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## Review Article

# Clinical Outcomes of Endoscopic Submucosal Dissection for Early Gastric Cancer in Different Indications

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### ABSTRACT

Gastric cancer still threatens the health of people, which is the fifth most common cancer and the fourth leading cancer-related death worldwide. The stage of the disease is critical for the 5-year survival of gastric cancer; the 5-year survival rates could reach 90% for gastric cancer detected at early stages. At present, endoscopic submucosal dissection (ESD) is the main treatment for early gastric cancer. Referring to the treatment guideline of the Japan Gastric Cancer Association, the indications for ESD mainly include absolute indications, expanded indications, and relative indications. Many studies have reported favourable long-term outcomes after undergoing ESD, and compared with surgery, ESD preserves the entire stomach and improves the quality of life of patients. However, it has also been reported that the recurrence rate of gastric cancer after ESD is high, so regular follow-up and careful examination are needed, even for patients with early gastric cancer who met absolute indications.

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### Introduction

Gastric cancer still threatens the health of people and is responsible for over one million new cases and an approximated 769,000 deaths in 2020, which is the fifth most common cancer and the fourth leading cancer related death worldwide. Eastern Asia and Eastern Europe particularly have the highest morbidities [1]. However, the stage of disease is critical for 5-year survival of gastric cancer. Actually, the 5-year survival rates could reach 90% for gastric cancer detected at early stages [2-4]. In Korea, endoscopic screening for gastric cancer has been started since 1999, the rate of detection of early gastric carcinoma reached to 70% [5, 6]. In Japan, endoscopic screening for gastric cancer as a public policy based on the guidelines published by the National Cancer Center of Japan has been conducted in 2015, the rate of detection in the early stage of gastric cancer is increasing gradually [7].

Early gastric cancer (ECG) is defined as tumor invasion is confined to the mucosa or submucosa, regardless of lymph node metastasis (LNM) [8]. At present, endoscopic resection and gastrectomy with D1 or D2 lymphadenectomy are surgical options for treating early gastric cancer. Endoscopic resection of early gastric cancer has become a trend in terms of treatment cost, postoperative complications and quality of life [9-12]. The main risk is lymph node metastasis in gastric cancer at early stage. The incidence of LNM in ECG invaded submucosa is significantly higher than that of gastric cancer confined to the mucosa (0-25% vs. 2%-5%) [13-15]. Therefore, it is crucial to accurately recognize those patients with high risk of LNM when selecting the appropriate curative strategy for patients with ECG.

According to the guidelines for endoscopic submucosal dissection (ESD) issued by Japan Gastroenterological Endoscopy Society and Japanese Gastric Cancer Association for ECG, there are two indications:

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absolute indications for standard treatment and expand indications for investigational treatment [16]. However, undifferentiated histology or ulceration, lymphovascular invasion, massive submucosal invasion is discovered in a part of specimen after ESD, which result in beyond the expanded indication [17]. We would update information and discuss the clinical outcomes of endoscopic submucosal dissection for early gastric cancer under different indications.

**Endoscopic Resection (ER)**

Endoscopic resection mainly includes Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD). EMR was first used in the treatment of intramucosal gastric cancer but was limited to differentiated cancers without ulceration less than 2cm in size. EMR can be roundly divided into two basic types. Non-suction method includes the submucosal injection-excision method (polypectomy method), submucosal injection-lift-excision method, submucosal injection-precut-excision method, etc. The suction method includes EMR-cap and EMR with band ligation. ESD is a new technology developed on the basis of EMR. According to lesions at different positions, sizes and depth of infiltration, suitable special electric knives, such as IT knife, Dua knife and Hook knife, are selected to gradually separate the tissues between mucosal musculus propria under endoscopy, and finally completely strip the mucosal layer and submucosal of lesions [18-21]. Although ESD has disadvantages compared to EMR, including higher complication rates, such as delayed bleeding and perforation, ESD has lots of advantages, such as high en bloc rate and accurate histopathological assessment.

**Indications for Endoscopic Resection**

In terms of indications for EMR and ESD, the main difference between the two methods lies in the size and depth of lesion resection. EMR limited the size of the lesions and only the mucosal lesions that could be

excised by en bloc. ESD has no size limitation and can resect SM1 layer lesions. Compared with EMR, ESD has higher rates of en bloc resection and complete resection in the treatment of early gastric cancer as well as recurrence, but higher incidence of complications such as perforation [18, 22]. Nowadays, endoscopic resection is mainly based on the operating guidelines of the Japan Gastroenterological Endoscopy Society (JGES). For tumors that have absolute indication, endoscopic resection is the standard treatment if the risk of lymph node metastasis is less than 1%. Moreover, the long-term outcome is expected to be equivalent to gastrectomy. The tumors eligible for the expanded indication are treated with endoscopy as investigational therapy, meaning that the risk of lymph node metastasis may be less than 1%, but there is insufficient evidence of long-term prognosis after endoscopic resection. Tumors that meet the relative indications refer to those tumors that usually require surgical resection but may be cured by endoscopic resection. Endoscopic resection could be an option when surgical treatment cannot be performed due to various clinical conditions (elderly and high surgical risks with serious complications) [16, 23].

**I Absolute Indications for EMR/ESD**

Clinically intramucosal (cT1a) differentiated-type carcinomas with a long diameter measuring 2cm or less without ulcer (UL0).

**II Absolute Indications for ESD (Table 1)**

- i. UL0 cT1a differentiated-type carcinomas with a long diameter greater than 2cm;
- ii. UL1 cT1a differentiated-type carcinomas with a long diameter measuring 3cm or less;
- iii. UL0 cT1a undifferentiated-type carcinomas with a long diameter than 2cm or less.

**Table 1:** Absolute indications for endoscopic submucosal dissection according to the Japan Gastroenterological Endoscopy Society (JGES).

Absolute indications			
Histology	Differentiated	Differentiated	Undifferentiated
Tumor size in cm	Any	≤3	≤2
Ulceration	Negative	Positive	Negative
Depth invasion	cT1a(M)	cT1a(M)	cT1a(M)

cT1a (M): Intramucosal Cancer (preoperative diagnosis).

**Evaluation of Curability**

En bloc resection refers to continuous monolithic resection after endoscopic resection. Curative resection refers to en bloc resection, lesion size less than 20mm, differentiated type, pT1a, no residual tumor at the margin and lymphovascular invasion. The evaluation of curability depends mainly on local factors and risk factors for lymph node metastasis. There are three levels of curability.

**I Endoscopic Curability A (eCuraA): Curative Resection**

The resection has the same and better outcome than surgical resection in terms of long-term outcomes. However, there is no prognosis evidence for differentiated carcinomas with undifferentiated components.

**II Endoscopic Curability B (eCuraB)**

The resection does not have adequate long-term results, but curable outcomes could be expected. However, if there are undifferentiated components in the submucosal infiltration of the lesion, the lesion is considered to be eCuraC-2.

**III Endoscopic Curability C (eCuraC)**

The resection does not conform to the criterions of eCuraA and B, it is considered to be eCuraC and there is a possibility of tumor residue. When lesions of eCuraC are differentiated and meet other eCuraA or eCuraB criteria but were not resected en bloc or had a positive horizontal margin, they are classified as eCuraC-1. Other lesions of eCuraC are thought to be eCuraC-2 (Table 2).

**Table 2:** Evaluation of curability according to tumor-related factors based on the JGES [16].

	eCuraA			eCuraB			eCuraC-2		
Histology	Differentiated	Differentiated	Undifferentiated	Differentiated	Differentiated	Undifferentiated	Differentiated	Undifferentiated	Any
Size in cm	Any	≤3	≥2	≤3	>3	>2	>3	Any	Any
Ulceration	Negative	Positive	Negative	Any	Positive	Negative	Any	Positive	Any
Invasion	pT1a(M)	pT1a(M)	pT1a(M)	pT1b1(SM1)	pT1a(M)	pT1a(M)	pT1b1(SM1)	pT1a(M)	pT1b2(SM2)

pT1a (M): Intramucosal cancer (histopathological diagnosis); pT1b (SM): Submucosally invasive cancer (histopathological diagnosis).

### Efficacy and Long-Term Outcome of ESD for EGC

A prospective multicenter cohort study analysed 712 patients with 737 EGCs and found 49 patients (6.9%) exhibited delayed bleeding and 12 patients (1.7%) exhibited perforations. ESD is a high curative resection rate for EGCs met absolute indications [24]. A multicenter collaborative study observed the 5-year overall survival rate and the 5-year disease-specific survival rate in 4648 with absolute-indication lesions and 3056 patients with expanded-indication lesions. This study conducted the 5-year overall survival rate was 91.6% after curative resection of absolute-indication lesions and 90.3% after curative resection of expanded-indication lesions. The 5-year disease-specific survival rate was 99.9% after curative resection of absolute-indication lesions and 99.7% after curative resection of expanded-indication lesions. Meanwhile, this research found 5 (16%) of 3056 patients with expanded indication lesions that were curatively resected by ESD died of gastric cancer. Moreover, the study compiling and analyzing data on more than 12000 patients from 126 Japanese hospitals showed good short-term and long-term outcomes in patients with EGC after endoscopic treatment [25]. Another multicenter collaborative study in Japan evaluated long-term outcomes of ESD in 6456 patients with 7979 lesions who met the absolute indications for ESD and 4202 patients with 5781 lesions who met the expanded indications for ESD and thought the long-term outcomes of ESD in patients with absolute indication-lesions were equivalent to those of curative surgery and ESD had an extremely low metastatic recurrence in patients who met expanded indications [26].

A prospective multicenter cohort study in South Korea enrolled 697 patients with 722 early gastric cancers, and found complete resection was achieved in 81.3%, curative resection was achieved in 86.1%, the overall survival rate was 96.6% and the disease specific free survival rate was 90.6% during 5-year follow-up. This study revealed excellent long-term clinical outcomes after ESD and recommended ESD can be a curative treatment for patients with EGC who met the expanded criteria [27]. A Western study compiled 53,84 and 27 patients with EGCs respectively met the absolute indications, expanded indications and beyond the expanded indications groups and showed the en bloc resection rate was 98.4% for absolute criteria, 89.0% for expanded criteria lesions and 89.7% for beyond the expanded indications. The curative resection rate was 90.2% for the absolute indication lesions, 73.6% for expanded indication lesions. However, the curative resection rate was 0% for beyond the expanded indication lesions. Among the patients with curative resection, none had local recurrence or metastasis. The local recurrence rate was 4.8% for the expanded indication lesions and 11.1% for beyond the expanded indication lesions. Metastatic rate was 1.2% for patients with expanded indication lesions but 11.1% patients for expanded indication lesions. The metachronous recurrence rate was 7.1% for expanded indication lesions and 7.4% for beyond the expanded indication lesions. But the metachronous recurrence rate was as high as 15.1% for absolute indication lesions. Although the sample size of this study was small, it is considered that ESD could reach high rates of long-term curative treatment for patients with expanded criteria lesions in Western Countries (Table 3) [28].

**Table 3:** Efficacy and long-term outcome of ESD<sup>a</sup> for ECG<sup>b</sup> in different indications.

	Fan <i>et al.</i> (2021) [17]			Probst <i>et al.</i> (2017) [28]		
	AI <sup>c</sup>	EI <sup>d</sup>	BEI <sup>e</sup>	AI <sup>c</sup>	EI <sup>d</sup>	BEI <sup>e</sup>
Follow-up period Median (mo.)	58.1			51	56	36
No. of patients	265	137	93	53	84	27
En bloc resection. %	100.0	100.0	93.0	98.4	89.0	89.7
Curative resection. %	98.5	97.8	0	90.2	73.6	0
Local recurrence %	0.4	0	0	0	4.8	11.1
Metastatic recurrence %	2.5	0.8	0	0	1.2	11.1
Metachronous lesion %	0.4	0	2.3	15.1	7.1	7.4

<sup>a</sup>ESD: Endoscopic Submucosal Dissection; <sup>b</sup>ECG: Early Gastric Cancer; <sup>c</sup>AI: Absolute Indication; <sup>d</sup>EI: Expanded Indication; <sup>e</sup>BEI: Beyond the Expanded Indication.

In addition, a retrospective study analysed the short-term and long-term clinical outcomes of ESD met beyond the expanded indication. A total of 265, 137 and 93 patients with EGCs respectively met the absolute indications, expanded indications and beyond the expanded indications groups. The patients met the absolute indications and expanded indications were in line with the en bloc resection. The en bloc resection was only 93.0%. The curative resection rate was 98.5% for the absolute indication lesions, 97.8% for expanded indication lesions. However, the curative resection rate was 0% for beyond the expanded indication

lesions. The local recurrence rate was 0.4% for absolute indication lesions, 0% for expanded indication lesions and 0% for beyond the expanded indication lesions. Metastatic rate was 2.5% for absolute indication lesions, 0.8% for expanded indication lesions and 0% for beyond the expanded indication. The metachronous recurrence rate was 0.4% for absolute indication lesions, 0% for expanded indication lesions and 2.3% for beyond the expanded indication lesion (Table 3) [17]. The efficacy for ESD patients beyond the expanded indications groups was

worthy of recognition, but those patients were needed to be carefully checked.

### Endoscopic Submucosal Dissection Versus Surgery for EGC

A prospective cohort study assessed the health-related quality of life of 48 EGC patients underwent ESD and 113 EGC patients who underwent surgery. This study observed the surgery group had significantly lower scores than the ESD group for factors except emotional and cognitive functioning, economic problems and anxiety at 1-month post-treatment. In terms of eating restriction, dysphagia, physical functioning, diarrhea and body image, ESD group was significantly better than the surgery group for more than 1-year post-treatment. Moreover, the ESD group had significantly lower treatment-associated complications than the

surgery group (2.1% vs. 15.0%). The 5-year overall survival was not different between both the groups (99.7% vs. 99.1%) [29]. Hahn *et al.* retrospectively compared the clinical between ESD and surgery (817 vs. 1206) and showed that early complication rates 8.1% vs. 18.1%. The incidence of recurrent gastric cancer was 2.18% and 0.19% in the ESD and surgery group, respectively. The 5-year overall and disease specific survival rates were not significantly different between the ESD group and surgery group (96.4% vs. 97.2%; 99.6% vs. 99.2%) (Table 4) [10]. Several meta-analysis lectures showed compared with surgery, ESD can provide better health-related quality of life benefits for EGC patients. Meanwhile, ESD is a treatment with lower cost, less trauma and faster recovery for patients with EGCs. But it is necessary to careful surveillance after ESD [9, 12, 30-32].

**Table 4:** Endoscopic Submucosal Dissection (ESD) versus surgery for EGC.

	Hahn <i>et al.</i> [10]		Kim <i>et al.</i> [29]	
	ESD	Surgery	ESD	Surgery
No. of patients	817	1206	48	113
Early complication %	8.1	18.1	2.1	15.0
Recurrence %	2.18	0.19		
5-Year overall survival %	96.4	97.2	99.7	99.1
5-Year disease-specific survival %	99.6	99.2		

### The Efficacy of Non-Curative Endoscopic Submucosal Dissection

For patients with non-curative ESD, the guidelines suggested additional open or laparoscopic surgical resection and lymph node dissection due to the high risk of lymph node metastasis. However, since most patients are elderly and the incidence of postoperative complications is high, additional surgical treatment after ESD is a challenge for both patients and doctors. A retrospective study showed distant metastasis as the common recurrence mold after non-curative ESD without additional radical surgery for EGC [33]. A multicenter study found the local recurrence rate was higher in non-curative resection. But the overall survival rates were respectively 99.4%, 98.9% and 96.8% at 3, 5, and 10 years. The disease-specific survival rates were respectively 99.6%, 99.3% and 99.3% at 3, 5 and 10 years in 661 patients who underwent non-curative resection of ESD [34]. Noboru *et al.* reported 5-year disease-specific survival rate was similar in the two groups which enrolled 323 patients underwent additional surgery after non-curative ESD and 183 patients without additional surgery after non-curative ESD [35]. Tumor size  $\geq 20$ mm, positive horizontal margin, lymphovascular invasion and submucosal invasion were risk factors for local recurrence after ESD.

Some patients who do not want to undergo additional surgery because of their advanced age or financial burden can be treated under endoscopic resection again. A study showed when positive lateral margins (pLMs) as the only non-curative factor after ESD for patients with EGCs, additional ESD or APC may be an acceptable treatment for patients who are elderly, intolerance of surgery according to the favourable long-term outcomes [36]. For the elderly, ESD is a good option even for non-curative treatment. Yosuke *et al.* evaluated clinicopathology and long-term outcomes in 87 patients with EGCs aged  $\geq 75$  years after non-

curative ESD and found overall survival rates were 89.7% and 79.3% after 3 and 5 years, respectively [37].

### Conclusion

ESD could be a preferred treatment for patients who met absolute or expanded indications, but regular and close follow-up examinations are needed, especially for patients with expanded indications. However, a more precise assessment of long-term outcomes requires prospective multicenter studies. Patients with undifferentiated type EGC may have better long-term outcomes after curative resection. For non-curative ESD with high risk of lymph node metastasis, additional surgical resection with lymph node dissection should be recommended.

### Conflicts of Interest

None.

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