

Endoscopic resection for gastrointestinal tumors (esophageal, gastric, colorectal tumors): Japanese standard and future prospects

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Abstract: Endoscopic resection (ER) techniques such as polypectomy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are widely accepted as a less invasive treatment for gastrointestinal (GI) tumors. Since there is a limit to the size that can be resected by EMR and it is often divided, it is not possible to accurately evaluate the degree of cancer progression, and the cancer remains or causes recurrence. ESD is a technology that overcomes these weaknesses. ER techniques are considered for tumors that have a very low possibility of lymph node metastasis and are suitable for en-bloc resection. As ESD became more widespread, the difficulty of treating ESD was gradually resolved by the development of technology and equipment, the curative resection rate increased, and the complication rate decreased. ER techniques have become the standard treatment for early cancer and precancerous lesions in Japan, and the therapeutic indications are expanding day by day. The indications for whether endoscopic treatment can be performed are defined by the guidelines for each organ such as the esophagus, stomach, and colorectum. In the coming aging society, it is also necessary to evaluate the indications for endoscopic treatment and invasive treatment. In addition, recent advances in endoscopic technology are making it possible to remove submucosal tumors that previously required surgery. In this review, we summarize the recent Japanese standard indications of ER for each GI location and future prospects of ER.

Keywords: endoscopic mucosal resection, endoscopic resection, endoscopic submucosal dissection, gastric cancer, esophageal cancer, colorectal cancer

Introduction

The endoscopic resection (ER) techniques of gastrointestinal (GI) neoplasms are very beneficial for patients because of its low invasiveness and low risk of complications. Polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) are the endoscopic treatment methods of ER. ESD has been approved by the Ministry of Health, Labor, and Welfare of Japan for the stomach as the earliest since 2006, followed by esophagus in 2008 and colorectum in 2012, and is now the standard nationally approved insurance treatment. However, ER adaptation is limited because ER is considered for tumors that have a very low possibility of lymph node metastasis and are suitable for en-bloc resection. The indications for whether endoscopic treatment can be performed are defined by the guidelines for each organ such as the esophagus, stomach, and colorectum. It is necessary to make an accurate preoperative diagnosis in order to perform treatment according to the indications (1-3). Preoperative diagnosis is usually performed with endoscopic observation, dyeing, image-enhanced endoscopy, and endoscopic ultrasonography.

This article gives an overview of the current Japanese state of ER, recently developed technologies, and desired technologies for the future.

Methods of endoscopic resection (ER)

Polypectomy

In this technique, a snare is placed on the stalk of the lesion, and the lesion is electrocauterized using a high frequency current. This method is mainly used for protruding lesions.

Endoscopic mucosal resection (EMR)

In this technique, the lesion is elevated by local injection of a liquid such as physiological saline into the submucosa. The lesion is electrocauterized the same as in the case of polypectomy.

Endoscopic submucosal dissection (ESD)

In this technique, the lesion is elevated by local injection of a liquid such as sodium hyaluronate solution

into the submucosa of the perilesional area; then, circumferential incision of the mucosa surrounding the lesion and dissection of the submucosa is performed with a high-frequency electric knife.

The principles of indication for ER

ER is considered for tumors that have a very low possibility of lymph node metastasis and are suitable for en-bloc resection.

Esophagus

i) Treatment of squamous cell carcinoma. Absolute indication: cancer infiltration remains up to the lamina propria (EP, LPM), cancer involving less than three-quarters of the esophageal circumference. *Expanded indication:* cancer depth reaches the muscularis mucosae, stays within the submucosal layer 200 μm. If mucosal resection occupies more than three-quarters of the lap, stenosis is expected to occur after resection, so sufficient discussion and prevention of stenosis are required (4,5).

ii) Treatment of Barrett's cancer. It is similar to that of squamous cell carcinoma. ER is indicated for those whose wall depth remains within the lamina propria (EP [remains in the epithelium (non-invasive lesions)], SMM [remains in the superficial muscularis mucosae], and LPM [does not reach the deep muscularis mucosae]) (6).

iii) Criteria for additional treatment after ER of esophageal tumors. If tumor was pT1a-MM with positive vascular invasion or pT1b (200 μm or more), additional treatments, such as surgical resection and chemoradiotherapy, are strongly recommended because of the high metastasis rate (6). Argon plasma coagulation (APC) and photodynamic therapy (PDT) are considered as additional treatment for residual marginal lesions

for cases with difficulty in raising the mucosa during additional ER after radiation therapy, and cases with bleeding tendency (6,7).

iv) Follow-up observation after endoscopic treatment of esophageal tumors. It is reported that local recurrence often occurs within 1 year after the initial treatment. Long-term follow up is required because lymph-node recurrence or organ recurrence may be detected 2-3 years later. When it comes to occurrence of stenosis, it is strongly recommended to perform prophylactic balloon dilatation, local steroid injection, or oral steroids to prevent stenosis after endoscopic treatment of esophageal cancer (8-10).

Gastric cancer

i) Absolute indication: differentiated-type adenocarcinoma without ulcer (UL), differentiated-type adenocarcinoma with UL, diameter ≤ 3 cm.

ii) Expanded indication: undifferentiated, mucosal cancer ≤ 2 cm without UL.

iii) Criteria for additional treatment after ER of gastric cancers. Figure 1 shows the criteria of indication and curability for ER of early gastric cancer (EGC) in the Japanese Gastric Cancer Association (JGCA) guidelines version 5, which were performed in 2018 (11). eCuraC is equivalent to conventional non-curative resection, with careful follow-up or additional treatment for lesions in C-1 and additional surgical resection in C-2. It has been reported that 17-29% of patients with ER will have endoscopic non-curative resection (12-15).

iv) Follow-up observation after ER of gastric cancers. Follow-up with annual or biannual endoscopy is recommended for curative resection. *Helicobacter pylori* eradication is recommended for all cases because eradication therapy reduced the annual incidence of

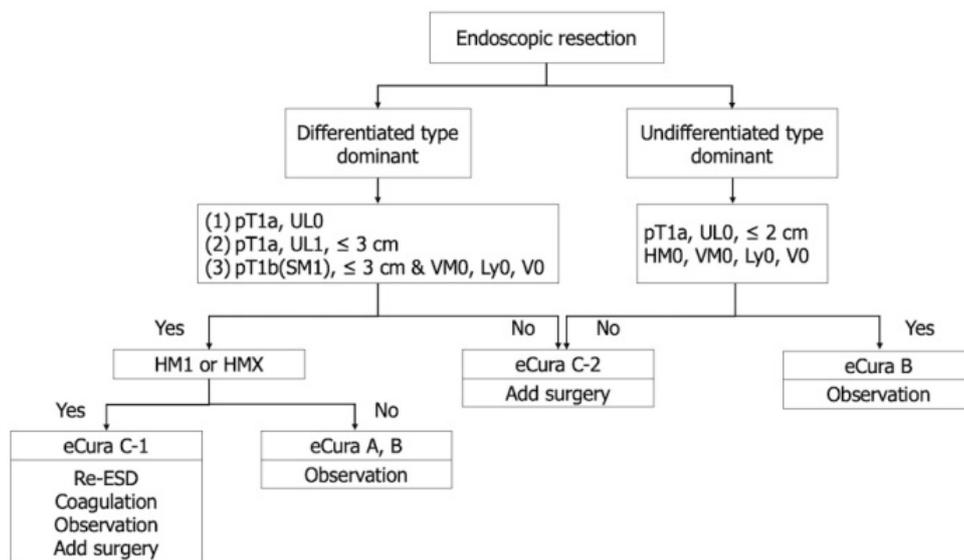


Figure 1. Criteria of the indication and curability for ER of EGC in the JGCA guidelines version 5 (11). ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; M: intramucosal invasion; SM1: mucosa Underlayer invasion (less than 500 μm from mucosal muscle plate); SM2: submucosal invasion (more than 500 μm from mucosal muscle plate); UL, ulcer.

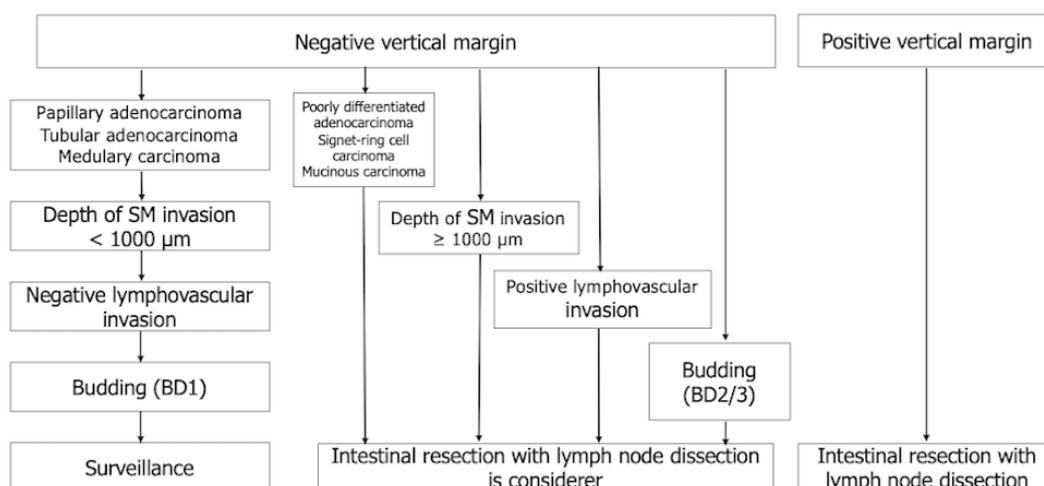


Figure 2. Treatment strategies for pT1 colorectal cancer after endoscopic resection (2).

metachronous gastric cancer (16). However, some studies showed that eradication therapy after ER had no impact on the development of metachronous cancer (17,18). Further investigations are needed on this issue.

Colorectal tumors

i) Indication criteria: early colorectal cancer limited to the mucosa or with slight submucosal invasion (< 1,000 µm below the muscularis mucosa; sm1) (19), 20 mm is the largest size that can be easily resected en bloc by polypectomy or snare EMR (20).

ii) Criteria for additional treatment after ER of colorectal tumors. Surgical resection with lymph node dissection is recommended when the vertical margin is positive and any of the findings in Figure 2 are observed in histological examination of the resected specimen (2).

iii) Follow-up observation after ER of colorectal tumors. Recurrence after endoscopic treatment for pT1 cancer is often within three years. When en bloc endoscopic resection is completed with a negative margin, annual endoscopic follow-up is recommended. Semi-annual surveillance with endoscopy is recommended with a positive horizontal margin (21,22). When an additional intestinal resection is not carried out for pT1 cancer, image diagnoses such as CT and tumor markers surveillance should be performed (2). In 2020, colonoscopic screening and surveillance guidelines were proposed by the Japanese Society of Gastroenterology. If there are no more than two adenomas, except for advanced adenoma, on the first total colonoscopy, follow-up after 3-5 years is required. If there are 3-9 adenomas except for advanced adenoma or advanced neoplasia follow-up after 3 years is recommended. If 10 or more non-advanced adenomas, Tis/pT1 cancer, or over 20 mm neoplasia are found and resected, follow-up after 1 year surveillance by TCS is

recommended (23).

Outcomes of ER

Long-term outcomes after ER

Table 1 and Table 2 show recent reports list of complete resection rate, recurrence rate, underwent additional treatment rate and 5 years outcomes after ER for tumors of esophagus, stomach and colorectum. For esophageal cancer, 5-year cause specific survival rate for EP/LPM cancer, MM-SM1 and SM2 cancer were 98-100%, 93-100% and 100%, respectively (24-28). Besides, it was reported that the 5 years survival rate was 84.8% for complete resection, and 78.2% for incomplete resection (29). The long-term outcome after ER for MM/SM1 ESCC was favorable with additional prophylactic therapy (25). For gastric cancer, 5-year cause specific survival rate was reported as 99.9-100%, local recurrence rate was reported as 0.24-0.63% after ER (30-33). For colorectal cancer, 5-year cause specific survival rate was 98.6-100% (24,34). Komeda *et al.* reported that piecemeal resection was the only significant risk factor associated with local recurrence after ER (35). Although it has been reported, it has been considered that "death from metachronous cancer after ESD" has become a new issue in the ESD era, and it is necessary to raise awareness of the need for long-term (permanent) surveillance.

Complications

Major complications are bleeding and perforation. Table 3 shows the complication rate of ER for tumors of esophagus (28,29,36), stomach (30-32) and colorectum (24,34,37). Bleeding occurred in 0-1.2%, 4.2-6.3%, and 0-2.4%, respectively. Perforation occurred in 0-1.6%, 1.5-3.3%, and 0-6%, respectively. The incidence of post-

Table 1. complete resection rate, recurrence rate and underwent additional treatment rate of endoscopic resection

site	lesions	complete resection rate(%)	local recurrence rate (%)	additional treatment (%)	Author	Ref.
Esophagus	396	73.5	3.3	4.5	Oda <i>et al.</i> 2020	(26)
	1,070	93.6	-	-	Tachimori <i>et al.</i> 2019	(29)
Stomach	785	-	-	6.1	Mizumoto <i>et al.</i> 2018	(27)
	204	-	2.0	-	Nakagawa <i>et al.</i> 2014	(36)
Colorectum	10,926	91.6	-	7.8	Suzuki <i>et al.</i> 2019	(32)
	10,658	-	0.63	-	Tanabe <i>et al.</i> 2017	(14)
	1332	95.4	0.45	0.45	Nakamura <i>et al.</i> 2015	(31)
	421	92.9	0.24	0.24	Tanabe <i>et al.</i> 2014	(30)
	1,412	-	2.2	-	Komeda <i>et al.</i> 2019	(35)
	150	85.4	1.1	-	Kuwai <i>et al.</i> 2017	(34)
	482	92.9	0.2	-	Takahashi <i>et al.</i> 2017	(24)
	150	97.3	-	Nawata <i>et al.</i> 2014	(37)	

Abbreviations: -; No data

Table 2. outcomes of endoscopic resection

site	lesions	Depth	5-Year Overall Survival (%)	5-Year Cause Specific Survival (%)	Author	Ref.
Esophagus	396	HGN/EP/LPM/MM	95.1	99.1	Oda <i>et al.</i> 2020	(26)
	1,131	EP	84.7	-	Tachimori <i>et al.</i> 2019	(29)
		LPM/MM	86.4	-		
		SM1/SM2	74.5	-		
	102	MM/SM1	84.1*	97.5*	Takahashi <i>et al.</i> 2018	(25)
	60	HGN/EP/LPM	95	100	Nagami <i>et al.</i> 2017	(28)
	19	MM/SM1	84*	100*		
4	SM2	75*	100*			
Stomach	1,537		92.6	99.9	Suzuki <i>et al.</i> 2016	(33)
	1,332		92.3	-	Nakamura <i>et al.</i> 2015	(31)
	421		-	100	Tanabe <i>et al.</i> 2014	(30)
Colon	150		94.1	98.6	Kuwai <i>et al.</i> 2017	(34)
	482		-	100	Takahashi <i>et al.</i> 2017	(24)

Abbreviations: HGN: High-grade neoplasia; EP: invasion to the depth of the epithelium; LPM: invasion to the depth of the lamina propria; MM: invasion to the depth of the muscularis mucosae; SM1: submucosal invasion to 200 μ m or less; SM2: deep submucosal invasion exceeding 200 μ m; *:patients took additional therapy was included; -: no data

Table 3. Complication rate of endoscopic resection

site	lesions	bleeding	perforation	Author	Ref.
Esophagus	1,207	0.1	1.6	Tachimori <i>et al.</i> 2019	(29)
	83	1.2	0	Nagami <i>et al.</i> 2017	(28)
	242	0	0.44	Nakagawa <i>et al.</i> 2014	(36)
Stomach	10,926	4.4	2.3	Suzuki <i>et al.</i> 2019	(32)
	1,332	4.2	1.5	Nakamura <i>et al.</i> 2015	(31)
	421	6.3	3.3	Tanabe <i>et al.</i> 2014	(24)
Colon	150	2.4	0	Kuwai <i>et al.</i> 2017	(34)
	482	1.6	6	Takahashi <i>et al.</i> 2017	(24)
	150	0	0	Nawata <i>et al.</i> 2014	(37)

ER stenosis in esophageal cancer was 2.7-16.7% (4,5,29).

Future perspectives

In Japan, with the aging of the population, there are increasing opportunities to treat elderly patients aged 75 and over. Therefore, the safety and efficacy of ER in elderly patients are important. It was reported that the short or long-term outcomes of the elderly and the younger groups were comparable, although the rate of additional treatments was low in the elderly (24,38). Similarly, a trial on indications of endoscopic submucosal

dissection for elderly patients with early gastric cancer (JCOG1902) has been conducted. Additional treatment might be too invasive for the elderly or patients with severe comorbidities. The risk of additional therapy should be considered against the risk of lymph node metastasis, considering the life expectancy of such patients.

In April 2014, laparoscopic and endoscopic cooperative surgery (LECS) was covered by insurance as a combination of endoscopic surgery and laparoscopic local gastrectomy. In this technique, full-thickness excision of the lesion using the ESD technique and

suturing the gastric wall defect with a laparoscope is performed. LECS for gastric cancer is contraindicated due to the possibility of intraperitoneal cancer cell dissemination and is currently mainly used for gastrointestinal stromal tumor (GIST) of the stomach (39). Recently, a combination of laparoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET) and non-exposed endoscopic wall-inversion surgery (NEWS) has been devised and are expected to be minimally invasive treatments for patients with EGC (40,41).

Conclusion

Many endoscopic treatment technologies have been developed or improved in Japan, many of which are at the forefront of the world. In Japan, where endoscopic treatment has become the standard for early cancer and precancerous lesions, the quality of endoscopic treatment is high, and the development of more advanced and safe endoscopic technology is expected in the future. In an aging society, it is necessary to consider whether to provide additional treatment for the patient's life expectancy and risk of lymph node metastasis. In the future, it is desirable to develop a minimally invasive technique and apply additional resection according to the patient's background.

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