



# Endoscopic Resection for the Treatment of Superficial Esophageal Neoplasms

Ga Hee Kim, M.D., Ph.D., Hwoon-Yong Jung, M.D., Ph.D., AGAF, FASGE

Department of Gastroenterology, Asan Digestive Disease Research Institute, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

## ARTICLE INFO

**Received** May 6, 2020

**Revised** May 23, 2020

**Accepted** May 25, 2020

## Corresponding author

Hwoon-Yong Jung

**Tel** 82-2-3010-3197

**Fax** 82-2-476-0824

**E-mail** [hyjung@amc.seoul.kr](mailto:hyjung@amc.seoul.kr)

**ORCID**

<https://orcid.org/0000-0003-1281-5859>

<sup>†</sup>This article was presented at the 6th Esophageal Cancer Symposium (lecture on November 16th, 2019, Samsung Medical Center, Seoul, Korea).

Superficial esophageal neoplasms (SENs) are being diagnosed increasingly frequently due to the screening endoscopy and advances in endoscopic techniques. Endoscopic resection (ER) is a relatively noninvasive treatment method with low morbidity and mortality that provides excellent oncologic outcomes. Endoscopic submucosal dissection is associated with higher rates of en bloc, complete and curative resections and lower rates of local recurrence than endoscopic mucosal resection. The most serious complication of ER is stricture, the treatment and prevention of which are crucial to maintain the patient's quality of life. ER for SEN is feasible, effective, and safe and can be considered a first-line treatment for SENs in which it is technically feasible.

**Keywords:** Superficial esophageal neoplasm, Endoscopic submucosal dissection, Endoscopic mucosal resection, Esophageal squamous cell carcinoma, Endoscopy

## Introduction

Recently, cases of superficial esophageal neoplasm (SEN) has been increasing common due to advances in endoscopic screening and techniques, image-enhancement and narrow-band imaging in Korea and Japan [1-4]. In Western countries, adenocarcinoma (ADC) associated with Barrett's esophagus is the most commonly diagnosed esophageal cancer (EC). In contrast, squamous cell carcinoma (SCC) is the most common histologic type of EC diagnosed in Asian countries. The scope of options regarding, treatment methods for SEN has expanded, with endoscopic resection (ER) considered the standard treatment. The endoscopic treatment of SENs, including early-stage EC and esophageal dysplasia, has attracted interest as an alternative therapy. The results of ER are comparable to those of conventional surgery, with superior safety and acceptable oncologic outcomes [5-7]. However, although ER represents an excellent treatment option, the misjudgments of indications for its use or the incorrect assessment of curability can result in unfavorable clinical outcomes.

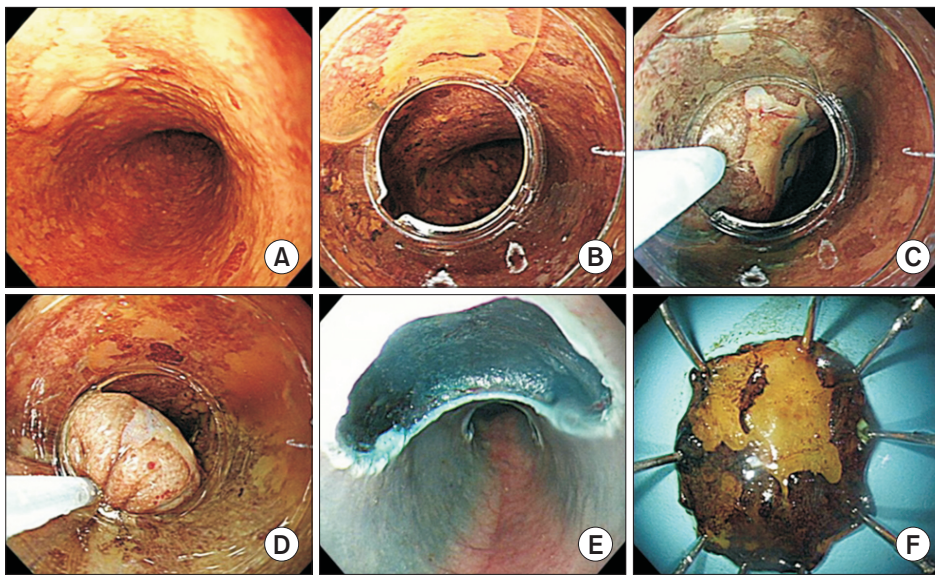
In this review article, we discuss the indications for ER

of SENs with squamous cell histology, the subsequent oncologic outcomes, and the management of complications associated with this treatment method. We hope that this information will lead to improved patient management.

## History of endoscopic resection

ER encompasses 2 main techniques; endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The use of EMR in the esophagus was first reported in 1990 by Inoue and Endo [8] from Japan as a tool in the management of patients with both high grade dysplasia and superficial esophageal cancer (SEC). EMR is used to remove sessile, flat, or discrete mucosal lesions smaller than 2 cm in diameter and involving less than two-thirds of the circumference of the esophageal wall. EMR can assist in determining the local stage, the degree of differentiation, and the lymphovascular invasion (LVI) of neoplastic lesions [9]. This technique requires the use of a standard endoscope without any additional equipment or procedural assistance and has the advantage of being relatively simple (Fig. 1). However, EMR cannot be used for the en bloc





**Fig. 1.** Endoscopic mucosal resection of superficial esophageal cancer. (A) A 1-cm sized flat elevated lesion on the mid-thoracic esophagus. (B) Chromoendoscopy with Lugol's solution demarcating the lesion. (C) Submucosal saline injection. (D) Performing resection using a snare. (E) An artificial ulcer after endoscopic resection. (F) Chromoendoscopic findings of the en bloc resection specimen.

removal of lesions larger than 2 cm in size. Furthermore, the piecemeal resection of tumor lesions larger than 2 cm is associated with a relatively high risk of local recurrence [5,10,11]. In addition, EMR may be technically difficult in certain cases (e.g., in recurrent or non-lifting lesions).

Compared to EMR, ESD is reported to have a high rate of en bloc resection with a low rate of local recurrence, regardless of lesion size. However, it requires advanced endoscopic skills [12].

## Indication criteria

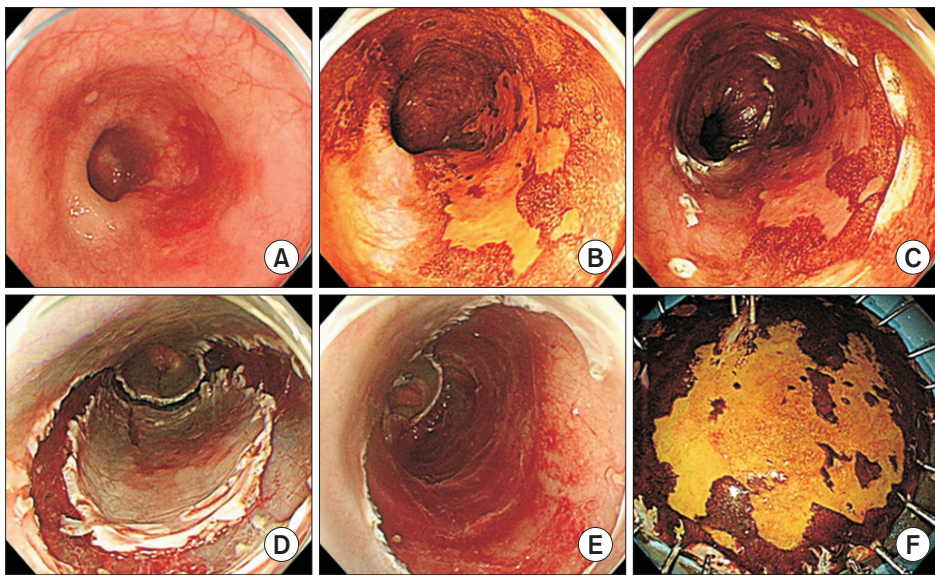
ER is an accepted curative treatment method for SEC if the risk of lymph node metastasis (LNM) is minimal [13]. The risk of LNM is associated with tumor differentiation, histology, depth, and LVI. According to the Japan Esophageal Society, ER is a sufficient method of treatment for lesions confined to the epithelium of the mucosa (M1) and the lamina propria (M2). Lesions extending up to the muscularis mucosae (M3) or lightly infiltrating the submucosa (<200  $\mu\text{m}$ ) are also amenable to mucosal resection; however, they are associated with an elevated risk of LNM. These are some of the relative indications [14,15]. The European Society of Gastrointestinal Endoscopy recommends that ESD as the initial treatment option for superficial esophageal SCC. This recommendation is based on a series of 15 studies involving the use of ESD for superficial esophageal SCC. Among these studies, en bloc resection rates were 83%–100%, complete resection rates were 78%–100%, and local recurrence rates were as low as 0%–2.6% [16].

Morphological assessments are performed according to

the Paris classification system, and can assist in predicting the depth of invasion [17]. Invasion into the submucosa is more common protruding lesions and excavated than in completely flat lesions, which are associated with the lower risk of submucosal invasion [18]. Endoscopic ultrasound (EUS) is reported to be the most accurate modality for TNM staging of advanced EC. In a meta-analysis of superficial SCC and ADC, the overall accuracy of EUS was 81% for SCC and 84% for ADC. The specificity and sensitivity of EUS for T1a tumors were 87% and 85%, respectively, while the specificity and sensitivity of this technique for T1b tumors were both 86% [19]. While EUS is the gold standard for TNM staging of advanced EC, the role of EUS in the staging of SEC is more controversial due to the potential for over- or under-staging. In a report by Pouw et al. [20], EUS was found to have a minimal clinical impact on the staging of SEN, strengthening the role of diagnostic ER as a possible final step in diagnosis. Pathologic evaluation of the resected specimen is still the most important first staging tool [21]. The intrapapillary capillary loops (IPCL) of esophageal mucosa demonstrate characteristic changes of tissue atypism and provide an estimate tumor depth [22,23]. In early SCC, the vascular pattern of the IPCL can be watched using high definition endoscopy, which can help to classify and predict the depth of the tumor [24].

## Principles of endoscopic submucosal dissection

ESD is a procedure used to resect tumors via the dissec-



**Fig. 2.** Endoscopic submucosal dissection of superficial esophageal cancer. (A) A 2.5-cm flat hyperemic lesion on the mid-thoracic esophagus. (B) Chromoendoscopy with Lugol's solution demarcating the lesion. (C) Markings made around the lesion. (D) Circumferential mucosal pre-cutting. (E) An artificial ulcer after submucosal dissection. (F) Chromoendoscopic findings of the en bloc resection specimen.

tion of the submucosal layer. With this procedure, relatively large tumors can be resected en bloc, effectively yielding histologic information through complete oncologic resection [10].

Prior to performing procedure, endoscopic examination (using white-light imaging, narrow band imaging, and chromoendoscopy with Lugol's solution) is performed to determine the exact margin of the tumor (Fig. 2B). Lugol's solution is applied to highlight abnormal areas, and mucosal markings are made through coagulation 0.5 cm from the border of the tumor (Fig. 2C). After several dots are drawn around the lesion, normal saline mixed with epinephrine and indigo carmine is injected into the submucosal layer. A small incision is made with a HookKnife (Olympus, Tokyo, Japan) followed by a circumferential mucosal incision outside the marking. A circumferential incision was made with a HookKnife (Olympus) (Fig. 2D). Various knives, including the IT NanoKnife, HookKnife, and DualKnife (Olympus) were used to dissect the submucosal layer parallel to the muscle layer until the lesion is completely removed (Fig. 2E). Hemostasis is achieved with hemostatic forceps (FD-410LR; Olympus), hemoclips, or argon plasma coagulation. All visible non-bleeding vessels are coagulated after the completion of ER.

## Long-term outcomes

Several previous reports including long-term follow-up have identified ESD as a favorable treatment modality for the curative resection of SEC [25-32]. In a meta-analysis of 21 studies of ESD in the treatment of early EC, the pooled

en bloc resection rate was 99% [33]. The pooled complete (R0) resection rate was 90% (95% confidence interval [CI], 87%–94%), while for large tumors (those with diameters greater than 2.5 cm), the R0 rate was 85% (95% CI, 80%–90%). Relative to esophagectomy, ESD is a minimally invasive operation. ER of the mucosal lesions allows preservation of the normal anatomical structure of the digestive system without leading to postoperative reflux or weight loss [34]. This largely preserves the patient's short- and long-term quality of life. As of yet, no randomized trials have compared ESD and esophagectomy. Recently, 2 retrospective studies compared the outcomes of ESD and surgery for the treatment of T1 esophageal SCC (Table 1). In a Korean study by Min et al. [6], the ESD group exhibited lower procedure-related morbidity than the esophagectomy group. The overall rates of survival, disease-specific survival, and recurrence-free survival were comparable between the ESD and surgery groups. ESD can be considered a first-line treatment for patients with SEC without clear evidence of submucosal invasion [6]. In another study of patients with T1a-M2/M3 or T1b SEC who underwent ESD or esophagectomy in China, no significant difference was observed in overall survival recurrence, or metastasis in patients with T1a or T1b SEC treated with ESD or esophagectomy [7]. Furthermore, significantly fewer severe adverse events were reported in the ESD group than in the esophagectomy group (15.2% versus 27.7%,  $p < 0.001$ ).

## Adverse events

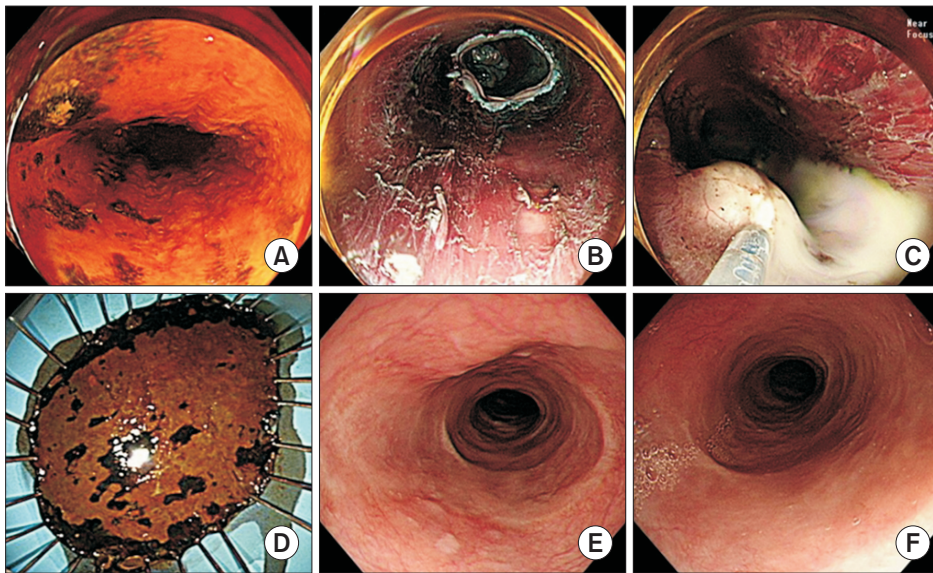
Complications of ESD for the treatment of SEN include



**Table 1.** Comparison of long-term outcomes between ER and SR for T1 SCC

Author (publication year)	No. of patients		FU period (mo)		R0 resection (%)		5-Year RFS (%)		5-Year OS (%)		5-Year DSS (%)	
	ER	SR	ER	SR	ER	SR	ER	SR	ER	SR	ER	SR
Min et al. [6] (2018)	157	191	43	63.5	NA	NA	92.8	95.3	93.9	91.2	100.0	97.4
Zhang et al. [7] (2019)	322	274	23	21	91.9	98.2	NA	NA	79.4	71.5	NA	NA
Yuan et al. [28] (2018)	69	47	43.8	49.4	92.7	100	NA	NA	91.5	97.1	98.5	100
Gong et al. [29] (2019)	78	128	NA	NA	73.1	100	NA	NA	NA	NA	NA	NA

ER, endoscopic resection; SR, surgical resection; SCC, squamous cell carcinoma; FU, follow-up; RFS, recurrence-free survival; OS, overall survival; DSS, disease-specific survival; NA, not available.



**Fig. 3.** Superficial esophageal cancer treated via circumferential ESD. (A) A 5-cm flat Lugol voided lesion on the mid thoracic esophagus. (B) An artificial ulcer appeared immediately after ESD and resulted in a mucosal defect affecting >75% of the circumference (C) Local injection of steroids. (D) The tumor was removed en bloc with tumor-free lateral and basal margins. (E) Follow-up endoscopy 7 months after ESD revealed no postprocedural stricture. (F) Follow-up endoscopy 15 months after ESD revealed no postprocedural stricture. ESD, endoscopic submucosal dissection.

bleeding (1.5%–1.8% of patients), perforation (1.5%–4.6% of patients), and strictures (6.5%–11.6% of patients), all of which can be managed endoscopically without serious long-term complications [25,35].

Esophageal ESD is characterized by the rare occurrence of postoperative bleeding, relative to ESD of the stomach and colorectum [36,37]. Acute bleeding during ESD can be successfully managed with hemoclips or coagulation forceps. Delayed bleeding is defined as sudden blood loss with hematemesis, melena, or an acute decrease in hemoglobin level of >2 g/dL occurring up to 1-month post-procedure; this complication may require an emergency endoscopy. The management of postprocedural hemorrhage during the repeated procedure is similar to the management of any other acute upper gastrointestinal hemorrhage. A prevention strategy can be useful to avoid bleeding-related complications. Visible blood vessels (1 mm or larger) in the submucosal layer should be preemptively subjected to hemostasis with a coagulation current. In addition, larger vessels should be grasped with a coagulation grasper and

treated with soft coagulation. Perforation during the procedure can be treated either with endoscopic closure involving a combination of an endoloop and clips or with stent placement. Delayed perforation due to the development of artificial ulcers following ESD is rare, but may require surgical intervention.

The most common late adverse event is esophageal stricture [38]. The reported incidence rate of strictures after ESD is 6.9%–18% [27,39]. Previous studies have reported that resection margins extending up to 75% of the entire esophageal circumference, M2 invasion depth, a >3-cm length of the mucosal defect, and excessive cautery during the procedure were independent risk factors of post-ESD esophageal stricture formation [39,40]. Endoscopic balloon dilatation (EBD) has been reported to be effective method in controlling post-ESD stricture [41]. Various innovative preventive modalities (including intralesional injection or oral administration of steroids and endoscopic transplantation of cell sheets, EBD followed by the administration of anti-inflammatory drugs, and the insertion of stents) can

be beneficial in managing the risk of stricture formation. The most prevalent method to prevent post-ESD stricture formation is the local injection of steroids or the administration of oral prednisolone (Fig. 3). The administration of steroids (odds ratio [OR], 0.108; 95% CI, 0.020–0.578;  $p=0.009$ ), specifically oral steroids (OR, 0.109; 95% CI, 0.019–0.622;  $p=0.013$ ), has been found to be associated with a lower rate of post-ESD strictures [42]. Since dysphagia secondary to post-ESD stricture decreases quality of life of patients, clinicians should be keep in mind that the size and circumferential extension of the tumor are associated with the risk of post-ESD esophageal stricture.

## Conclusion

In summary, ER of SENs has shown favorable clinical outcomes, suggesting that it may be an effective and safe treatment strategy. For clinical T1a (M1–M2) disease, ER can be a curative modality. For clinical T1a (M3) or T1b (SM1–SM2) disease, diagnostic ESD may be safely applied for organ preservation. Complications, such as strictures, may arise; therefore, the treatment and prevention of strictures may be crucial to preserve the patient's quality of life. Further studies of the technical aspects of ESD, as well as, detailed investigations with long-term follow-up data, are needed to determine the feasibility of ESD for the treatment of SEC that has invaded the muscularis mucosa (T1a M3) or submucosa (T1b).

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

## ORCID

Ga Hee Kim: <https://orcid.org/0000-0002-7652-2580>

Hwoon-Yong Jung: <https://orcid.org/0000-0003-1281-5859>

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