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Worldwide experiences of endoscopic submucosal dissection: Not just Eastern acrobatics

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Abstract

The high incidence of gastric cancer has led to the initiation of cancer screening programs. As a result, the number of early gastric cancer cases has increased and consequentially, the cancer mortality rate has decreased. Moreover, the development of minimally invasive endoscopic treatment has been introduced for these early lesions. Endoscopic submucosal dissection (ESD) is now recognized as one of the preferred treatment modalities for premalignant gastrointestinal epithelial lesions and early gastric cancer without lymph node metastasis. We review the results of ESD including experiences in Japan and Korea, as well as western countries.

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INTRODUCTION

The high incidence of gastric cancer in Japan and Korea has led to the initiation of national cancer screening programs. As a result, the number of early gastric cancer (EGC) cases has increased dramatically and accounts for up to 50% of all gastric cancer diagnoses^[1,2]. In addition, as a result of these programs, the mortality rate from gastric cancer has decreased^[3]. Moreover, the development of minimally invasive endoscopic treatment has been introduced for these early lesions.

Initially, EGC was treated using endoscopic mucosal resection (EMR) techniques that included an injection that lifts the lesions, which are then cut. EMR can be used with a cap (EMR-C) and with ligation (EMR-L). These techniques are limited by the size of the lesions; only lesions of a relatively small size (< 2 cm) can be resected *en bloc*, due to the restricted size of the snare, cap and ligation devices. If EMR is attempted for lesions > 2 cm, the risk of piecemeal resection might increase, which makes it difficult to determine whether the lateral resection margins are free of disease. Previous studies of EMR have reported an approximately 75% *en bloc* resection rate. However, there is a high risk of local recurrence (2%-35%) with this procedure, especially when EMR cannot achieve *en bloc* resection^[4-7].

To avoid the problems associated with EMR, endoscopic submucosal dissection (ESD) has been introduced

for safe *en bloc* resection. ESD can be used for larger lesions and those with ulceration, regardless of their location^[7-9]. Although ESD techniques require advanced skill and might have a higher complication rate, including bleeding and perforation, they increase the rate of *en bloc* resection and complete histological analysis, and might ultimately reduce local disease recurrence rate^[7,10].

ESD is now recognized as one of the preferred treatment modalities for premalignant gastrointestinal epithelial lesions and EGC without lymph node metastasis. The ESD procedure starts by making several marking dots around the lesion; a lifting solution is injected into the submucosal layer, followed by endoscopic circumferential incision of the lesion with various knives; dissection starts at the lateral edges, and proceeds through the lifted submucosal layer until the lesion is resected in one piece. According to a PubMed search, a total of 517 articles on ESD have been published up to January 2010. Most of the studies have been published from Asia, mainly Japan; however, recently there have been an increasing number of papers from Korea and China.

In this chapter, ESD for EGC is reviewed, including experiences from Japan and Korea, as well as western countries.

BACKGROUND OF ENDOSCOPIC RESECTION

EGC is defined by tumor invasion confined to the mucosa or submucosa, regardless of lymph node metastasis^[11]. According to the outcomes after gastrectomy, 5- and 10-year survival rates for patients that have a diagnosis of mucosal EGC have been reported to be 96% and 92%, respectively^[12]. The long-term outcomes after EMR for EGC < 2 cm has demonstrated excellent results with disease-specific 5- and 10-year survival rates of 99% and 99%, respectively; this was even with patients that had major organ complications, who were not good candidates for surgery^[13]. Clinical experience suggests that complete resection of the cancer is possible, and cure can be achieved as long as the potential for metastatic spread is accurately excluded.

The accepted indications for EMR and ESD are lesions diagnosed as well-differentiated adenocarcinoma by histology, which are elevated and < 2 cm in diameter, and small (≤ 10 mm), depressed, well-differentiated tumors without ulcer formation^[14]. However, these indications are rather strict, which leads to many patients being subjected to unnecessary surgery. Actually, endoscopic resection has also been used for larger lesions without lymph node metastasis by many Japanese investigators. Lymphovascular involvement, ulcer formation, and tumor size > 3 cm are independent risk factors for lymph node metastasis in EGC that is limited to the mucosa^[15]. A large study on post-gastrectomy outcomes with lymph node dissection has shown that the overall risk for lymph node metastasis among patients with EGC that involved the mucosa was 2.7%. The risk increased to 18.6% when the cancer invaded the submucosa. The absence of submucosal lympho-

vascular involvement in moderately or well-differentiated adenocarcinoma was found to correlate with a nominal risk for lymph node metastasis. In lesions < 3 cm, the risk of lymph node metastasis is very low regardless of the presence of ulceration. In lesions without ulceration, the risk is unaffected by the size of the tumor^[16]. Therefore, according to the *Treatment Guidelines for Gastric Cancer in Japan*, the expanded criteria for ESD are as follows: (1) a differentiated mucosal cancer without ulceration, no lymphatic-vascular invasion, regardless of size; (2) a differentiated mucosal cancer with ulceration, no lymphatic-vascular invasion, tumor < 3 cm; (3) an undifferentiated type of mucosal cancer without ulceration and tumor < 2 cm in diameter, and absence of lymphatic-vascular invasion; and (4) when a differentiated adenocarcinoma, which has not invaded deeper than submucosal level 1 (< 500 μ m) and lymphovascular invasion is absent, additional lymph node dissection is not necessary^[14].

However, expanding the indications for endoscopic resection remains controversial because the long-term outcomes of these indications have not been fully documented. Several publications have reported lymph node metastasis in EGC that meet the extended criteria^[17-19]. Jee *et al*^[19] have reported lymph node status in a total of 181 patients who met expanded indications for ESD and had undergone surgical resection. They reported lymph node metastasis in 2.3% of 129 patients with mucosal cancer. This included one ulcerated differentiated cancer < 3 cm in diameter, and two undifferentiated cancers < 2 cm in diameter without ulceration. Also, in a study of lymph node metastasis in 4% of 52 patients with submucosal cancer, those were two differentiated tumors.

Therefore, considering the indications for ESD, surgery is preferentially recommended for undifferentiated mucosal cancer, although several recent studies have shown that the rate of lymph node metastasis is negligible in small and undifferentiated mucosal cancer^[20-24].

WORLDWIDE ESD RESULTS

The results of recent studies have suggested that the technique of ESD achieves a high rate of *en bloc* resection (92%-97%) and complete resection (73.6%-94.7%) with various rates of complications including bleeding (0.1%-15.6%) and perforation (1.2%-9.7%). Furthermore, they have revealed excellent long-term outcomes (5-year overall and disease-specific survival rates of 97.1% and 100%, respectively) (Table 1).

Japan

Oda *et al*^[6] have performed a multicenter retrospective study to determine the nationwide results of endoscopic resection for EGC. Seven hundred and fourteen EGCs (EMR, 411; ESD, 303) that met the expanded criteria, except for the undifferentiated type of mucosal cancer, from 655 consecutive patients and 11 Japanese institutions were evaluated. Technically, 71.6% of the lesions were resected in one piece. The rate of *en bloc* resection by ESD (92.7%) was significantly higher than by EMR (56.0%). The rate of

Table 1 Recent outcomes of endoscopic resection for early gastric cancer

Author	Yr	No. (lesion/ patient)	Method	En bloc rate (%)	Complete resection rate (%)	Follow-up (mo/range)	Complications (%)		Local recurrence rate (%)	3-yr residual/ free recurrence rate (%)	3-yr overall survival rate (%)	5-yr overall survival rate (%)	5-yr disease- specific survival rate (%)
							Bleeding	Perforation					
Oda <i>et al</i> ^[6]	2006	714/655	EMR 411 ESD 303	56.0 92.7	61.1 73.6	38 (6-60)	0.1	1.2	7.5	92.5	99.2	NA	NA
Oka <i>et al</i> ^[7]	2006	1025/896	EMR 825/711 ESD 195/185	43.4 92.8	24.6 92.8	83.2 19.4	3.9	0.5	3.5 (31/825) 0 (0/195)	NA	NA	NA	NA
Imagawa <i>et al</i> ^[8]	2006	196/185	ESD	93.0	84.0	17.6 (1.3-45.7)	6.2	9.7	0 (0/164)	NA	NA	NA	NA
Jung <i>et al</i> ^[28]	Retrospective 2007	1327/NA	EMR-P 775 ESD 552	NA	91.0 95.1	NA	6.3	0.8	NA	NA	NA	NA	NA
Takenaka <i>et al</i> ^[34]	Retrospective 2008	306/275	ESD	NA	80.4	26 (26-64)	7.6	2.7	0 (0/177)	NA	NA	NA	NA
Isomoto <i>et al</i> ^[10]	Prospective 2009	589/551	ESD	94.9	94.7	30 (6-89)	1.8	4.5	0 (0/468)	NA	> 97.2	97.1	100
Goto <i>et al</i> ^[25]	Retrospective 2009	276/231	ESD	96.7	91.7	36 (2-93)	5.1	4.0	0.9 (2/212)	99.1	96.2	96.2	100
Nakamoto <i>et al</i> ^[26]	Retrospective 2009	202/177	EMR 80 ESD 122	53.8 94.3	37.5 92.6	54 (12-89) 34 (14-62)	1.6	2.5	17.5 (14/80) 0	82.5 ¹ 0	100	100	100
Chung <i>et al</i> ^[29]	Retrospective 2009	1000/952	ESD	95.3	87.7	NA	15.6	1.2	NA	NA	NA	NA	NA
Jang <i>et al</i> ^[30]	Retrospective 2009	402/402	ESD	89.7	87.9	30 (9-49)	7.4	2.9	5.1 (10/198)	94.9	NA	NA	NA
Min <i>et al</i> ^[31]	Retrospective 2009	(107 LGD/97 HGD/198 EGC) 346/243	EMR-P 103 ESD 243	77.7 95.9	75.7 88.9	29 (4-44) 17 (4-37)	3.9	1.9	0 (0/80) 0 (0/191)	NA	NA	NA	NA
Chang <i>et al</i> ^[32]	Retrospective 2009	70/70	ESD	91.4	92.8	NA	5.7	4.3	2.8	NA	NA	NA	NA

¹Overall 5-year recurrence free rate. LGD: Low-grade dysplasia; HGD: High-grade dysplasia; NA: Not applicable; EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; EMR-P: precutting followed by snare resection.

curative resection by ESD (73.6%) was significantly higher than by EMR (61.1%). Bleeding was found in 0.1% of cases. The frequency of perforation with ESD and EMR was 3.6% and 1.2%, respectively. All complications were managed endoscopically, and there was no procedure-related mortality. The median follow-up period was 3.2 years. The 3-year cumulative residual-free/recurrence-free rate in the ESD group (97.6%) was significantly higher than that in the EMR group (92.5%).

Oka *et al.*^[7] have reported on a comparative study between EMR and ESD of 1020 EGCs that met the expanded criteria. Eight hundred and twenty-five EMRs and 195 ESDs were performed. In cases without ulceration, the *en bloc* and curative resection rates were significantly higher with ESD (both 92.8%) than with EMR (43.4% and 24.6%), regardless of tumor size. The average operation time was significantly longer for ESD than for EMR (84.4 min *vs* 12.6 min), regardless of tumor size. In addition, the frequency of intraoperative bleeding was significantly higher with ESD (22.6%) than with EMR (7.6%). The frequency of delayed bleeding did not differ. No patient experienced recurrence after ESD.

Imagawa *et al.*^[8] have analyzed 196 EGCs that met the expanded criteria and were treated by ESD, in relation to lesion size, location and the presence or absence of ulceration. The rate of *en bloc* resection was 93%, the curative resection rate was 84%, with a perforation rate of 6.1%, and a mean procedure time of 68 min. The rate of curative *en bloc* resection differed significantly depending on the location of the lesion (upper *vs* middle *vs* lower, 74% *vs* 77% *vs* 91%), as well as on the size of the lesion (> 20 mm *vs* ≤ 20 mm, 59% *vs* 89%). There were also significant differences in the mean procedure time in relation to the location of the lesion (upper *vs* middle *vs* lower, 105 min *vs* 81 min *vs* 45 min) and the size of the lesion (> 20 mm *vs* ≤ 20 mm, 124 min *vs* 55 min), as well as the presence of ulceration (positive *vs* negative, 97 min *vs* 65 min). They showed that the difficulty of ESD depends on the location and size of the lesion, as well as on the presence of ulceration.

Isomoto *et al.*^[10] have published the first long-term follow-up results of 589 EGCs treated by ESD, which met the expanded criteria. *En bloc* resection was achieved in 94.9%. Curative resection was achieved in 94.7%. *En bloc* resection was the only significant factor associated with curative ESD. Patients with a non-curative resection developed local recurrence more frequently. The 5-year overall and disease-specific survival rates were 97.1% and 100%, respectively.

Goto *et al.*^[25] have carried out a retrospective investigation of ESD to determine long-term outcomes. Two hundred and seventy-six node-negative EGCs that met the expanded criteria, except for the undifferentiated type of mucosal cancer, were enrolled. The *en bloc* and complete resection rates were 96.7% and 91.7%, respectively. During a median follow-up of 3 years, there were two local recurrences (0.9%). The 5-year overall and disease-specific survival rates were 96.2% and 100%, respectively.

Nakamoto *et al.*^[26] have performed a comparative study

of EMR and ESD for 202 EGCs. The overall *en bloc* and complete resection rates were lower in patients undergoing EMR compared to ESD (*en bloc*: 53.8% *vs* 94.3%, complete: 37.5% *vs* 92.6%). The overall 5-year recurrence-free rate was lower in the EMR group than in the ESD group (82.5% *vs* 100%). However, with regard to tumor size, EMR was comparable to ESD for the small lesions (< 5 mm).

Korea

The number of publications on ESD in Korea has been increasing. The results of ESD including the *en bloc* resection rate, complete resection rate, and long-term follow-up survival rates are similar to those from Japan. The Health Insurance Review and Assessment Service of Korea have reported that 74 institutions, mainly tertiary hospitals, have performed ESD in 2008.

Kim *et al.*^[27] have published the first multicenter retrospective study of endoscopic resection in Korea. They collected 514 EGCs in 506 patients during January 2000 to December 2002 by use of the on-line database registry system. The most commonly used technique was circumferential precutting followed by snare resection (EMR-P, 52.3%). The second most common procedure was the injection and cut technique (24.3%). ESD was used only in 6.6% of cases at that time. Complete resection was confirmed in 77.6% of the lesions, and the mean tumor size was 1.76 cm. However, ESD is now in the mainstream for endoscopic resection of early gastric lesions in Korea.

Jung *et al.*^[28] have reported an 11-year experience of endoscopic resection performed by a single endoscopist. Seven hundred and seventy-five EMR procedures were performed after precutting (EMR-P) during the first 9 years and 552 ESDs over the following 2 years. The median specimen sizes were 33 mm for EMR-P and 45 mm for ESD. The complete resection rates were 91% and 95.1% and the respective complication rates were 7.1% and 10.7%.

The Korean ESD study group has published a retrospective six university hospital experience with ESD for 1000 gastric neoplasms^[29]. The rate of *en bloc* resection and complete resection was 95.3% and 87.7%, respectively. The rate of delayed bleeding and perforation was 15.6% and 1.2%, respectively. The rate of *en bloc* resection differed significantly based on the location of the lesions and presence of a scar. Procedure times were increased in cases in the upper stomach that had a large lesion (> 40 mm), with the presence of an ulcer, and the presence of a scar.

Jang *et al.*^[30] have reported the results of ESD for 402 gastrointestinal neoplasms at a single hospital. *En bloc* resection and complete resection were achieved in 89.7% and 87.9%, respectively, and the local recurrence rate was 5.1%. The 3-year cancer-free survival rate was 94.9%.

Min *et al.*^[31] have published a comparative study of ESD and EMR after circumferential precutting (EMR-P) of 346 EGCs. *En bloc* resection and complete resection were achieved in 77.7% and 75.7% of the EMR-P group, respectively, and 95.9% and 88.9% of the ESD group. For EGCs > 20 mm, ESD demonstrated a significantly higher *en bloc* resection and complete resection rate compared to

EMR-P. In cases with completely resected differentiated cancer, neither group showed local recurrence during a median 29 and 17 mo follow-up, respectively.

Taiwan

Chang *et al.*^[32] have published a retrospective multicenter review of ESD of 70 EGCs in Taiwan. The *en bloc* resection rate was 91.4%. The bleeding and perforation rates were 5.7% and 4.3%, respectively. Emergency surgery was performed in the patients with perforations. The local recurrence rate was 2.8%. Another small study has been published in Taiwan^[33]; however, the results have indicated that the procedure requires more experience.

Western countries

As a result of the low incidence of EGC in the west, relatively few institutions use ESD and there have been only a few clinical studies on the outcomes^[34-42]. However, the reported outcomes of western studies have not been substantially different from those in eastern countries. Cardoso *et al.*^[35] have published an initial experience with ESD for 15 EGCs < 30 mm with no ulceration or scarring from Brazil. The mean procedure time was 140 min. The *en bloc* and complete resection rate was 80% and perforations occurred in 20% of cases. Catalano *et al.*^[36] have published their experience with EMR and ESD on 48 gastric lesions in Italy. After an initial experience with 36 EMRs, the procedure was changed to ESD. Out of 36 EMR procedures, *en bloc* and complete resection were achieved in 72% and 56%, respectively. However, among the 12 ESD cases, the rates both increased to 92%. Bleeding and perforation occurred in one case each. Dinis-Ribeiro *et al.*^[37] have published the results of ESD for 19 gastric lesions in Europe. ESD was performed under general anesthesia with a 79% *en bloc* resection rate. Probst *et al.*^[38] have published ESD results for 71 epithelial or submucosal tumors, and have demonstrated a learning curve that resulted in a decrease in the procedure duration and increased rate of complete *en bloc* resection over time (65.7% to 72.2%). Although there have been a limited number of studies outside Asia, the number of endoscopy centers that are performing ESD is slowly increasing worldwide^[43].

WHAT IS UNIQUE ABOUT ESD IN EASTERN ASIA?

In Eastern Asia, endoscopic resection methods have been widely accepted as the standard treatment for gastric tumors, and many trained endoscopists are familiar with EMR techniques. Compared to other organs including the esophagus or colon, tumors of the stomach are relatively easy to remove by endoscopic resection. The basic techniques of EMR overlap with those of ESD. This allows for a stepwise approach to a variety of lesions. For example, one might start with the frequently encountered easier lesions in the distal portion of the stomach, move to lesions in the proximal stomach, and then lesions in the esophagus or colon as the final step^[9,44]. However, in the

west, because of the lower frequency of gastric cancer, endoscopists have relatively less experience with EMR techniques. In addition, the high incidence of Barrett's esophagus, the treatment for which is technically demanding, makes it difficult for beginners to gain extensive experience with ESD^[45]. Training programs specifically aimed at advancing experience with ESD are useful^[46,47]. Although data on the learning curve for ESD are limited, Choi *et al.*^[48] have shown that, for an experienced endoscopist, approximately 40 cases of gastric EMR with a circumferential mucosal incision in a low risk location are necessary for satisfactory training.

Kakushima *et al.*^[49] have reported a retrospective study on the learning curve for 383 ESD procedures by two principal operators and 11 (< 30 cases) endoscopists with less experience. For the two main operators, there was no significant difference between 25 consecutive patients with regard to the *en bloc* resection and complication rates. The size of the lesions increased as the number of patients increased, whereas the average procedure time decreased significantly. For the endoscopists with less experience, there was a similar treatment outcome and complication rate, mainly due to the easier location of the tumors in their cases. A constant rate of both treatment outcomes and complications was achieved over a 5-year period of experience with ESD. A decrease in the procedure time was found to be a marker for operator proficiency with this technique. Yamamoto *et al.*^[44] have reported on the learning curve for three resident endoscopists that had already learned the basic procedures. They performed ESD under supervision for 30 consecutive lesions each. They obtained a good overall complete resection rate of 93%, with an acceptable complication rate of 4.4% with appropriate supervision; however, there was difficulty in achieving a sufficient rate of finishing up alone for submucosal dissection.

ESD was first performed in Korea in 1999. The Korean Society of Gastrointestinal Endoscopy (KSGE) organized the ESD research group to investigate and expand the ESD procedure nationwide in 2003. Prior to 2006, only 22 hospitals had the facilities to perform ESD. The KSGE developed ESD hands-on courses and traveled nationwide to introduce the ESD procedure and the devices with animal models on eight occasions^[50]. As a result, the number of registered ESD facilities increased to 77 according to data from National Health Insurance Review and Assessment Service in 2008. Furthermore, an international ESD live demonstration has been held every year since 2006. Such support from the KSGE, including the ESD research group, a joint symposium with the Korean Pathology Society, ESD live demonstrations, multicenter studies, and training models for teaching ESD have made it possible to standardize ESD guidelines and techniques in Korea.

ESD EAST TO WEST

Minimally invasive approaches provide a substantially better quality of life compared to conventional open surgery. There is currently not enough long-term follow-up outcome data on ESD compared to open surgery; however,

if careful patient selection is maintained, excellent oncological outcomes with ESD are attainable by experienced endoscopists. Although ESD procedures have not been performed in western countries with as much experience as in eastern countries, improved techniques can be achieved with additional experience. In spite of the low incidence of gastric lesions in the west, there is a relatively high incidence of colon lesions, including large sessile and flat polyps. The novice might start with a modified EMR technique including the adoption of some of the methods used for ESD, such as circumferential marginal incision, which has been used to teach ESD techniques during the past decade in Korea. Furthermore, training programs can be developed to teach ESD^[47], and close collaboration between western and Asian centers and attending live demonstrations can help to gain such experience. On the other hand, modern medical science and technology continue to develop at a rapid pace. The recent development of accessories and traction devices might help in the acquisition of the skill and experience needed to make ESD easier to learn and apply^[51-53].

CONCLUSION

ESD is an effective and safe therapeutic modality for management of early gastrointestinal tract neoplasms, although it has a relatively longer operation time and high risk of complications. In spite of the late start for ESD in the west, the results have been being similar to those from Japan. In the same manner, although there is a problem to overcome the flat learning curve in view of the low number of detected cases in western countries, close collaboration between western and Asian centers is required for improvement of the ESD technique and its clinical application.

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