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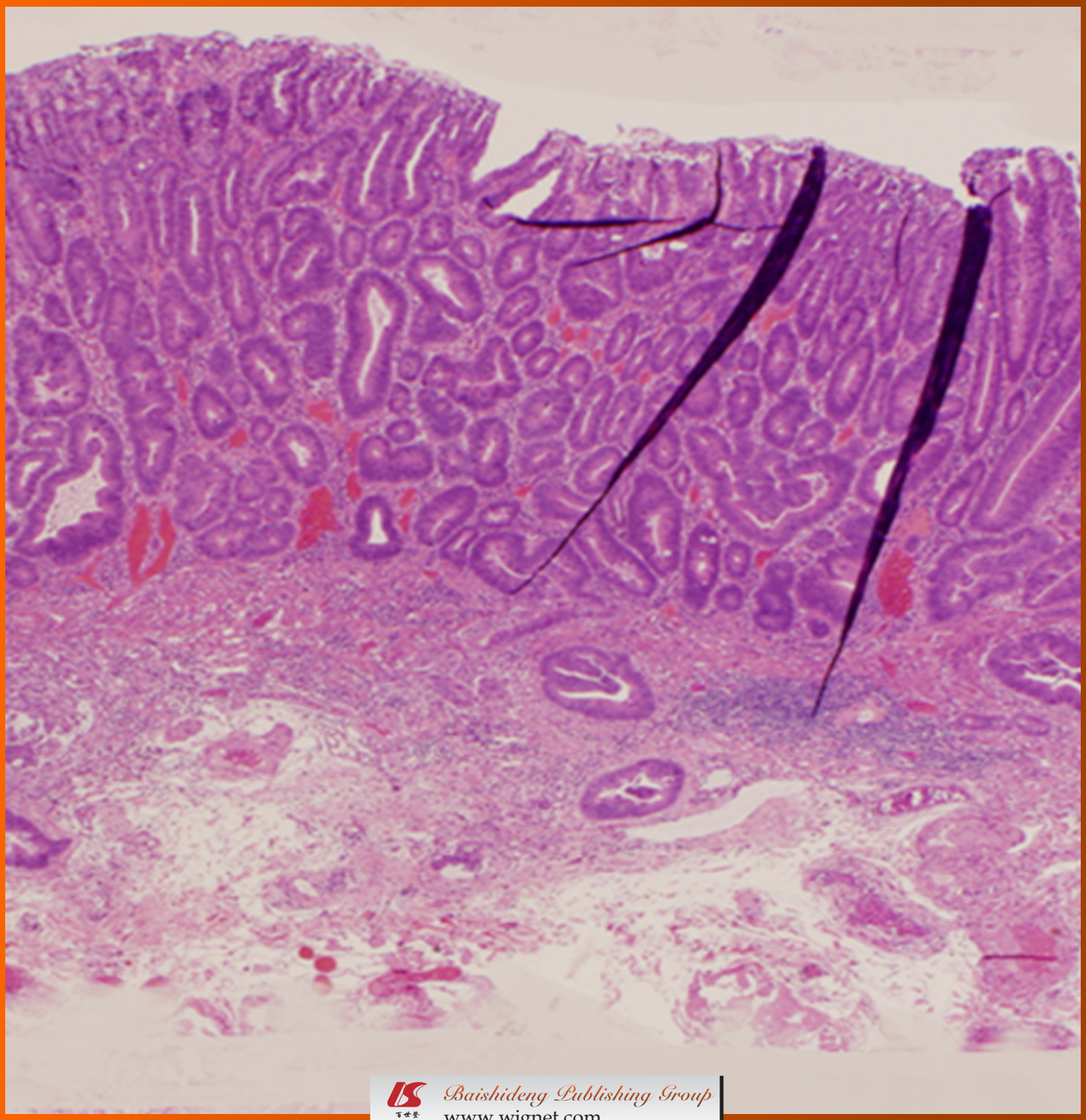

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EDITORIAL

Endoscopic submucosal dissection for superficial esophageal squamous cell neoplasms

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Abstract

Endoscopic resection is an effective treatment for non-invasive esophageal squamous cell neoplasms (ESCNs). Endoscopic mucosal resection (EMR) has been developed for small localized ESCNs as an alternative to surgical therapy because it shows similar effectiveness and is less invasive than esophagectomy. However, EMR is limited in resection size and therefore piecemeal resection is performed for large lesions, resulting in an imprecise histological evaluation and a high frequency of local recurrence. Endoscopic submucosal dissection (ESD) has been developed in Japan as one of the standard endoscopic resection techniques for ESCNs. ESD enables esophageal lesions, regardless of their size, to be removed *en bloc* and thus has a lower local recurrence rate than EMR. The development of new devices and the establishment of optimal strategies for esophageal ESD have resulted in fewer complications such as perforation than expected. However, esophageal stricture after ESD may occur when the resected area is larger than three-quarters of the esophageal lumen or particularly when it encompasses the entire circumference; such a stricture requires multiple sessions of endoscopic balloon dilatation. Recently, oral prednisolone has been reported to be useful in preventing post-ESD stricture. In addition, a combination of chemoradiotherapy (CRT) and ESD might be an alternative therapy for submucosal esophageal cancer that has a risk of lymph node metastasis because esophagectomy is extremely invasive; CRT has a higher local recurrence rate than esophagectomy but is less invasive. ESD is likely to play a central role in the treatment of superficial esophageal squamous cell neoplasms in the future.

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Key words: Endoscopic submucosal dissection; Esophageal cancer; Esophageal neoplasm

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INTRODUCTION

Endoscopic resection (ER) is an effective treatment for esophageal squamous cell neoplasms (ESCNs) without nodal metastasis. A number of retrospective studies involving histopathological analyses of surgically resected specimens of esophageal squamous cell carcinomas (SCCs) have shown that cases of non-invasive epithelial carcinoma (EP, carcinoma *in situ*) and intra-mucosal invasive carcinoma limited to the lamina propria mucosae (LPM) had an extremely low risk of lymph node and dis-

tant metastasis[1-7]. Based on these findings, the Japanese guidelines state that the indication for ER of esophageal SCC is a lesion limited to EP or LPM. The lymph node metastasis rates of SCC invading to the muscularis mucosae (MM SCC) and SCC invading the submucosa less than 200 μm below the muscularis mucosae (SM1 SCC) are reported as 9.3% and 19.6%, respectively[8]. Thus, ER is a relative indication for MM-SM1 SCC according to the Japanese guidelines. On the other hand, SM2-grade cancer (that invading the submucosa more than 200 μm below the muscularis mucosae) has a high frequency of lymph node metastasis (around 40%) and therefore ER is not recommended[1,9].

Endoscopic mucosal resection (EMR) has been developed for small localized ESCNs as an alternative to surgical therapy because it shows similar effectiveness and is less invasive than esophagectomy[10-16]. However, EMR is limited in resection size and therefore piecemeal resection is performed for large lesions, resulting in an imprecise histological evaluation and a high frequency of local recurrence[17].

Endoscopic submucosal dissection (ESD) for ESCNs is an endoluminal therapeutic technique to dissect directly along the submucosal layer. ESD was developed in Japan for the surgical treatment of gastric cancer and gave high curative resection rates for early gastric cancer, regardless of tumor size[18-23]. Hence, the technique has also been introduced for the esophagus[24] and was approved for the treatment of esophageal cancer by the Japanese government in 2008. ESD allows *en bloc* resection regardless of the size and precise histological assessment of the specimens, which are excised in one piece with tumor-free lateral basal margins, therefore preventing residual disease and local recurrence[24,25]. Recent technical advances in ESD enable *en bloc* resection of lesions, even if they occupy the entire circumference of the esophageal lumen. However, according to the guidelines in Japan, ER is principally limited to lesions that do not exceed two-thirds of the luminal circumference because of postoperative esophageal stricture. Postoperative esophageal stricture after esophageal ESD might be observed frequently and this problem should be resolved before the widespread use of ESD for ESCNs.

In this review, we describe the present techniques, outcomes, complications and future perspectives of esophageal ESD for ESCNs.

ESOPHAGEAL ESD PROCEDURE

EMR is a technique for resection of the mucosa containing the lesion *via* a snare wire. The lesion is strangulated by the snare wire and then resected after creating a submucosal cushion. To strangulate the lesion-containing mucosa firmly, several EMR methods, such as 2-channel EMR[26], EMR-C (EMR using a cap-fitted endoscope)[27] and esophageal endoscopic mucosal resection (EEMR)[28], have been developed. In 2-channel EMR, grasping forceps passed through another channel grasp the area near the lesion to help the snare wire strangulate the lesion. In EMR-C, the mucosa, including the lesion, is aspirated into a plastic cap attached to the tip of a forward-viewing endoscope; it is then strangulated by a small-diameter snare wire pre-looped within the cap and resected. These EMR methods are relatively easy and safe; thus, EMR has been used for the treatment of superficial ESCNs, especially small lesions that can be treated by EMR with *en bloc* resection. However, *en bloc* resection of lesions larger than 20 mm is difficult by EMR. Piecemeal resection of large lesions by EMR is insufficient for histological assessment and leads to local recurrence of ESCNs[17,29].

Detail of the ESD procedure has been described elsewhere[30,31]. Esophageal ESD comprises four steps (Figure 1): (1) circumferential marking: markings for the incision are made outside the margin with an electrosurgical knife; (2) submucosal injection: fluid such as sodium hyaluronate (0.5%) is injected into the submucosa to elevate the lesion from the muscle layer[32,33]. By mixing in a small amount of dye, the sodium hyaluronate can be easily distinguished from the non-injected area; (3) mucosal incision: a mucosal incision around the lesion is then made with an electrosurgical knife. Several knives have been developed for this purpose, such as the insulation-tip knife[34,35], hook knife[24,36], flex knife[37,38], flush knife[39], ball-tipped flush knife[40] and triangle-tipped knife[41]. Usually, the distal half of the mucosal incision is completed first, followed by the proximal half; and (4) submucosal dissection: dissection of the submucosa proceeds from the proximal to the distal end, using the same knife that was used for the mucosal incision.

Esophageal ESD is considered more difficult to perform than gastric ESD. The esophageal lumen is narrow and the esophageal wall moves continuously with respiratory movements and cardiac pulsation. Moreover, because the esophageal wall is thinner than that of the stomach, perforation during esophageal ESD occurs more frequently than during gastric ESD. This can result in mediastinal or subcutaneous emphysema and sometimes respiratory failure.

In Japan, the use of esophageal ESD has spread rapidly and has been attempted in several hospitals. As a result, the esophageal ESD procedure is now thought to be relatively straightforward. This is because: (1) it is easy to inject the fluid into the submucosal layer and to separate the mucosa from the muscle layer; (2) the submucosal layer is easily recognized because of the lesion located in a tangential direction; and (3) the submucosa of the esophagus contains few vessels that could lead to massive bleeding; thus, minimum hemostatic effort is required.

Esophageal ESD using conventional knives is a longer procedure and requires highly skilled endoscopists. This makes the acceptance of esophageal ESD in other countries more difficult. Grasping-type scissor forceps (GSF), which can grasp and incise the targeted tissue using an electrosurgical current, are a newly developed device for ESD[42-44]. Akahoshi *et al*[43] reported the usefulness of GSF for early gastrointestinal tract neoplasms because of their safety and simplicity. GSF can easily grasp the submucosal layer injected with fluid because

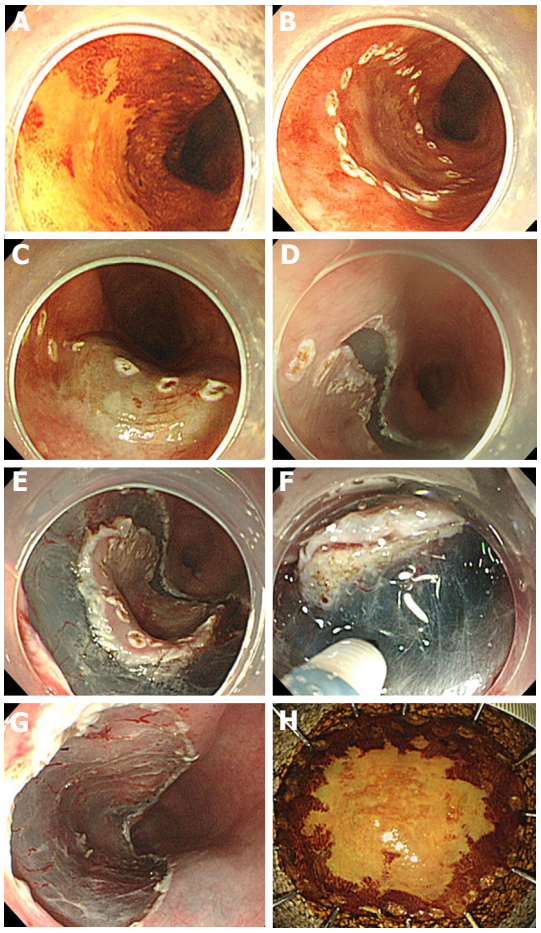

Figure 1 Steps of esophageal endoscopic submucosal dissection. A: Iodine-unstained lesion revealed by chromoendoscopy with iodine staining; B: Marking around the lesion; C: Submucosal injection to generate a submucosal cushion; D: Mucosal incision around the marking dots from the distal side; E: Mucosal incision from the proximal side; F: Submucosal dissection beneath the lesion; G: Artificial ulcer after removal of the lesion; H: Resected en bloc specimen.

the lesion is located in a tangential direction. Thus, GSF might be particularly useful for safely dissecting the submucosal layer in esophageal ESD.

OUTCOMES OF ESOPHAGEAL ESD

En bloc resection and local recurrence rates

The outcomes of esophageal ESD are shown in Tables 1 and 2. The *en bloc* resection rate is greater than 90% (90.6%-100%)[24,29,45-49]. *En bloc* resection, meaning resection in a single piece, facilitates an accurate histological assessment and reduces the risk of recurrence. In fact, the local recurrence rate after esophageal ESD is extremely low (0%-3.1%)[24,29,45-49]. In contrast, the local recurrence of SCCs after EMR was reported to be as high as 20% because *en bloc* resection by EMR is difficult and multiple resections are required for large lesions[17]. In a large scale study comparing 116 patients treated by ESD with 184 patients treated by EMR for superficial SCCs, Takahashi *et al*[48] reported that *en bloc* resection and the local resection rate were significantly better in the ESD group (100% and 0.9%, respectively) than in the EMR group (53.3% and 9.8%, respectively) (Table 2). In both groups, 19 of 300 patients experienced a local recurrence and 68.4% of all the local recurrences (13/19) were treated by piecemeal EMR. Thus, the EMR procedure is itself considered a risk for local recurrence. Ishihara *et al*[29,49] reported a comparison of ESD and EMR (EMR-C and 2-channel EMR) for esophageal cancers of both < 20 mm and ⩾ 20 mm (Table 2). For the larger, latter group, they compared 32 lesions treated by ESD with 46 lesions treated by EMR. The *en bloc* resection rates of EMR and ESD were 10.9% (5/46 lesions) and 90.6% (29/32 lesions), respectively. Lesions treated by EMR also had significantly more recurrences (23.9%; 11/46) than those treated by ESD (3.1%; 1/32). There were no recurrences of lesions treated by *en bloc* resection. For the smaller lesions, Ishihara *et al*[29,49] compared 64 lesions treated by ESD with 36 lesions treated by EMR (21 EMR-C and 15 2-channel EMR). As shown in Table 2, the *en bloc* resection rate of ESD was superior to that of EMR-C or 2-channel EMR, even for a lesion < 20 mm in size.

Although *en bloc* resection seems to be ideal for reducing the local recurrence rate, it is technically difficult to achieve by EMR. For *en bloc* resection of large lesions, ESD would be the best method. The procedure time for ESD is notably longer than that for EMR (as shown in Table 2). Further improvement to reduce the procedure time of this method is needed before ESD could become a standard treatment.

Complications

Minor bleeding during esophageal ESD is well controlled by hemostasis performed using the same knife as that used for submucosal dissection, hemostatic forceps (HDB2422/HDB2418; Pentax HOYA Co, Tokyo, Japan) or a coagrasper (FD-410LR; Olympus Medical Systems Co Tokyo, Japan). Massive bleeding complications are rarer in esophageal ESD than in gastric ESD.

As mentioned above, perforation during esophageal ESD has been considered to occur more frequently than during gastric ESD and can result in mediastinal or subcutaneous emphysema and sometimes respiratory failure. However, perforation is relatively rare (0%-4%), as shown in Tables 1 and 2. In these studies, all cases of perforation were cured conservatively without surgery. If perforation diagnosed by endoscopic findings of tearing of the muscle layer occurs, ESD can be completed after immediate closure of the perforation by endoscopic clipping.

On the other hand, pneumomediastinum (mediastinal emphysema) without perforation during esophageal ESD occurs frequently if the muscular layer is exposed. In a study of 58 patients treated for esophageal neoplasms by ESD, Tamiya *et al*[47] demonstrated that the incidence of pneumomediastinum detected by computed tomography (CT) was 56.3% (18/32) in the group with muscle exposure, although it was 0% (0/26) in the group without exposure of muscular layer. However, the presence of pneumomediastinum by CT did not imply overt esophageal perforation and did not influence the post-

Table 1 Recent outcomes of esophageal endoscopic submucosal dissection

Authors	Year	Total lesions/cases	Mean size (mm)	Operation time (min)	*En bloc* resection (%)	Local recurrence (%)	Perforation (%)	Stricture (%)
Oyama *et al*[24]	2005	102/102	28 (4-64)	-	95 (95/102)	0 (0/102)	0 (0/102)	7.4 (7/95)
Ono *et al*[45]	2009	107/84	22.9 (1-66)	-	100 (107/107)	1.2 (1/84)	4 (4/107)	18 (15/84)
Tamiya *et al*[47]	2010	58/58	30.4 (4-67)	180	100 (58/58)	0 (0/58)	0 (0/58)	6.9 (4/58)
Nonaka *et al*[46]	2010	27/25	21 (2-55)	88	100 (27/27)	0 (0/25)	3.7 (1/27)	12 (3/25)

procedural clinical course. Thus, pneumomediastinum associated with muscle exposure is a minor complication.

Postoperative esophageal stricture might be observed more frequently after resections in the esophagus because ESD permits resection of large specimens, even completely circumferential resections. Stricture is reported to occur in 6.9%-18.0% of cases (Table 1). Stricture after esophageal ESD may occur when the resected area is larger than three-quarters of the circumference of the esophageal lumen. Mizuta *et al*[50] retrospectively evaluated 42 superficial esophageal cancer lesions in 33 patients who underwent ESD and showed that the predictive factors for post-ESD esophageal stricture were a circumferential mucosal defect size of more than 71% (sensitivity 100%, specificity 97.1%) and a circumferential tumor size of more than 59% (sensitivity 85.7%, specificity 97.1%).

MANAGEMENT OF ESOPHAGEAL STRICTURE AFTER ESD

Strictures have almost always been treated with repeated endoscopic balloon dilatation (EBD). Ono *et al*[45] reported that 15 of 84 (18%) patients treated by esophageal ESD experienced esophageal stricture and were successfully managed with EBD in a median of two sessions (range 1-20). Moreover, the authors recommended preventive EBD for cases of mucosal defect exceeding 75% of the esophageal circumference. However, the EBD procedure itself carries a risk of esophageal perforation. There are only a few studies concerned with dilatation of esophageal strictures after ESD. Takahashi *et al*[51] reported the risk of perforation and its specific risk factors during dilatation of post-EMR/ESD esophageal stricture. Seven perforations (1.1%, 7/648 procedures or 9.0%, 7/78 patients) were observed in this study. Two of these patients developed a thoracic abscess and needed drainage, although all the patients recovered without surgery.

Another treatment option for post-ESD esophageal stricture is endoscopic placement of a stent. Saito *et al*[52] reported two cases in whom biodegradable stents for post-ESD esophageal strictures were successfully placed. In both lesions, the mucosal defect had extended to seven-eighths of the circumference.

Recently, systemic steroid administration has been reported to be effective for post-EBD stricture and might resolve the problems of EBD, such as multiple EBD sessions reducing the patient's quality of life and increasing the risk of esophageal perforation[53]. Isomoto *et al*[54] described seven patients with superficial SCC who underwent completely circumferential ESD. Of the seven patients, four were treated with an 8 wk course of oral prednisolone that was administered at a dose of 30 mg daily on the third post-ESD day and tapered off gradually (30 mg/d, 30 mg/d, 25 mg/d, 25 mg/d, 20 mg/d, 15 mg/d, 10 mg/d and 5 mg/d for 7 d each). Administration of oral prednisolone effectively either prevented esophageal stricture or reduced the number of EBD sessions. Two patients required no EBD and two patients required fewer EBD sessions (2 and 11 sessions, respectively) than the three patients (30, 20 and 48 sessions, respectively) who had not received oral prednisolone. In a retrospective study in 41 patients with esophageal stricture after complete circular or semicircular ESD for esophageal SCCs involving more than three-quarters of the lumen, Yamaguchi *et al*[55] compared an oral prednisolone group with a pre-emptive EBD group. Oral prednisolone was administered as in Isomoto *et al*[54]'s report. Pre-emptive EBD was started on the third day post-ESD and continued twice weekly for 8 wk. An additional EBD was performed on demand in both groups whenever dysphagia appeared. The average number of EBD sessions was significantly decreased in the oral prednisolone group compared with in the pre-emptive EBD group (1.7 *vs* 15.6, respectively). In this study, there were no complications related to the EBD itself in either group and no adverse events related to the oral prednisolone occurred. Oral prednisolone may offer a safe and effective option for the prevention of post-ESD stricture, potentially reducing or eliminating the need for EBD.

LONG-TERM OUTCOMES AFTER ESD

For esophageal ESD, in the 2007 annual meeting of the Japanese Gastroenterological Endoscopy Society, the 3 year survival rates for EP-LPM cancer and MM-SM1 cancer were 95.1% and 86.7%, respectively.

Ono *et al*[45] reported the long-term outcomes for 84 patients treated by ESD for ESCNs. Histopathologically, 58 patients were diagnosed with a high-grade intraepithelial neoplasm (HGIN), including EP or LPM cancer, and were followed-up without additional therapy. Only

Table 2 Esophageal endoscopic submucosal dissection vs endoscopic mucosal resection

Authors	Year	Method	Total lesions	Mean size (mm)	Operation time (min)	*En bloc* resection (%)	Local recurrence (%)	Perforation (%)
Takahashi *et al*[48]	2010	ESD	116	30 (4-95)	73.9 (21–307)	100 (116/116)	0.9 (1/116)	2.6 (3/116)
		EMR	184	20 (4-60)	44.4 (11–258)	53.3 (98/184)	9.8 (18/184)	1.6 (3/184)
Ishihara *et al*[29]	2008	ESD	32	> 20	110 (30–245)	90.6 (29/32)	3.1 (1/32)	0 (0/32)
		EMR	46	> 20	35 (10–90)	10.9 (5/46)	23.9 (11/46)	0 (0/46)
Ishihara *et al*[49]	2008	ESD	31	16	64	100 (31/31)	0 (0/31)	3.2 (1/31)
		EMR-C	68	13	21	87 (59/68)	0 (0/68)	0 (0/68)
		2-channel EMR	72	12	15	71 (51/72)	2.8 (2/72)	0 (0/72)

ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; EMR-C: EMR using a cap-fitted endoscope.

one patient, whose lesion was identified as HGIN with Rx (lateral) resection, had a local recurrence after 6 mo and was successfully treated with additional ESD. The cause-specific survival rate at 5 years was 100% for patients with HGIN or LPM cancer. On the other hand, 28 patients were histopathologically diagnosed with MM or SM cancer. Fifteen of the 28 patients underwent additional therapies [chemoradiotherapy (CRT)/radiotherapy, 6; surgery, 9]. Three patients with MM or SM cancer died of esophageal SCC after ESD. The cause-specific survival rate at 5 years was 85% for patients with MM or SM cancers.

ESOPHAGEAL ESD COMBINED WITH CRT

Surgery is recommended for SM SCCs because of the high frequency of lymph node metastasis. However, esophagectomy is extremely invasive and is associated with significant morbidity and mortality, particularly in patients of advanced age or those with cardiac or pulmonary complications. Such patients may be treated with CRT. Although CRT has a favorable survival rate and mild toxicity in patients with a stage I lesion (UICC-TNM classification: T1N0M0), the local recurrence rate of CRT is higher than that of esophagectomy[56]. ESD with subsequent CRT for SM SCCs might be useful for preventing residual lesion or local recurrence. A randomized controlled study is now ongoing in Japan, in which patients with suspected SM1 or SM2 SCC are treated with ER, and whether subsequent CRT is performed is based on the histological findings. Patients with SCC occupying larger than three-quarters of the circumference of the esophageal lumen are excluded in this study.

In our experience, EBD for post-ESD stricture during subsequent CRT requires multiple sessions even if treated with steroids and therefore decreases the patient's quality of life. Thus, CRT and subsequent ESD might be a useful therapeutic option for large esophageal lesions that have a risk of postoperative esophageal stricture and for residual or recurrent esophageal lesions.

Saito *et al*[57] reported three cases of superficial esophageal cancer treated with CRT followed by ESD. One patient refused surgery and the other two patients suffered from severe cardiopulmonary disease complications. In all three patients, CRT was effective in reducing tumor size and the residual tumors were completely resected by ESD. In this report, one patient had a superficial SCC occupying the entire circumference of the lumen at a site 15-25 cm from the upper incisor. The esophageal lesion was markedly reduced in size by CRT and the small residual lesion was resected *en bloc* by ESD. If ESD had been used initially in this case, esophageal stricture might have occurred and required several sessions of EBD. The combination of CRT plus subsequent ESD may also be useful for patients with superficial esophageal cancer who need completely circumferential ESD to avoid esophageal stricture.

CONCLUSION

In summary, ESD for the management of superficial ESCNs is an effective and safe therapeutic modality. ESD is well established in Japan, although esophageal ESD requires highly skilled surgeons. ESD is recommended for EP or LPM esophageal cancers, especially those larger than 2 cm. ESD is also indicated for lesions invading to the MM–SM or occupying the entire circumference of the lumen. ESD followed by CRT, or ESD after CRT, may be an alternative therapeutic option for patients unwilling to undergo esophagectomy or for high-risk patients with MM–SM cancer. The management of esophageal stricture after ESD is one of the major problems. The administration of prednisolone may be useful for esophageal stricture after ESD, reducing the requirement for EBD sessions. Although extensive controlled, randomized studies are necessary to evaluate the usefulness of these treatments, there is no doubt that ESD will play a central role in the treatment of superficial ESCNs in the future.

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REVIEW

Importance of histological evaluation in endoscopic resection of early colorectal cancer

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Abstract

The diagnostic criteria for colonic intraepithelial tumors vary from country to country. While intramucosal adenocarcinoma is recognized in Japan, in Western countries adenocarcinoma is diagnosed only if the tumor invades to the submucosa and accesses the muscularis mucosae. However, endoscopic therapy, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is used worldwide to treat adenoma and early colorectal cancer. Precise histopathological evaluation is important for the curativeness of these therapies as inappropriate endoscopic therapy causes local recurrence of the tumor that may develop into fatal metastasis. Therefore, colorectal ESD and EMR are not indicated for cancers with massive submucosal invasion. However, diagnosis of cancer with massive submucosal invasion by endoscopy is limited, even when magnifying endoscopy for pit pattern and narrow band imaging and flexible spectral imaging color of enhancement are performed. Therefore, occasional cancers with massive submucosal invasion will be treated by ESD and EMR. Precise histopathological evaluation of these lesions should be performed in order to determine the necessity of additional therapy, including surgical resection.

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Key words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Early colorectal cancer; Histopathology

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INTRODUCTION

The diagnostic criteria for colonic epithelial tumors vary from country to country. In Japan, intraepithelial tumors that display malignant cytological or architectural features are diagnosed as intramucosal adenocarcinoma according to Japanese Classification of Colorectal Carcinoma[1]. On the other hand, in western countries, including England and America, intramucosal epithelial tumors are diagnosed only as dysplasia and adenocarcinoma is diagnosed only if the tumor invades to submucosa be-

yond the muscularis mucosae[2,3]. One reason for this is that intramucosal epithelial tumors are clinically benign and do not metastasize to the lung, liver or lymph nodes. In this review, we compare the criteria for diagnosis of colorectal intraepithelial tumors in Japan and in Western countries and also describe the World Health Organization (WHO) classification and Vienna classification of these tumors[4,5].

Despite these differences in diagnostic criteria, endoscopic therapy, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) of adenoma and early colorectal cancer, is performed worldwide[6,7]. Precise histopathological evaluation of these lesions is important for the long-term success of these therapies, as inappropriate endoscopic therapy causes local recurrence of the tumor that may develop into fatal metastasis. We describe the use and therapeutic limitations of EMR and ESD and also show the importance of detailed histopathological evaluation of specimens resected by EMR and ESD. Moreover, we reveal the proper endoscopic method for obtaining appropriate specimens for histopathological evaluation by EMR and ESD.

DIFFERENCES IN THE HISTOPATHOLOGICAL DIAGNOSIS OF COLORECTAL EPITHELIAL TUMORS BETWEEN JAPAN AND WESTERN COUNTRIES

The diagnostic criteria for colonic epithelial tumors vary from country to country. In Japan, the terms "low-grade adenoma," "high-grade adenoma" and "intramucosal adenocarcinoma" are used to describe intraepithelial tumors based on their degrees of cytological or architectural atypia, according to the Japanese colorectal cancer criteria (Table 1)[1]. Intramucosal adenocarcinoma is characterized by malignant glandular epithelium exhibiting a tubular or papillary architecture or producing mucus. In contrast, in Western countries, including England and America, intraepithelial tumors are diagnosed only as dysplasia[2,3] and the term "adenocarcinoma" is used only if the tumor invades the submucosa and accesses the muscularis mucosae. In detail, "mild dysplasia," "moderate dysplasia" and "severe dysplasia" are used in England to classify intraepithelial tumors according to the states of their nuclei, glandular patterns and interglandular spaces (Table 1)[2]. Mild dysplasia and moderate dysplasia are almost similar to the Japanese definitions of low-grade and high-grade adenoma, and severe dysplasia is almost identical to the Japanese definition of adenocarcinoma. In America, "low-grade adenoma" and "high-grade adenoma" are used to describe intraepithelial tumors according to the states of their crypts and nuclei (Table 1)[3]. Low-grade adenoma is almost similar to the English categories of mild and moderate dysplasia, while high-grade adenoma is almost similar to the English category of severe dysplasia. However, the WHO classification, which was revised in 2010, defines dysplasia as histopathologically unequivocal neoplastic epithelium without evidence of invasive growth[4]. The term "dysplasia" is thus only appropriate when cytological and/or architectural features of neoplasia are present. The term "intramucosal adenocarcinoma" is applied to lesions that show histological evidence of invasion into the lamina propria or muscularis mucosa but not into the submucosa.

Table 1 The differences in the histopathological diagnosis of colorectal intraepithelial tumors between Japan and Western countries

	Intramucosal epithelial tumor		
Japan	Low grade adenoma	High grade adenoma	Intramucosal adenocarcinoma
United Kingdom	Mild dysplasia	Moderate dysplasia	Severe dysplasia
United States	Low grade dysplasia		High grade dysplasia

The Vienna classification of gastrointestinal epithelial neoplasia is represented as resolving the histopathological diagnostic differences among other countries[5] and applies to the diagnosis of both biopsy specimens and resected specimens. Epithelial neoplastic lesions are classified as Categories 1 through 5. The detailed criteria are as follows: Category 1, negative for neoplasia/dysplasia; Category 2, indefinite for neoplasia/dysplasia; Category 3, non-invasive low-grade neoplasia; Category 4, non-invasive high-grade neoplasia; and Category 5, invasive neoplasia, including intramucosal carcinoma and submucosal carcinoma or beyond. The revised Vienna classification of gastrointestinal epithelial neoplasia was reported in 2002[8]. This revised classification includes the intramucosal carcinoma in category 4 instead of category 5, which fits better with the possibility of endoscopic therapy of this subtype of carcinoma. However, this Vienna classification system is seldom used clinically in Japan.

The diagnostic criteria for submucosally invasive cancer also vary among countries. As submucosally invasive cancer has a risk of metastasizing, it is generally treated by surgical resection worldwide. However, the risk of metastasis is reported to be about 10%[9]. In Japan, the depth of submucosal invasion is measured as part of the evaluation of submucosally invasive cancer because it affects the risk of metastasis to the lymph nodes[1] (Figure 1). The depth of submucosal invasion is calculated as follows. When the muscularis mucosae can be identified, it is used as the baseline and the vertical distance from this line to the deepest extent of invasion represents the submucosal depth (Figure 2). When the muscularis mucosae cannot be identified due to carcinomatous invasion, the most superficial aspect of the submucosally invasive cancer is used as the baseline and the vertical distance from this line to the deepest portion is determined and defined as the depth of submucosal invasion (Figure 3)[9,10]. The Japanese guide-

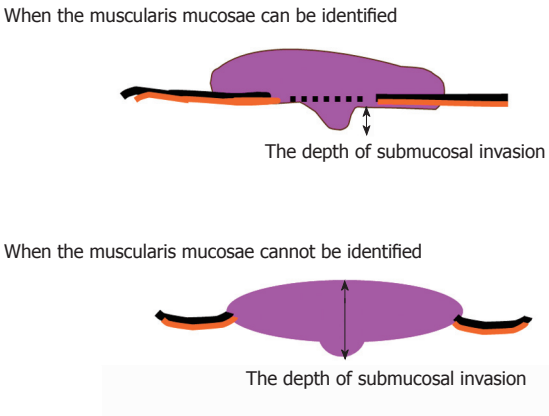

Figure 1 The Japanese system for measuring the depth of submucosal invasion in submucosally invasive cancer. When the muscularis mucosae can be identified, it is used as the baseline and the vertical distance from this line to the deepest extent of invasion represents the depth of submucosal invasion. When the muscularis mucosae cannot be identified due to carcinomatous invasion, the most superficial aspect of the submucosally invasive cancer is used as the baseline and the vertical distance from this line to the deepest extent of invasion is the depth of submucosal invasion.

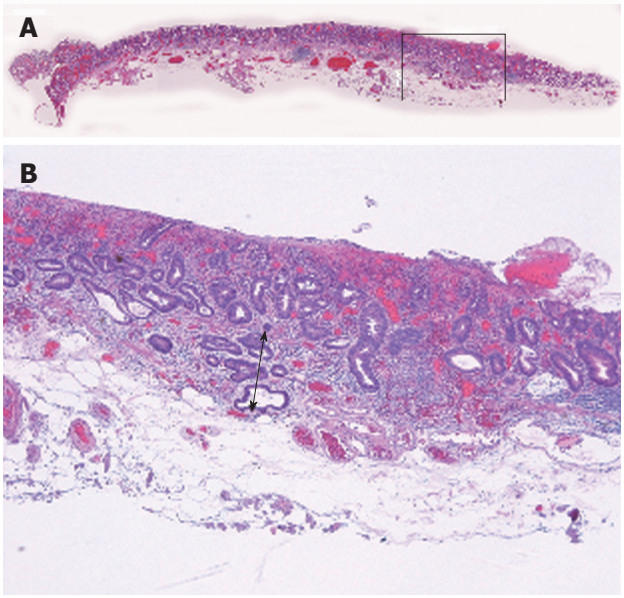

Figure 2 A submucosally invasive cancer with identifiable muscularis mucosae. A: Submucosal invasion (black box) with partial destruction of the muscularis mucosae was detected by histological examination of hematoxylin and eosin stained sections; B: The muscularis mucosae was identified. The depth of submucosal invasion was 500 μm (black arrow).

lines for colorectal cancer report the following risk factors for lymph node metastasis of submucosally invasive colorectal cancer: (1) depth of submucosal invasion more than 1000 μm; (2) lymphatic or venous invasion; (3) poorly differentiated histology; (4) the vertical margin of the resected specimen positive for cancer; and (5) grade 2 or 3 tumor cell budding[10,11]. Evaluation of these risk factors determines whether endoscopically resected submucosally invasive cancer is further treated by surgical resection. In Japan, submucosally invasive cancer in surgically resected specimens is also classified clinically as SM1, SM2 or SM3 according to the degree of invasion into the submucosa[12].

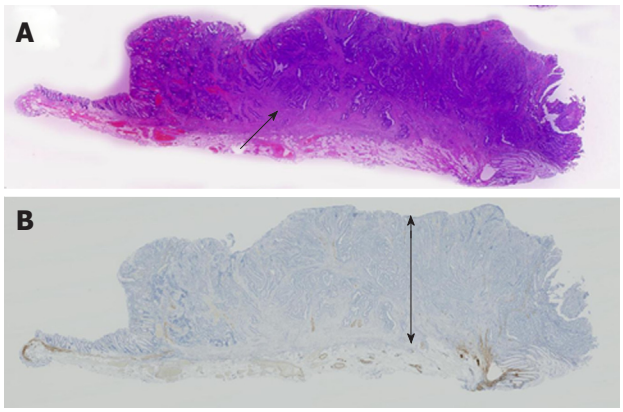

Figure 3 A submucosally invasive cancer with unidentifiable muscularis mucosae. A: Submucosal invasion (black arrow) with complete destruction of the muscularis mucosae was detected by histological examination of hematoxylin and eosin stained sections; B: Immunohistological staining for desmin showed that the muscularis mucosae could not be identified. The depth of submucosal invasion was 3500 μm (black arrow).

The phrase "massive submucosal invaded cancer," which is frequently used in clinical reports, is synonymous with tumor invasion of SM2 or SM3 or with depth of submucosal invasion of more than 1000 μm[9,13-14]. For pedunculated submucosally invasive cancer that has disrupted the muscularis mucosae, the depth of submucosal invasion is the distance between the deepest extent of the invasion and a reference line defined as the boundary between the tumor head and the pedicle, according to Haggitt's classification[15]. When the cancer does not invade past the reference line, it is defined as "head invasion" and has no possibility of metastasis. When cancer has invaded above this baseline, it is defined as "stalk invasion" and additional surgery should be considered to reduce the risk of lymph node metastasis.

INDICATIONS FOR AND THERAPEUTIC LIMITATIONS AND HISTOPATHOLOGICAL EVALUATION OF EMR AND PIECEMEAL EMR

EMR is generally performed for early colorectal cancers worldwide. The saline injection-assisted method was first described by Rosenberg, who identified it as a safety factor for the removal of rectal and sigmoid polyps, and was reintroduced by Tada *et al*[16-18] in 1984. 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[19-24]. The rates of *en bloc* and complete resection have been reported to be 62.85% and 58.66%, respectively[6]. The rate of *en bloc* resection by EMR of tumors greater than 20 mm in diameter is especially insufficient (Table 2)[19-24]. Many additional injection solutions have been used to achieve sustained mucosal elevation, definitive *en bloc* resection and prevention of perforation during EMR. Hypertonic saline, glycerol, dextrose and fibrinogen in-

Table 2 The rates of *en bloc* resection and local recurrence of tumors larger than 20 mm in diameter treated by endoscopic mucosal resection

Author	Injection solution	No. of cases	Rate of *en bloc* resection (%)	Rate of local recurrence (%)
Saito *et al*[18]		228	33.0	14
Tanaka *et al*[19]	Glycerol	178	39.3	7.9
Tajika *et al*[20]		104	48.1	15.4
Iishi *et al*[21]	NS	56	25.0	-
Kobayashi *et al*[22]		56	37.5	21.4
Uraoka *et al*[23]	NS	44	20.5	18.6
	Glycerol	39	23.1	15.2
Our data	HA	35	42.8	10

HA: Hyaluronic acid; NS: Not significant.

Table 3 The rates of *en bloc* resection and complete resection by endoscopic submucosal dissection

Author	No. of cases	Rate of *en bloc* resection (%)	Perforation rate (%)	Post-operative bleeding rate (%)
Saito *et al*[7]	1111	88.0	4.9	1.5
Toyonaga *et al*[32]	468	98.9	1.5	1.5
Isomoto *et al*[33]	292	90.1	8.2	0.7
Yoshida *et al*[34]	250	86.8	6.0	2.4
Fujishiro *et al*[35]	200	91.5	10.4	1.0
Zhou *et al*[36]	74	93.2	8.1	1.3
Tanaka *et al*[37]	70	80.0	10.0	1.4
Our recent data	410	92.6	4.1	1.9

duce longer-lasting mucosal elevation than achieved by normal saline (NS)[24-26]. Uraoka *et al*[24] demonstrated that the rates of *en bloc* and complete resection by EMR were improved by using glycerol rather than NS. Moreover, the increased tumor-free margin achieved using glycerol improved the rate of complete resection. Yamamoto *et al*[27] first reported the efficacy of hyaluronic acid (HA) for novel endoscopic resection of a large colorectal polyp and this procedure was subsequently termed ESD. We also demonstrated that 0.13% HA was effective for achieving sustained mucosal elevation in resected porcine colon and in living minipig colon. HA has been shown to produce higher and more sustainable mucosal elevation than achieved by NS[28]. However, some authors have raised concerns about the theoretical carcinogenetic risk of HA[29]. This should be confirmed by further studies.

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. Although specimens resected by EMR sometimes show positive margins even if the tumor was successfully resected *en bloc*, most of such tumors cause no local recurrence. Burning of the resected specimens probably affects this situation. However, some of these tumors recur locally. Therefore, endoscopists are obligated to perform EMR with tumor-free margins. In our department, we have adopted HA as our injection liquid in order to improve our rate of complete resection, especially of large tumors (Table 2).

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%) (Table 2). Most recurrent adenomas, including partial intramucosal adenocarcinomas, can be cured by additional endoscopic therapy[30]. If possible, the indications for the use of piecemeal EMR should be examined carefully before endoscopic therapy by magnifying endoscopy and image-enhanced endoscopy[31,32]. However, piecemeal EMR does not allow for precise histopathological evaluation in some cases; 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. In these cases, the patient will not be advised to undergo additional surgical resection, allowing recurrence a few years later[30]. In some cases, recurrence may occur as lung, liver and/or lymph node metastasis and these patients are very difficult to cure. Therefore, laparoscopic-assisted colectomy (LAC) is regarded throughout the world as the standard therapy for large colorectal tumors[33]. However, as LAC is more invasive than endoscopic treatment, ESD is still performed in some areas, especially in Japan.

INDICATIONS FOR AND THERAPEUTIC LIMITATIONS AND COMPLICATIONS OF ESD

In Japan and some other Asian as well as Western countries, ESD is reported to be an efficient treatment with a high rate of *en bloc* resection for large colorectal tumors and it is less invasive than LAC[7,34-39]. ESD allows removal of large early colorectal cancer lesions but can be a time-consuming procedure and carries a risk of perforation higher than that of EMR[36,40-41]. A list of situations in which ESD is appropriate has been proposed by a Japanese ESD specialist group[39]. These are, firstly, lesions more than 20 mm in diameter for which endoscopic therapy are indicated but for which *en bloc* resection by snare EMR would be difficult and, secondly, lesions that are suspected to be submucosally invasive, which should be resected *en bloc* by ESD. Other lesions in addition to these categories can also be candidates for ESD, including mucosal lesions with fibrosis caused by prolapse due to biopsy or peristalsis, local residual early cancer after endoscopic resection, and sporadic localized tumors in cases of chronic inflammation such as ulcerative colitis. The rate of *en bloc* resection for large colorectal tumors has been reported to be 80.0%-98.9% (Table 3)[7,34-39]. However, the procedure has not been standardized due to its associated technical difficulties. The colon is winding in nature and has many folds. Moreover, the colonic wall is thinner than the gastric wall. The main complications

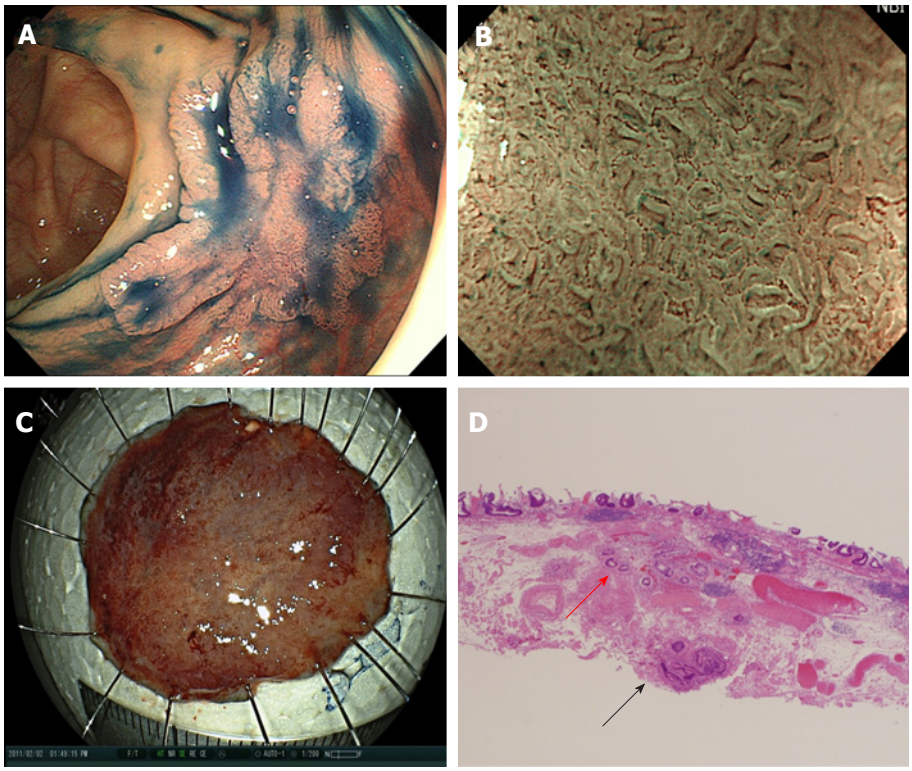

Figure 4 A submucosally invasive cancer with venous infiltration. A: A tumor graded 0-IIa, measuring 20 mm, located in the ascending colon. The surface of the tumor was slightly depressed (shown by indigo carmine dye); B: Magnifying endoscopy with NBI revealed Type C1/C2 according to Hiroshima classification[43]. The tumor was diagnosed as shallow submucosally invasive cancer and endoscopic submucosal dissection (ESD) was performed; C: *En bloc* resection was performed. The ESD operation time was 50 min; D: The histopathological diagnosis of the specimen resected by ESD was massive submucosally invasive cancer. The depth of submucosal invasion was 1300 μm and both a positive vertical margin of the tumor (black arrow) and venous infiltration (red arrow) were detected. The appropriate depth of dissection allowed detection of the positive vertical margin and venous infiltration. Additional surgical intervention was performed and no residual tumor or lymph node metastasis was detected. ESD: Endoscopic submucosal dissection; NBI: Narrow band imaging.

of ESD are postoperative perforation and hemorrhage, similar to those of EMR. In particular, the rate of perforation is higher for ESD than for EMR (1.5%-10.4%). Perforation of the colon can cause fatal peritonitis. Most cases of perforation are treated conservatively by endoscopic clipping, without urgent surgical intervention[40,41]. 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 without blood transfusion. A safe strategy, suitable knife, adoption of other equipment and animal training are necessary in order to minimize the complications, including perforation, of ESD[42].

IMPORTANCE OF THE HISTOPATHOLOGICAL EVALUATION OF SUBMUCOSALLY INVASIVE CANCER IN ESD SPECIMENS

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[7]. 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%-25.0%)[35-37,39]. Moreover, the proportion of massive submucosally invasive cancers in these studies was reported to be 30.0%-58.3%[35-37,39]. Massive submucosal invasion is not in fact an indication for colorectal ESD and EMR; however, endoscopic diagnosis of massive submucosally invasive cancer is limited even when magnifying endoscopy for pit pattern, narrow band imaging (NBI) and flexible spectral imaging color of enhancement (FICE) are performed. The sensitivity of detail-magnifying observation for massive submucosally invasive cancer is only 63.8%-84.8%[32,43-46]. Therefore, some number of massive submucosally invasive cancers may be diagnosed as mucosal cancer or shallow submucosally invasive cancer and scheduled for resection by ESD or EMR (Figure 4). The probability of curative resection of submucosally invasive cancer 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 as shown (Table 4). The average tumor size was 26.5 mm in the SM (submucosally invasive cancer) group and 35.1 mm in the M group ($P < 0.01$). The ratio of the number of tumors in the colon to that in the rectum was 18:15 in the SM group, 87:57 in the M (intramucosal

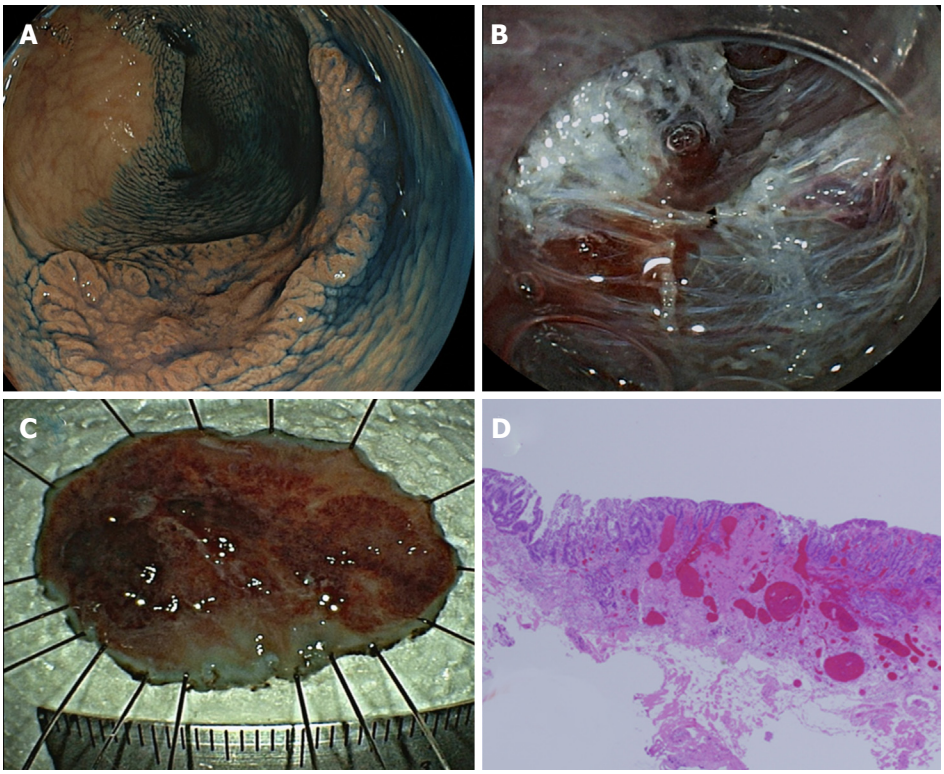

Figure 5 A submucosally invasive cancer with severe fibrosis. A: A tumor graded 0-IIa, measuring 35 mm, located in the descending colon. The surface of the tumor was slightly depressed. The tumor was diagnosed by magnifying endoscopy as shallow submucosally invasive cancer and endoscopic submucosal dissection (ESD) was performed; B: Severe fibrosis was detected during ESD and was dissected with a scissor-type knife; C: *En bloc* resection was performed. The ESD operation time was 160 min. There was no perforation or postoperative hemorrhage; D: Histopathological diagnosis of the specimen resected by ESD was shallow submucosally invasive cancer. The depth of submucosal invasion was 800 μm, and there was severe fibrosis in the submucosa. ESD: Endoscopic submucosal dissection.

Table 4 Characteristics of colorectal tumors resected by endoscopic submucosal dissection

	SM	M	A	*P* value
Number of tumors	33	144	157	
Median age (yr) (range)	65.5 (46-83)	67.9 (48-87)	67.5 (39-87)	
Male/female	21/12	86/58	81/76	NS
Tumor size (mm) (range)	26.5 (10-60)	35.1 (10-130)	27.0 (10-80)	$P < 0.01$
Location (colon/ rectum)	18:15	87:57	124:33	$P < 0.01$ SM:A
Morphology (protruding/ superficial)	14:19	32:112	12:145	$P < 0.01$
Operation time (min) (range)	109 (20-240)	118 (30-420)	92 (10-300)	NS
Severe Fibrosis (%)	18.1	5.5	6.3	$P < 0.05$ SM:M
En bloc resection (%)	90.9	90.9	89.1	NS
Complete resection (%)	72.7	84	81.5	NS
Perforation (%)	6	7.6	1.9	NS
Postoperative hemorrhage (%)	0	6.2	1.2	NS

ESD: Endoscopic submucosal dissection; SM: Submucosally invasive cancer; M: Intramucosal cancer; A: Adenoma; NS: Not significant.

cancer) group and 124:33 in the A group. The proportion of tumors in the rectum was higher in the SM group than in the A (adenoma) 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%) ($P < 0.05$) (Figure 5). 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*[47] showed that severe fibrosis complicated ESD and was associated with perforation. The median operation time for the 7 cases in the SM group with severe fibrosis was 147 min, which was longer than that for those in 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, a scissor-shaped knife called the "clutch cutter" (Fujifilm Medical Co., Tokyo, Japan) 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[48].

Among the submucosally invasive cancers, the average depth of submucosal invasion was 449 μm (range: 120-950 μm) in the SM1 group and 5728 μm (range: 1100-8000 μm) in the SM2-3 group. In total, 7 cases of venous invasion (21.2%) and 6 of lymphatic invasion (18.1%) were detected in the SM1 and SM2-3 groups (Table 5). In detail, the rates of venous invasion were 7.6% in the SM1 group and 30.0% in the SM2-3 group, and the rates of lymphatic invasion were 15.3% in the SM1 group

Table 5 Characteristics of submucosally invasive cancer resected by endoscopic submucosal dissection

	SM1	SM2-3	*P* value
Number of tumors	13	20	
Tumor size (mm) (range)	30.7 (20-60)	23.7 (10-60)	NS
Location (colon/ rectum)	8:5	10:10	NS
Morphology (Ⅰs, Ⅰsp/ Ⅱa, Ⅱc, Ⅱa + Ⅱc)	4:9	10:10	NS
Operation time (min) (range)	121 (50-240)	98 (20-230)	NS
Severe fibrosis (%)	15.3	20	NS
En bloc resection (%)	90.9	89.1	NS
Venous invasion (%)	1 (7.6)	6 (30.0)	NS
Lymphatic invasion (%)	2 (15.3)	4 (20.0)	NS
Positive of horizontal margin (%)	3 (23.0)	3 (15.0)	NS
Positive of vertical margin (%)	1 (7.6)	4 (20.0)	NS
Perforation (%)	7.6	1.9	NS

SM: Submucosally invasive cancer.

and 20.0% in the SM2-3 group. Even in shallow submucosally invasive cancers, it was necessary to dissect to the appropriate submucosal depth for the precise detection of venous and lymphatic invasion (Figure 5). If the depth of dissection was too shallow, some cases of venous and lymphatic invasion could not be detected; moreover, the vertical margin could not be evaluated (Figure 6). Therefore, the depth of dissection of colorectal ESD should be carefully considered.

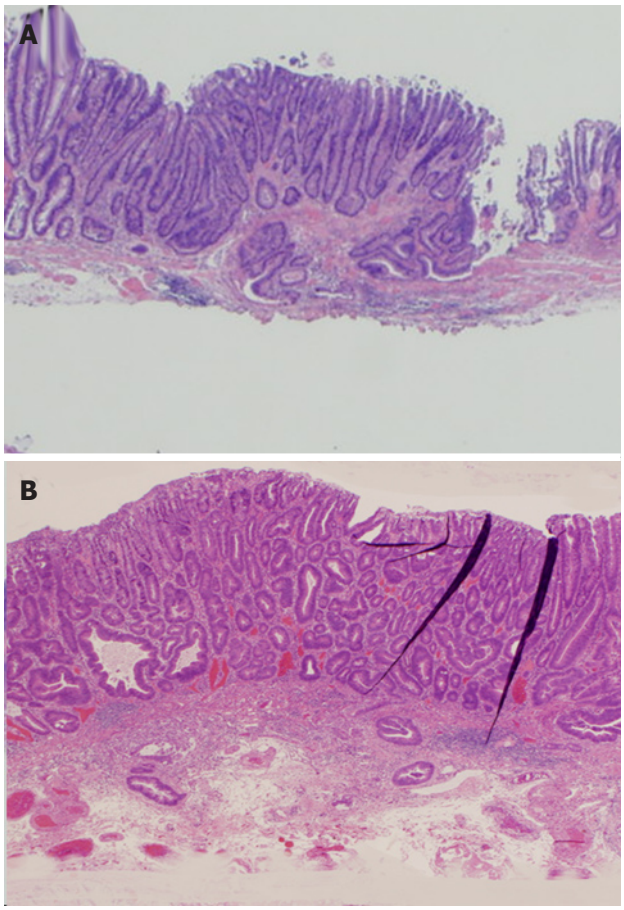

Figure 6 The depth of submucosal dissection in resection of submucosally invasive cancer by endoscopic submucosal dissection. A: The dissection in this case was too shallow. Insufficient submucosa is seen in the resected specimen, which was dissected at the submucosa slightly below the muscularis mucosae. Submucosal invasion can be detected; however, the presence of venous-lymphatic invasion cannot be evaluated; B: This case was dissected appropriately. An adequate amount of submucosa is seen in the resected specimen, which was dissected at the middle-deep submucosa sufficiently below the muscularis mucosae. Both submucosal invasion and venous-lymphatic invasion can be detected.

CONCLUSION

In this review, we describe the different diagnostic criteria for colonic epithelial tumors used around the world. In brief, intramucosal adenocarcinoma is recognized in Japan, while in Western countries adenocarcinoma is diagnosed only if the tumor invades the submucosa and accesses the muscularis mucosae.

Endoscopic treatment, including EMR and ESD, is performed for adenomas and early colorectal cancers worldwide. Precise histopathological evaluation is important for the long-term success of these therapies. Inappropriate endoscopic therapy can lead to local recurrence of the tumor, which sometimes progresses to fatal metastasis. Submucosally invasive cancer is sometimes treated by ESD or EMR. In these cases, very precise histopathological evaluation should be performed in order to determine the necessity of additional therapy, including surgical resection.

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3rd World Congress of Laparoscopic Surgeons and Gynecologists
Delhi, India

February 15-18, 2012
23rd Annual International Colorectal Disease Symposium
Fort Lauderdale, FL, United States

February 16-18, 2012
7th Congress of ECCO
Barcelona, Spain

February 21-23, 2012
International Scientific Conference on Bacteriocins and Antimicrobial Peptides - BAMP2012
Kosice, Slovakia

February 24-26, 2012
Advances in Hepato Bilary Pancreatic Endoscopy
Hyderabad, India

February 25-March 2, 2012
29th AGC Course 2012, 29th International Gastrointestinal Surgery Workshop
Lupsingen, Switzerland

March 13-16, 2012
12th Annual Gastroenterology and Hepatology: Viva la Vida
San Juan, Puerto Rico

March 1-4, 2012
Mayo Clinic 2012 Gastroenterology and Hepatology
Coronado, CA, United States

March 22-24, 2012
1st Gallen EORTC Gastrointestinal Cancer Conference: Primary Therapy of Early GI Cancer with International Treatment Consensus
St Gallen, Switzerland

March 1-3, 2012
International conference on nutrition and growth
Paris, France

May 1-4, 2012
19th International Surgical Pathology Symposium
Zagreb, Croatia

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 20-23, 2012
European Association for Endoscopic Surgery 20th International Congress 2012
Brussels, Belgium

June 23- 27, 2012
International Society of University Colon and Rectal Surgeons 25th Biennial Conference 2012
Bologna, Italy

October 10-13, 2012
ISPAD 2012 - 38th Annual Meeting International Society for Pediatric and Adolescent Diabetes
Istanbul, Turkey

October 15-17, 2012
13th World Congress of the International Society for Diseases of the Esophagus
Venice, Italy

October 18-20, 2012
Kongress Essstörungen 2012/Eating Disorders Alpbach 2012 The 20th International Conference
Tyrol, Austria

October 20-24, 2012
UEGW - 20th United European Gastroenterology Week
Amsterdam, The Netherlands

November 3-4, 2012
Modern technologies in diagnosis and treatment of gastroenterological patients
Dnepropetrovsk, Ukraine

November 14-15, 2012
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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

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