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CLINICAL PRACTICE GUIDELINE

Perspective on the practical indications of endoscopic submucosal dissection of gastrointestinal neoplasms

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Abstract

Endoscopic submucosal dissection (ESD) is a new endoluminal therapeutic technique involving the use of cutting devices to permit a larger resection of the tissue over the muscularis propria. The major advantages of the technique in comparison with polypectomy and endoscopic mucosal resection are controllable resection size and shape and *en bloc* resection of a large lesion or a lesion with ulcerative findings. This technique is applied for the endoscopic treatment of epithelial neoplasms in the gastrointestinal tract from the pharynx to the rectum. Furthermore, some carcinoids and submucosal tumors in the gastrointestinal tract are treated by ESD. To determine the indication, two aspects should be considered. The first is a little likelihood of lymph node metastasis and the second is the technical resectability. In this review, practical guidelines of ESD for the gastrointestinal neoplasms are discussed based on the evidence found in the literature.

Key words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Gastrointestinal neoplasm; Treatment guideline; Lymph node metastasis

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GENERAL CONCEPT TO APPLY ENDOSCOPIC SUBMUCOSAL DISSECTION FOR GASTROINTESTINAL NEOPLASMS

Endoscopic submucosal dissection (ESD) is a new endoluminal therapeutic technique involving the use of cutting devices to permit a larger resection of the tissue over the muscularis propria in three steps: injecting fluid into the submucosa to elevate the lesion from the muscularis propria, precutting the surrounding mucosa of the lesion, and dissecting the connective tissue of the submucosa beneath the lesion. The major advantages of the technique in comparison with polypectomy and endoscopic mucosal resection (EMR) are these: the resected size and shape can be controlled; *en bloc* resection is possible even for a large lesion; and the lesions with ulcerative findings are also resectable[1,2]. Retrospective analyses of the comparison between ESD and EMR for the stomach epithelial neoplasms showed that ESD increased *en bloc* and histologically complete resection rates compared with EMR but was associated with longer average operation times and a higher incidence of intraoperative bleeding and perforation[3,4].

Two aspects are considered to determine the application of ESD for each lesion by each operator (Figure 1). The first is a little likelihood of lymph node metastasis and the second is the technical resectability. The former has been determined by the large numbers of surgically resected cases in each organ before establishment of ESD and the latter may be determined by the applied technique, the expertise of the operators, the location of the lesions or their characteristics. In terms of technical resectability, *en bloc* resection is more desirable than piecemeal resection for accurate assessment of the appropriateness of the therapy, because the depth of invasion and lymphovascular infiltration of cancer cells (that are considerable risk factors for nodal metastasis) are not accurately assessed by piecemeal resection. Almost all possible node-negative epithelial neoplasms can be resected *en bloc* by

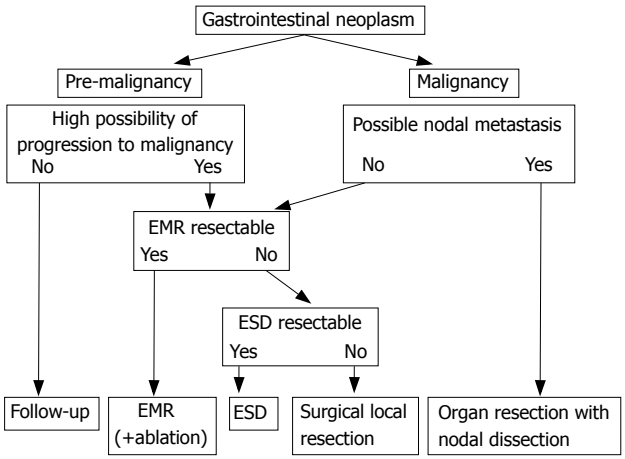

Figure 1 Algorism for endoscopic submucosal dissection of gastrointestinal neoplasms.

ESD, when they are treated by very experienced hands. This does not mean that all endoscopic resection should be performed as ESD. Polypectomy or endoscopic mucosal resection (EMR) are beneficial for patients with pedunculated neoplasms or small neoplasms because of the little invasiveness[5]. If the lesions are apparently pre-malignant neoplasms, piecemeal resection by using EMR may be permissible with the best balance of risks and benefits. Surgical organ resection with lymphadenectomy should be applied to those neoplasms with high probability of positive lymph nodes or failure in complete removal by ESD. Recurrent lesions can be also indicated for ESD, if they fulfill the criteria of no nodal metastasis, but indication should be carefully determined considering the risks of accompanying complications.

STOMACH EPITHELIAL NEOPLASMS

Aspects of nodal metastasis

Pre-malignant stomach epithelial neoplasms, gastric adenomas, have no nodal metastases. It is still controversial whether we should treat gastric adenomas endoscopically or follow them. A series with a small number of cases with a preoperative diagnosis of pre-malignant lesion revealed that 37% (16/43) of them were finally diagnosed as adenocarcinoma and a lesion > 1 cm was considered to pose a risk of malignancy[6]. Another study revealed that 6.8% (8/118) of cases were finally diagnosed as adenocarcinoma and high-grade dysplasia by endoscopic biopsy was considered to be an independent risk factor for malignancy[7]. Furthermore, preoperative diagnosis of depressed adenoma is considered to represent a higher risk of malignancy than protruding adenoma[8]. So, when the lesions have these characteristics, endoscopic treatments are recommended, similarly to intramucosal carcinomas. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques to remove the apparent gastric adenomas is allowed.

In terms of malignant stomach epithelial neoplasms, the following types of early gastric cancers without lymphovascular infiltration of cancer cells may have little likelihood of nodal metastases: (1) intramucosal, differentiated adenocarcinoma without ulcer findings of any size; (2) intramucosal, differentiated adenocarcinoma with ulcer findings when the lesion is ⩽ 3 cm; (3) intramucosal, undifferentiated adenocarcinoma without ulceration when the lesion is ⩽ 2 cm; and (4) differentiated adenocarcinoma with minute submucosal penetration (500 micrometers below the muscularis mucosa; sm1) when the lesion is ⩽ 3 cm[9].

Technical aspects

When the endoscopists are well trained for ESD, the technical aspects may not restrict indications to perform ESD, based on the above criteria of no nodal metastasis. However, in our opinion, cases of ulcer findings with fusion of the muscle layer and the mucosal layer and cases of undifferentiated adenocarcinoma may be excluded from the indication or be carefully resected, at least until now. The former cases occur in cancers that previously had a deep ulcer extending into the proper muscle layer, where it is difficult to identify the gastric wall plane during submucosal dissection, which increases the possibility of perforation or incomplete resection by ESD[10]. In the latter cases, first, the margin is very unclear and the possibility of incomplete resection is fairly high, second, the clinical course after recurrence may be more miserable than that of differentiated-type, and third, the differentiation between ulcerative finding or biopsy-inducing fibrosis is sometimes difficult, even though small intramucosal undifferentiated adenocarcinoma with ulcer findings may be associated with nodal metastases[9].

ESOPHAGEAL SQUAMOUS EPITHELIAL NEOPLASMS

Aspects of nodal metastases

Low- and high-grade squamous intraepithelial neoplasms, including carcinoma *in situ* (m1), have no nodal metastases. It is still controversial whether one should treat these intraepithelial neoplasms endoscopically or just follow them. However, when the lesions are diagnosed as high-grade intraepithelial neoplasms, endoscopic treatment is recommended, to avoid future development of invasive carcinoma or to contain foci of invasive carcinoma[11,12]. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques to remove the apparent intraepithelial neoplasms is allowed[13-15].

Esophageal squamous cell carcinomas invading the lamina propria (m2) pose little risk of nodal metastases. For those invading the muscularis mucosa (m3) and those with minute submucosal invasion (< 200 micrometers below the muscularis mucosa; sm1), the nodal metastases rate is 9.3% and 19.6%, respectively. The nodal metastases rate of m3 or sm1 cancers with 0-Ⅱ type, < 5 cm, well or moderately differentiated type, and no lymphovascular infiltration of cancer cells is 4.2%[16]. It has been reported that no nodal metastasis was found in patients with sm1, low

histologic grades, and no lymphovascular infiltration of cancer cells[17]. Therefore, for patients unwilling to undergo esophagectomy or chemoradiation and patients with comorbid diseases, ESD may be applied taking into consideration the risks of nodal metastases and treatment-related morbidity.

Technical aspects

When the endoscopists are well trained for ESD, the technical aspects by themselves may not restrict indications to perform ESD, except in special circumstances, such as lesions located in the diverticulum. When lesions spreading > 3/4 of circumference are resected as circular or semi-circular resection, post-operative stricture occurs to a high rate[18]. So, it is controversial to treat these lesions endoscopically. However, intensive balloon dilatations or tentative stent insertion may rescue from the stricture.

ESOPHAGEAL BARRETT NEOPLASMS

Aspects of nodal metastasies

Columnar intraepithelial neoplasms have no nodal metastases. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques and additional ablation therapy to remove the apparent intraepithelial neoplasms is allowed[19-23].

There are no data about nodal metastases from the large numbers of surgically resected cases due to limited number of cases of esophageal columnar epithelial carcinomas at an early stage, although a small number of cases revealed no nodal metastasis for the intramucosal and sm1 cancer, where sm1 was determined by upper third of the submucosa[24]. There is no consensus whether one should apply to this kind of malignancy the same criteria that are applied to stomach epithelial neoplasms or esophageal squamous epithelial neoplasms as far as the depth of sm1 to be measured. International workshops of esophagogastric neoplasms adopted the cut-off line of 500 micrometers below the deeper muscularis mucosae, similarly to the stomach[25,26].

Technical aspects

Similarly to esophageal squamous epithelial neoplasms, the technical aspects by themselves may not restrict indications to carry out ESD, when the endoscopists are well trained for ESD. When lesions spreading > 3/4 of the circumference of the esophagus (a situation which commonly occurs in long segment Barrett epithelium) are resected (with circular or semi-circular resection), post-operative strictures occur at a high rate[19-23].

RECTAL EPITHELIAL NEOPLASMS

Aspects of nodal metastases

Pre-malignant rectal epithelial neoplasms, rectal adenomas, have no nodal metastases. From the standpoint of adenoma-carcinoma sequence, all adenomas, including diminutive polyps, are targets for endoscopic resection[27,28], although some investigators agree with endoscopic removal only if the size is > 5 mm[29]. *En bloc* resection is not always necessary for rectal adenoma or intramucosal carcinoma. However, higher rate of local recurrence was reported when multiple resections were performed[30-32]. Intramucosal carcinomas and those with slight submucosal invasion (< 1000 micrometers below the muscularis mucosa; sm1) without lymphovascular infiltration have little risk of nodal metastasis[33].

Tumor morphology and surface pit pattern are good endoscopic indicators for submucosal invasion. From this aspect, depressed lesions, laterally spreading tumors of non-granular type (LST-NG) and large protruding tumors are considered as good candidates for ESD because these lesions have a high risk of submucosal invasion, which may be difficult to diagnose preoperatively, and a thorough histopathological assessment of the resected specimen is essential. It is controversial whether one should perform ESD or piecemeal EMR for laterally spreading tumors of granular type (LST-G), because most lesions are intramucosal and the endoscopic prediction of invasiveness is highly feasible[34].

Technical aspects

Even for lesions that meet the criteria above, laparoscopic or open surgery may be selected in some institutions considering the location and size of the lesion. The lesions with submucosal fibrosis due to previous endoscopic treatment or biopsy are also resectable by ESD, even though the indication should be carefully weighed considering risks and benefits of ESD *vs* surgery[35,36]. The rectum is fixed to the retroperitoneum, therefore the endoscope is more easily manoeuvred than in other organs of the gastrointestinal tract. Furthermore, panperitonitis may be less likely than in the rest of the colorectum, even if the muscularis propria is teared, although penetration leads to air accumulation in the retroperitoneal space, which may then spread to a wider area[37,38].

COLONIC EPITHELIAL NEOPLASMS

Aspects of nodal metastases

The criteria for absence of nodal metastases are the same as those of rectal epithelial neoplasms (see above).

Technical aspects

There are several tortuous folds in the colon. Peristalsis and residual feces may sometimes disturb ESD procedure. So it is commonly believed that the technical difficulty of colon ESD exceeds those of the stomach, the esophagus, and the rectum, although there are many differences. In all cases, should one consider the substantial risks and expected benefits of ESD. However, promising results of ESD are reported from very experienced endoscopists at advanced institutions, similarly to those of the rectal epithelial neoplasms[39-43].

EPITHELIAL NEOPLASMS IN THE SMALL INTESTINE, INCLUDING DUODENUM

Aspects of nodal metastases

Pre-malignant epithelial neoplasms in the small intestine have no nodal metastases. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques and ablation therapy to remove the apparent intraepithelial neoplasms is allowed[44]. There are no data about nodal metastases from the large numbers of surgically resected cases due to limited number of cases of epithelial carcinomas in the small intestine. There is no consensus whether one should apply the same criteria of stomach epithelial neoplasms or colorectal epithelial neoplasms to this malignancy.

Technical aspects

The small intestine, including the duodenum, is considered to be the most difficult organ where to perform ESD. The endoscope does not easily reach the target lesion and the organ is not fixed tightly except at the level of the duodenum, which results in fairly bad maneuverability. Peristalsis is the most active and the wall is the thinnest among the other gastrointestinal organs. Even is the resection is completed successfully, pancreatic juice and bile cause chemical damage to the mucosal wound, which may lead to prolonged bleeding and perforation. In our opinion, closure of the mucosal wound is recommended after ESD. When considering these issues, indication to perform ESD in the small intestine should be carefully assessed and limited. Due to the structural specificity of the papilla, ESD for ampullary neoplasms is not performed.

PHARYNGEAL EPITHELIAL NEOPLASMS

Aspects of nodal metastasis

Pre-malignant epithelial pharyngeal neoplasms have no nodal metastases. Although local recurrence should be taken into account, piecemeal resection by using EMR techniques and ablation therapy to remove the apparent intraepithelial neoplasms is permissible[45]. There are no data about nodal metastasis from the large numbers of surgically resected cases due to limited number of cases of pharyngeal epithelial carcinomas at an early stage. So, indication for invasive carcinoma is still controversial due to the lack of data. Owing to the structural differences, it is impossible to apply the criteria of esophageal squamous epithelial carcinomas for this malignancy.

Technical aspects

ESD is technically possible in this organ, and ESD may be the optimal endoscopic treatment not only because it enables an *en bloc* resection but also because it can prevent removal of excess mucosa of the pharynx, which is a very narrow and important organ related to swallowing and speech[46].

CARCINOID

Aspects of nodal metastasis

Carcinoids are classified based on organ site and cell of origin and occur most frequently in the gastrointestinal tract (67%) where they are most common in small intestine (25%), appendix (12%), and rectum (14%)[47]. Primary size > 2 cm, serosal penetration, and primary site in the small intestine are considered to be risk factors for metastases in the case of gastrointestinal carcinoids[48].

Nodal metastases are most commonly found with small intestine carcinoids (20%-45%), providing the rationale for an extended resection including the adjacent lymph node drainage area. Carcinoids of the appendix < 1 cm rarely metastasize, simply requiring appendectomy for treatment. Rectal carcinoids < 2 cm rarely metastasize, directing local excision, including endoscopic resection[49]. Another group revealed that colorectal carcinoids < 1 cm without lymphovascular infiltration could be curatively treated by local resection, but others would need radical nodal dissection[50]. Duodenal carcinoids < 2 cm may be excised locally because they rarely metastasize[51].

Multiple gastric carcinoids, usually no more than 1 cm, can be followed up by endoscopy and biopsy[52,53]. Sporadic gastric carcinoids should be treated by gastrectomy with lymphadenectomy, because some of those have nodal metastases even when they have a small size[54-56]. However, differentiation of types of gastric carcinoids is not always easy, so endoscopic resection, as a first step to obtain histology, may be acceptable for small gastric carcinoids < 1 cm to predict nodal metastases.

Technical aspects

Because almost all lesions for local resection are less than 1 cm in all the gastrointestinal organs, band ligation resection[57,58], cap-technique[59] or strip biopsy[60-62] result in good outcome. So the application of ESD for carcinoids may be limited. When the lesions are in intermediate size, such as 1-2 cm, or invade massively the submucosal layer, which may result in tumor-positive margin resection, ESD should be applied[36,63].

SUBMUCOSAL TUMOR

Aspects of metastases

Submucosal tumors (SMTs) are mesenchymal tumors, which may have very diverse origins. SMTs are classified and defined as benign or malignant based on a combination of size, histological, immunohistochemical, and ultrastructural criteria. The majority of them are classified into gastrointestinal stromal tumor (GIST), of muscular origin, of neurogenic origin, of vascular origin, and of adipose tissue origin. SMTs < 3 cm are generally considered benign tumors. SMTs > 3 cm with high mitotic counts are considered tumors at high-risk of malignancy. In case of GIST, the cutoff of the size between pre-malignancy and malignancy may be

2 cm. Sarcomas including malignant GIST generally do not metastasize to regional lymph nodes, but instead spread hematogenously to the liver or metastasize to the peritoneum[64]. Benign SMTs should generally only be treated if they are symptomatic. So the SMTs > 2 cm or 3 cm without evidence of metastasis may be candidates for local resection[65].

Technical aspects

From the rationale of ESD, the targets should originate from over the muscularis propria. The lesions originating from the inner layer of the muscularis propria may be resectable by careful resection over the outer layer of the muscularis propria, but the high probability of perforation and the artificial peritoneal dissemination by tear of the tumor capsule should be taken into consideration. When considering that the small size lesions located in the mucosal or submucosal layers are mostly benign, the indication of ESD for SMTs is quite limited, although some investigators reported promising results of ESD for SMTs[66,67].

FUTURE PERSPECTIVES

The perspectives on the current indication of ESD are described based on a review of data available in the literature until the end of 2007. Further investigations in both aspects, the assessment of nodal metastases and the technical innovations, may change widely the above perspectives in the future. Recently, a new application of ESD is being investigated in cooperation with laparoscopic surgeons for the treatment of possible node-positive gastric carcinoma and gastric GIST[68,69]. There is no doubt that these attempts will expand ESD into a new field, which will be added to the upcoming practical guidelines for ESD.

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