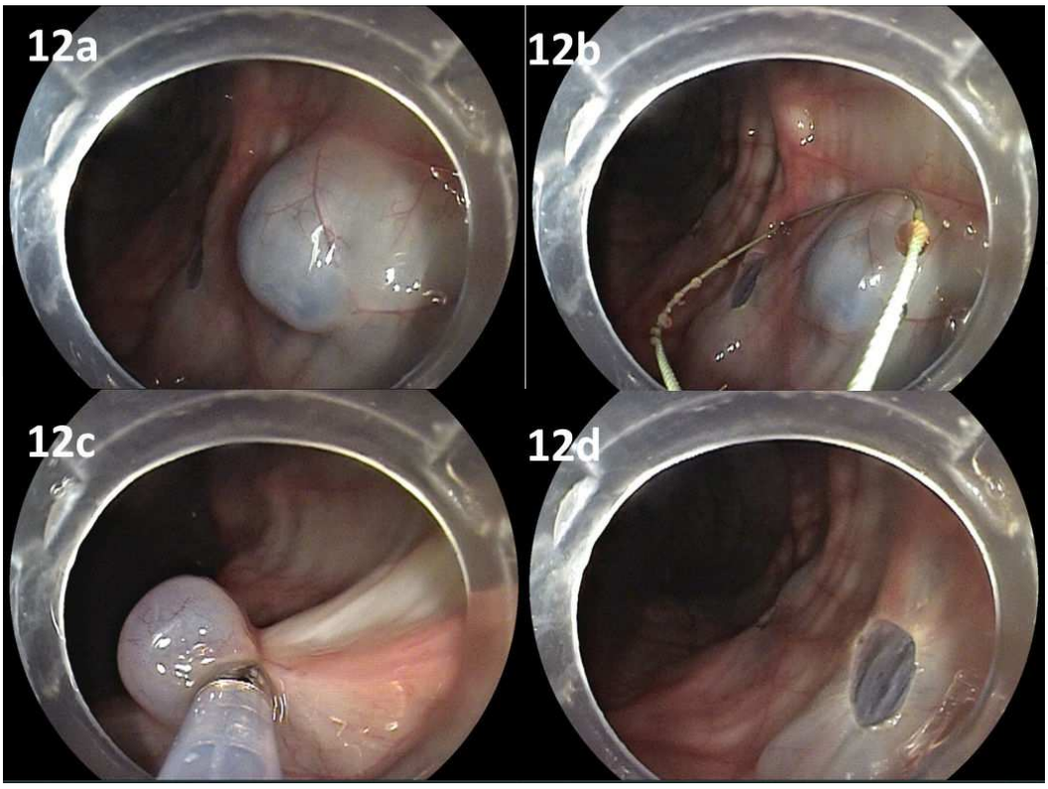

Figure 12. Animal model training for EMR. 12a. Injection is performed. 12b, 12c. Snaring is performed. 12d. Polyp is resected by electrocautery.

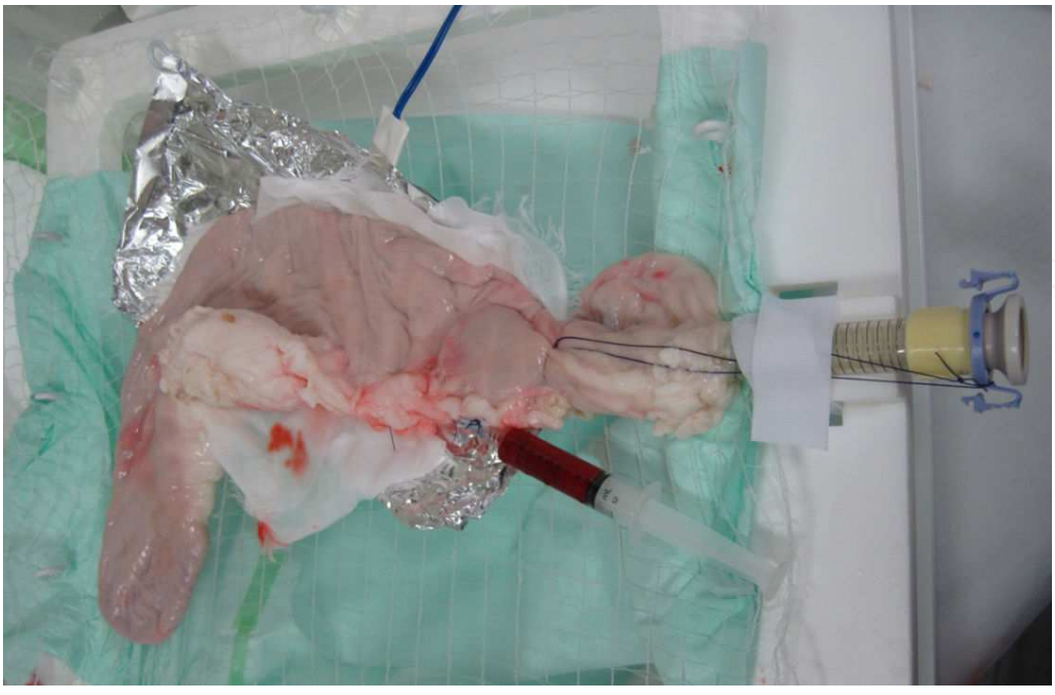

Figure 13. *Ex vivo* animal model with blood flow.

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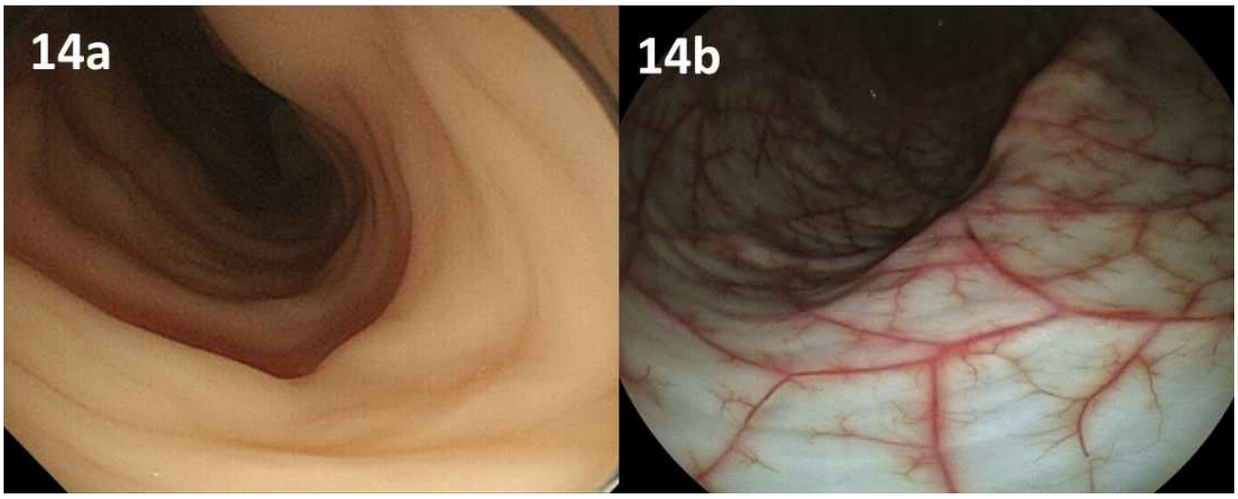

Figure 14. *Ex vivo* animal model with blood flow. 14a. The submucosal vessels were invisible before injection of red ink. 14b. The submucosal vessels were visible after injection of red ink.

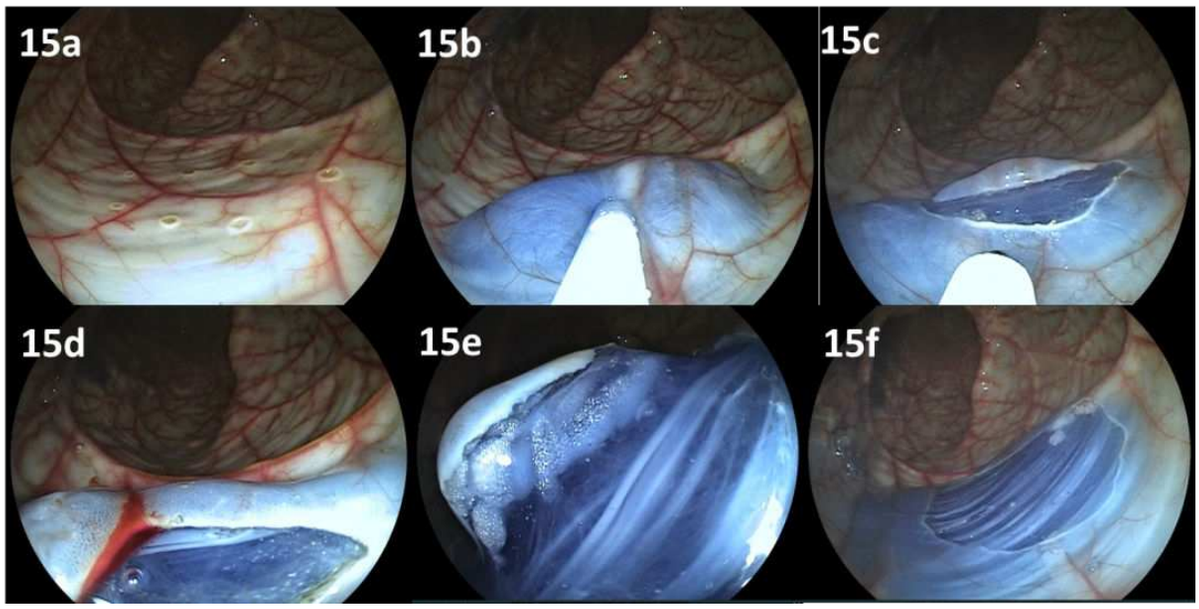

Figure 15. *Ex vivo* animal model with blood flow for whole ESD training including endoscopic hemostasis. 15a. Marking was performed to mimic the tumor. 15b. Mucosal injection was performed. 15c. Partial circumferential mucosal incision was performed. 15d. Perioperative hemorrhage was detected. 15e. Submucosal dissection was performed. 15f. En bloc resection was performed.

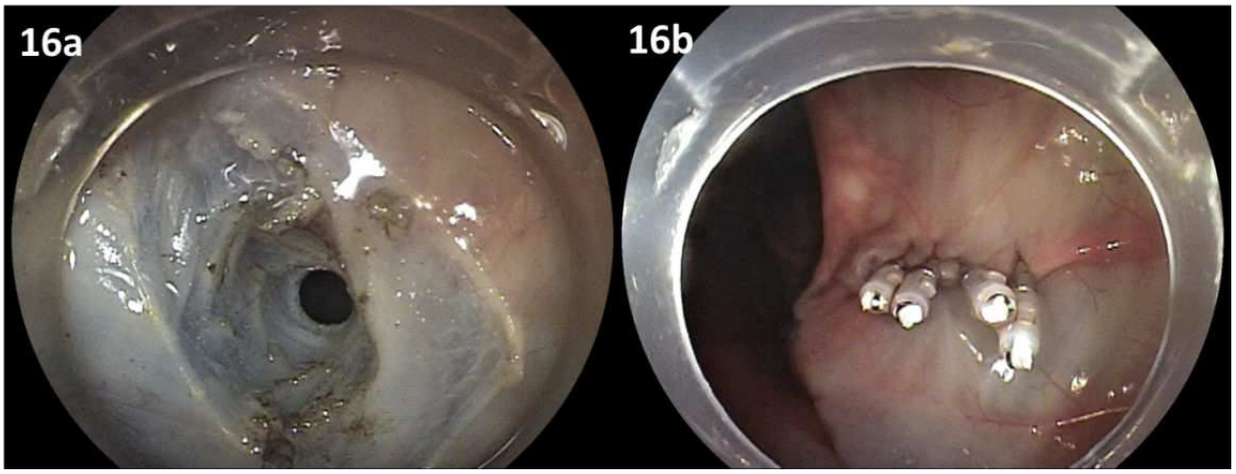

Figure 16. *Ex vivo* animal model with perforation for training of endoscopic closure 16a. After ESD, the endoscopic knife was used to make a 2–3 mm hole in the proper muscle layer of the ulceration. 16b. The endoscopic closure of the hole was performed with 4 endoscopic clips.

12. Conclusions

In this chapter, we have described the effectiveness of image-enhanced endoscopy (IEE) and the safe and definite strategies of therapeutic endoscopy, including endoscopic mucosal resection (EMR) and endoscopic mucosal dissection (ESD).

Acknowledgements

We thank Dr. Naoki Wakabayashi, Dr. Ken Inoue, and Dr. Yasutaka Morimoto and all members of the Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, for helping with our study.

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