REVIEW ARTICLE

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Current research status of endoscopic submucosal dissection for colorectal neoplasms

Abstract

Endoscopic submucosal dissection (ESD) has been applied to, and gradually standardized for, early gastric cancers; however, it has not yet been widely used for treatment of colorectal neoplasms. Compared with gastric ESD, the thinner colorectal wall and winding nature of the colon make colorectal ESD a much more difficult operative technique. Despite greater risks of postoperative complications, particularly perforation of the colon, more and more endoscopists are making an effort to study this new technique in terms of its capability of larger neoplastic resection, higher en bloc resection rate and lower local recurrence rate of neoplasms in comparison with other endoscopic treatments. Thus, colorectal ESD may become the standard treatment for early colorectal neoplasms in the future. This review article discusses the current research on endoscopic submucosal dissection for colorectal neoplasms.

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Endoscopic mucosal resection (EMR) has been widely performed for several types of colorectal neoplasms; however, it is difficult to perform en bloc resection by EMR for a colorectal tumor larger than 20 mm [1,2]. Although piecemeal EMR enables surgeons to remove large colorectal tumors, it has a high rate of local recurrence (up to 14%) [3]. Moreover, precise histopathological diagnosis is difficult when using separate, resected specimens of piecemeal EMR [4]. Thus, endoscopic submucosal dissection (ESD) for large colorectal neoplasms, with its higher rate of en bloc resection and lower recurrence rate [5-7], has prompted many endoscopists to consider this new technique. Colorectal ESD may be performed on tumors that are identified as carcinomas with intramucosal to shallow submucosal invasion. Moreover, ESD can be performed on lesions with submucosal fibrosis, which cannot be removed by conventional EMR, even if the size of the lesion is less than 20 mm [8]. Owing to the technical difficulties attributed to winding, the presence of many folds in the colorectum and the relatively thin colorectal wall, the technique of colorectal ESD has not yet been standardized. In the past several years, novel endoscopic equipment, such as knives, clips and forceps, have been developed in order to perform colorectal ESD safely. Concurrent progress in ESD techniques has meant that many of the technical difficulties of colorectal ESD have been overcome.

Indications of colorectal ESD

Endoscopic ultrasonography (EUS) for depth determination is used much less frequently for colorectal tumors than gastric tumors despite the fact that previous reports showed the accuracy of T1 staging of the colorectal cancer, using a high frequency (HF)-EUS probe, was as high as 90% [9,10]. Meanwhile, it has been reported that pit pattern, as determined endoscopically and classified into seven principal types, is related to the structure of the underlying crypt or gland. Furthermore, there appears to be an association between pit pattern and the histology of the cells in the gland (e.g., the branching carcinoma gland was thought to be the result of malignant transformation of the adenoma gland, the straight carcinoma gland was thought to be the result of malignant transformation of normal gland and the gland of the small round pit was thought to be the change from normal to the straight carcinoma gland via malignant transformation) [11]. Thus, tumor morphology and surface pit pattern are good endoscopic indicators for submucosal invasion. Magnification chromoendoscopy has the ability to magnify endoscopic images in real-time and allows for the topical application of stains or pigments to improve tissue localization and pit pattern characterization. In contrast, narrow band imaging (NBI) creates enhanced images of capil-

laries in the surface layers of the mucosal membranes and pit patterns on mucosal membranes by irradiating target areas with light (in two narrow wave bands; blue: 390-445 nm and green: 530-550 nm), which are strongly absorbed by circulating hemoglobin [12].

Intramucosal carcinomas, and those with slight submucosal (sm) invasion ($<1000\ \mu\text{m}$ below the muscularis mucosa) without lymphovascular infiltration, have less risk of nodal metastasis, so are suitable for colorectal ESD [13]. In addition, Sergio et al. [14] have reported 16 lesions with deep sm invasion ($>1000\ \mu\text{m}$ below the muscularis mucosa) have been removed by ESD without complications, demonstrating that deep sm carcinomas can be successfully resected by this technique as well. Laterally spreading tumors of non-granular type (LST-NG) are considered good candidates for ESD because these lesions have a high risk of submucosal invasion; however, whether one should perform ESD or piecemeal EMR for laterally spreading tumors of granular type (LST-G) is controversial, because most of these lesions are intramucosal [15]. Besides, ESD may be also indicated for recurrent superficial lesions, if the lesions fulfill the criterion of no nodal metastasis [16]. Konishi et al. [17] and Moon et al. [18] reported that colorectal carcinoids of $<1\ \text{cm}$ and without lymphovascular infiltration could be curatively treated by local resection, but tumours need radical, nodal dissection. Other reports demonstrated that when the lesions were in intermediate size, 1-2 cm, or had massively invaded the submucosal layer and so might result in tumor-positive margin resection, ESD should be applied [19,20]. Ishii et al. [21] reported that the accuracy of preoperative depth determination in rectal carcinoids with EUS was 100% and suggested preoperative assessment with EUS was effective in the treatment of rectal carcinoids with ESD.

Procedures of colorectal ESD

The procedures of endoscopic submucosal dissection for colorectal neoplasms have not yet been standardized; moreover, new techniques are constantly being explored and improved by a number of endoscopists.

Preoperative preparation of the patients

The day before ESD, the patients may eat only a low fiber diet, and 10 mL of 0.75% sodium picosulfate solution is prescribed before bed. In the early morning of the operation, 10 mg of mosapride citrate and 2 L of an isotonic polyethylene glycol electrolyte solution are used for bowel preparation [12]. Residual feces and liquid should be removed from the entire colon

even if the tumor is located at the rectum [8]. Since colorectal ESD is a highly complex endoscopic technique and sometimes needs long periods of time to be performed, conscious sedation is the standard care for the majority of ESD. Although few publications focus on anesthesia especially for colorectal ESD, Hata et al. [22] reported that an intravenous drip infusion of pentazocine and propofol was used to maintain the sedative condition on early-stage tumors of digestive tract. Bispectral index (BIS), which reflecting the hypnotic effects of anesthetic drugs on the central nervous system, was measured by a BIS monitor, and Hata et al. suggested that a BIS value between 70 to 75 is suitable for safe ESD.

Endoscopic equipment

Colorectal ESD is generally performed with a high-definition single-channel colonoscope. If the lesion is located within reach of an upper gastrointestinal endoscopes, a gastroscope can be adopted for greater maneuverability [23]. Ohya et al. [24] used a balloon overtube that acted as an endoscopic trocar sheath, helping to fix the endoscope within the enteric cavity and improving stability during the procedure. The balloon overtube was placed with a gastroscope to provide an endoscopic channel to the lesion in cases with preoperatively-identified accessibility difficulties. Ohya et al. found that use of a balloon overtube could improve access to the lesion and facilitate scope manipulation for colorectal ESD. A transparent attachment can be fitted on the tip of the endoscope to obtain a stable endoscopic view and to create tension on the connective tissue for the submucosal dissection [12]. In many institutions, the lesion is raised by injecting the submucosa with a combination of 1% hyaluronic acid solution and 10% glycerin solution, which achieves higher and longer duration of lesion elevation [8].

Various knives, such as the Flush knife (Fujifilm Medical, Tokyo, Japan), Dual knife (Olympus Medical Systems Co., Tokyo, Japan), B-knife (Zeon Medical, Tokyo, Japan) and Splash needle (Pentax Co., Tokyo, Japan), have been used in ESD for colorectal neoplasms [25-27]. Honma et al. [28] developed a new scissors-type device, named the stag beetle knife (SBK), for colorectal ESD. For the purpose of achieving better and more satisfactory operative processes and outcomes of colorectal ESD, much more novel endoscopic equipment has been invented or adapted.

Mucosal incision

Since the margins of colorectal neoplasms are clearly visible in the majority of cases, it is generally unnecessary to make cau-

tery markers around the lesion. A solution of hyaluronic acid and a small amount of indigocarmine, a blue dye, is usually injected to make a submucosal fluid cushion [12]. In our institution, methylene blue is also used as a staining solution. A mucosal incision is performed with the endocut mode (e.g., Output 40W, effect 2 in ICC200, ERBE Elektromedizin Ltd., Tübingen, Germany). A complete circumferential or partial circumferential incision is made, according to the practices at the different institutions and the characteristics of the lesion. In complete circumferential incision, injection of the hyaluronic acid solution into the submucosa is performed from the oral edge of the tumor. A mucosal incision is made after obtaining of adequate elevation of the submucosa. Then the solution is injected into the anal edge of the tumor and the mucosal incision is made. If a partial circumferential incision is used, the anal side of the tumor is the first to be incised after the injection of solution. In an initial complete circumferential incision, leakage of the injected hyaluronic acid can easily occur, after which submucosal elevation is lost. Moreover, injection into the oral side of the tumor causes the position of the tumor to be perpendicular to the endoscope, which makes submucosal dissection difficult to perform. However, the change of the neoplasm, caused by the residual mucosa in partial circumferential incision, is avoided in initial complete circumferential incision. Although higher elevation of the submucosa can be maintained with a partial circumferential incision, as the uncut residual mucosa on the oral side of the tumor, it is difficult to resect the residual mucosa on the oral side due to the presence of the partially resected tumor [8].

Submucosal dissection

Small lesions can be resected with an electrosurgical snare only after circumferential mucosal incision and without submucosal dissection, while large lesions, lesions with submucosal fibrosis or lesions located in a tortuous area should be dissected completely as for the mucosal incision [12]. Usually, the submucosa is dissected from the anal side of the neoplasm. In our institution, submucosal dissection is performed by using the endocut mode (e.g., Output 40W, effect 2 in ICC200, ERBE Elektromedizin Ltd., Tübingen, Germany). Tomiki et al. [29] invented a novel medical rubber band for use during submucosal dissection, the Latex Band, which is 5 mm in diameter, 1 mm in width, and 200 μ m in thickness (Okamoto Co. Ltd., Tokyo, Japan) through which a 4-0 green nylon thread is looped. The authors reported that traction with the Latex Band can be applied to any location in the colorectum and when traction is used, the space for the submucosal layer is widened, providing a clear visualization of the submucosal layer and the incision line.

Management after submucosal dissection

Generally, visible vessels of the resulting artificial ulcer should be treated with the hemostatic forceps to prevent delayed bleeding, but it should also keep in mind that the intensive coagulation within visible vessels on the exposed muscle layer may cause delayed perforation [12]. An overtube is often used to pick up large resected specimens. Chiba et al. [30] modified the overtube as the distal end with an oblique fashion and a slitted tip to increase the holding capacity of the overtube. Thus, a laterally spreading rectal tumor about 80 mm in size was picked up en bloc without injuring.

Outcomes of colorectal ESD

For the colorectal neoplasms that cannot be resected completely by other present endoscopic treatments, endoscopic submucosal dissection has become a promising procedure. Tajika et al. [2], through their comparison of endoscopic submucosal dissection and endoscopic mucosal resection for large colorectal tumors, indicated that tumors treated with ESD were larger, incurred a longer procedure time, and had a higher en bloc resection rate and a lower recurrence rate compared with EMR. Similar results were also shown by Lee et al. [31], Hotta et al. [7] and Toyonaqa et al. [32]. Toyonaqa et al. also considered ESD with snaring as a good option to fill the gap between EMR and ESD in the colorectum. Furthermore, Byeon et al. [33] reported that both the en bloc resection rate and the histologically complete resection rate for the lesions of <20 mm were not different for ESD vs. ESD with snaring, which indicates that ESD with snaring can be a good alternative to ESD for en bloc resection of colorectal lesions of <20 mm. In another publication, Oka et al. [34] indicated that the

local recurrence rate was higher in ESD compared with EMR. Details are listed in Table 1.

Complications of colorectal ESD

Perforation and hemorrhage are major complications of colorectal ESD.

Perforation

The thinness of the colorectal wall is likely responsible the higher perforation rate of colorectal ESD relative to that of gastric ESD. The rate of perforation has been reported to be from 1.4% to 10.4% [8]. Kim et al. [35] reported that tumor size and presence of fibrosis were independent risk factors for perforation. Yoshida et al. [36] found no statistical differences regarding the location of the tumor (i.e. in the colon or in the rectum) and that knife coagulation was the most common cause of perforation. Less common reasons for perforation include resection using a snare, coagulation by special hemostat forceps with soft coagulation, and endoscopic clipping onto coagulated submucosa. The majority of cases with perforation are treated conservatively without emergency surgery and small perforations can be closed by endoscopic clipping [37,38]. Sakamoto et al. [39] reported that large perforations could be closed with a new closure device consisting of a clip with a loop. Delayed perforation has been reported as a serious complication after ESD and the rate of delayed perforation is reported to be from 0.3% to 0.7% [23,40,41]. The reasons for delayed perforation are unknown, but it is reported to be related to excessive coagulation in the muscularis propria. It has been reported that delayed perforations are typically large in size and require treatment by emergency surgery [23,40,41]. Tanaka et al. [42] reported that the skill of endoscopists, choice

TABLE 1. Outcomes of colorectal ESD compared with EMR

Author	Method	Procedure time (min)	<i>En bloc</i> resection rate (%)	Recurrence rate (%)
Tajika <i>et al.</i> [2]	ESD	87.2±49.7	83.5	1.2
	EMR	29.4±26.1	48.1	15.4
Lee <i>et al.</i> [30]	ESD	/	92.7	0.8
	EMR	/	42.9	25.9
Toyonaqa <i>et al.</i> [31]	ESD	60	98.9	/
	EMR	19	83.3	/
Oka <i>et al.</i> [33]	ESD	/	/	2.3
	EMR	/	/	1.4

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection
Neoplasm sizes >20 mm diameter

TABLE 2. Complications of colorectal ESD compared with EMR

Author	Method	Perforation rate (%)	Hemorrhage rate (%)
Tajika <i>et al.</i> [2]	ESD	5.9	2.4
	EMR	0	2.9
Lee <i>et al.</i> [30]	ESD	8	/
	EMR	2.9	/
Oka <i>et al.</i> [33]	ESD	3.3	1.7
	EMR	0.91	1.4

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection

of appropriate surgical strategy for ESD and the choice of a suitable knife are all important for the prevention of perforations.

Hemorrhage

Hemorrhage occurs infrequently, is typically minor and can be treated successfully with colonoscopy. Yoshida *et al.* [43] developed a new effective hemostatic method using hemostatic forceps for the efficient treatment of submucosal thick vessels to prevent from perioperative hemorrhage: Firstly, a vessel was coagulated using the hemostatic forceps in the soft coagulation mode according to the standard procedure, and the coagulated vessel was removed using the forceps in the endocut mode. Secondly, the partial surrounding submucosa was dissected using the forceps in the endocut mode. The rate of postoperative hemorrhage in ESD has been reported to be from 0% to 1.6% [5,6,26,44]. Most cases of postoperative hemorrhage are treated only by endoscopic clipping and withholding oral intake, without the need for emergency surgery.

Complications of colorectal ESD compared with EMR have been listed in Table 2.

Conclusion

As with the more familiar gastric ESD, ESD for colorectal neoplasms has become an ideal minimally invasive approach. Although the development of colorectal ESD techniques is more advanced in Eastern countries (such as Japan, China and South Korea) than in Western countries, the principle of early diagnosis and early treatment of tumors is paramount. The novel colorectal ESD procedures have proven to be minimally invasive, with precise en bloc resection of the tumors, fast recovery times and satisfactory prognosis. Hotta *et al.* [45] suggested that approximately 80 procedures must be carried out to acquire skill with ESD for large colorectal tumors; however, we

found that approximately 40 procedures were sufficient to acquire skill in avoiding perforations during the ESD procedure. Colorectal ESD techniques are still not completely mature [46]; however they hold great promise and with continued research into node-negative neoplasms (e.g., EUS combined with pit pattern determined by magnification chromoendoscopy or NBI) to establish the appropriateness of colorectal ESD, improvements in endoscopic instruments, especially for colorectal ESD, and available and adequate training, ESD for colorectal neoplasms could become a standard therapy.

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