Endoscopic submucosal dissection for early esophageal neoplasia: A single center experience in South Taiwan

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Background/Purpose: Endoscopic submucosal dissection (ESD) is an advanced endoscopic procedure to resect early gastrointestinal neoplasm. It is technically more difficult and risky when used to treat early esophageal tumors. We report our experiences related to performing ESD for early esophageal neoplasia. The efficacy, complications, and outcome were also analyzed.

Methods: From December 2007 to April 2010, 22 patients with documented early esophageal neoplasm underwent ESD. All patients completed a meticulous endoscopic examination using conventional endoscopy followed by narrow-band imaging. Lugol’s staining was performed to identify the margin of the suspicious lesion. Insulation-tipped diathermic knife 2 was used for ESD.

Results: A total of 26 neoplastic lesions (including 13 tumors with high-grade dysplasia, 12 tumors with squamous cell carcinoma, and one tumor with adenocarcinoma) in 22 patients were enrolled. All patients were men. The mean age was 47.6 ± 8.6 years (range, 30–68 years). The mean size of tumors was 33.7 ± 21.7 mm (range, 8–80 mm). ESD was performed for 24 lesions in 20 patients. The mean size of resected specimens was 43.1 ± 19.2 mm (range, 15–90 mm). The mean operation time was 92.7 ± 69 minutes (range, 30–310 minutes). There were three ESD-related complications, including one with delayed bleeding, one with subcutaneous emphysema, and one with perforation. Two patients received additional operations after ESD due to deep submucosal invasion by cancer. Three lesions in two patients (12.5%) developed post-ESD esophageal stricture that needed repeated endoscopic bouginage. There was no procedure-related mortality. No local recurrence was found during the follow-up period.

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Introduction

For early esophageal neoplasia, endoscopic mucosal resection (EMR) has been shown to be a safer alternative, with long-term survival outcomes similar to those achieved with surgery.\(^1\) \(^4\) However, EMR is hampered by some technical limitations. Less than one-half of the patients treated with EMR have been reported to have an en bloc resection, and, in particular, en bloc resection of lesions larger than 20 mm is extremely difficult.\(^1\) \(^6\) Moreover, post-EMR recurrence or metachronous carcinoma has been reported in as many as 26% of the cases.\(^1\) \(^9\)

Using a new endoscopic knife, endoscopic submucosal dissection (ESD) was first developed for resection of early gastric cancer by Hosokawa and colleagues.\(^16\) ESD enables the endoscopist to achieve an en bloc resection regardless of the tumor size. Despite technical difficulties, ESD has been shown to be an effective and relatively safe treatment for the squamous cell carcinoma of the esophagus.\(^5\) \(^11\) \(^12\)

Esophageal cancer represents one of the most common malignancies worldwide and is currently the ninth leading cause of cancer death in Taiwan.\(^13\) Esophageal squamous cell carcinoma is a highly aggressive form of this malignancy with a 5-year survival rate of less than 20%.\(^14\) In Taiwan, only one report involved endoscopic mucosal resection of early esophageal neoplasia.\(^15\) Most preliminary applications of ESD have been performed exclusively in Japan; this is presumably because of the higher numbers of patients diagnosed with early esophageal cancer during screening endoscopy for asymptomatic patients.\(^16\)

To further enhance clinician’s understanding of the usefulness of this procedure and its related risks, we report our experiences in performing ESD for early esophageal neoplasia at E-Da hospital. The efficacy, complications, and outcome of ESD were also analyzed.

Materials and methods

From December 2007 to April 2010, patients at high risk of esophageal neoplasia (including cases of head and neck cancers and betel nut users) received meticulous screening of the esophagus with white-light endoscopy followed by magnifying endoscopy with narrow-band-imaging (NBI) system regardless of symptoms. When a well-demarcated brownish area with scattered brown spots, the microvascular pattern, was detected by the NBI system, further endoscopic magnification was employed to classify the intra-epithelial papillary capillary loop (IPCL) pattern (types I–V) according to the method proposed by Inoue and colleagues.\(^17\) \(^19\) For any lesion suspected to be neoplastic, Lugol staining was performed. All suspected lesions detected were biopsied for histological evaluation by a senior pathologist (Dr. J. C. Hwang). The final histopathologic diagnosis, which was based on the World Health Organization international histological classification,\(^20\) was either non-neoplasia (including inflammation, epithelial hyperplasia, and ulcer) or neoplasia (including low-grade dysplasia, high-grade dysplasia, and carcinoma). The diagnosis of “early” esophageal neoplasia included low-grade dysplasia, high-grade dysplasia, and carcinoma limited in the mucosa. Tumor location was classified as being in the upper, middle, lower third of the esophagus, or esophageal-cardiac junction. Endoscopic ultrasonography (EUS) was performed for invasion depth and regional lymph node. All patients underwent computed tomography (CT) of the chest and abdomen to confirm that there was no distant metastasis. Positron emission tomography (PET) was arranged in patients with biopsy-proved carcinoma or those with dysplasia but questionable regional lymph node detected by EUS or CT. Any patient with a suspicious submucosal-invasion lesion, or with any possibility of regional lymph node or distal metastasis by image study (EUS, CT, or PET) would not undergo ESD. Benefits and risks of ESD were informed to all patients and accompanied families. Informed consent was obtained for all of the patients.

ESD preparation and equipment

During the study period, 26 documented early esophageal neoplasia in 22 patients were enrolled for possible ESD at E-Da hospital in South Taiwan. A complete medical history was obtained before ESD, which included demographic and clinical data. Alcohol drinkers, betel nut chewers, and cigarette smokers were defined as those consuming any alcoholic beverage during the week, those who had chewed more than seven betel nuts per week, and those who smoked more than 10 cigarettes per week for at least 6 months, respectively.\(^21\) Dyspeptic symptoms were defined as nausea, vomiting, epigastric pain, or sensation of fullness. Reflux symptoms were defined as acid regurgitation or a retro-sternal burning sensation. Esophageal symptoms were defined as dysphagia or odynophagia. Patients underwent a fasting period in excess of 8 hours before receiving ESD. Endotracheal intubation and general analgesia were required and were performed by an anesthetist in one of our operating rooms. Patients were then placed in the left lateral decubitus position to receive ESD, which was conducted with a magnifying endoscope (GIF-H260Z, Olympus Optical Co., Ltd., Tokyo, Japan). The EVIS LUCERA SPECTRUM Video Imaging System (Olympus Optical Systems Co., Ltd., Tokyo, Japan) was employed for NBI. A distal attachment (D-201-11802; Olympus) was attached to the tip of the endoscope to obtain a constant endoscopic view
and to create tension on the connective tissue for the submucosal dissection.

**ESD procedure**

Prior to ESD, Lugol spraying was performed to demarcate the margin of the lesion. Several spots were marked at 2–3 mm outside the margin of the esophageal neoplasia by using argon plasma coagulation (ERBE, Tuebingen, Germany) to ensure a cancer-free margin. Next, using a 23-gauge disposable injector, 3–5 ml glycerol solution plus indigo-carmine with 0.0025% epinephrine was injected into the submucosa to lift the lesion. A circumferential incision was made initially, followed by submucosal dissection with the IT-knife 2 (KD-610L; Olympus Co. Ltd., Tokyo, Japan). To control bleeding, hemostatic forceps (FD-410LR; Olympus) were used in a soft coagulation mode (60-W output). This is shown in Fig. 1.

After resection, all patients were treated with oral sucralfate and an intravenously administered proton pump inhibitor (pantoprazole 40 mg) was given simultaneously for patients with lower esophageal lesions. The day after ESD, all patients received a second-look endoscopy to evaluate the condition of the wound. If there was no evidence of bleeding, the patient was put on a liquid diet followed by a soft diet the following day, and were then generally discharged within few days. If complications occurred, the patient’s schedules were changed according to the individual condition of each patient.

**Complications of ESD**

Immediate complications included massive bleeding, emphysema, and perforation during ESD. Latent complications included delayed bleeding and perforation after ESD. Massive bleeding was defined as blood loss >500 ml or a hemoglobin drop >2 g/dl. Perforation was diagnosed when other organs, extraluminal fat, or the extraluminal space were observed endoscopically through the muscle layer during ESD. Mediastinal emphysema was diagnosed by the presence of air in the mediastinal space. A postoperative stricture was defined as a stricture that required endoscopic treatment.

**Figure 1**  (A) Chromoendoscopy with Lugol staining revealed a 2 × 2 cm Lugol-voiding area in the mid esophagus; (B) an artificial ulcer after ESD; (C) a 3 × 3 cm resected specimen with the lesion in en bloc fashion is shown; (D) pathology revealed a well-differentiated squamous cell carcinoma with lamina propria invasion (hematoxylin and eosin, 40×). ESD = endoscopic submucosal dissection.
Histologic assessment

The resected specimens were fixed on a piece of board and immersed in 4% formalin for the final pathologic examination. After being embedded in 100% paraffin, all specimens were cut into 2-mm slices and stained with hematoxylin and eosin. The tumor size, depth of invasion, lymphovascular invasion, grade of differentiation, and resection margins were histopathologically examined. The depth of invasion was subclassified as intraepithelial cancer (m1), cancer invading the lamina propria (m2), and cancer invading the muscularis mucosae (m3). In patients in whom the cancer was invading the superficial portion of the submucosa, the invading depth was defined as sm-minor. On the other hand, if the cancer was invading the deep portion of the submucosa, the invading depth was defined as sm-massive. One-piece resection was defined as en bloc resection. R0 resection was considered to have a tumor-free margin when vertical and horizontal margins were free of tumor cells.

Follow-up

Post-ESD treatment (surgery or chemoradiation) was considered for patients with an incomplete resected margin at histology. In those patients in whom ESD was considered the definitive treatment, they received an upper GI endoscopy at follow-up 1 month after ESD and then again at regular follow-up every 3 months during the first year after ESD. After the first year, patients received this examination every 6 months and then annually thereafter. Lugol spraying was applied during follow-up and endoscopic biopsies were taken from any Lugol-voiding areas to identify any residual or recurrent neoplasia.

Results

Characteristics of the study population

A total of 26 early-stage esophageal neoplasia in 22 patients [including 13 (50%) lesions with high-grade dysplasia, 12 (46.2%) with squamous cell carcinoma, and 1 (3.8%) with adenocarcinoma] were detected during this period. The demographic characteristics of these patients are presented in Table 1. All of the patients were men. The mean age was 47.6 ± 8.6 years (range, 30–68 years). Smoking (100%), alcohol drinking (100%), and betel nut chewing (72.7%) were prevalent social behaviors. A total of 16 (72.7%) patients had history of head and neck cancers. One-half of the patients were asymptomatic, six (27.3%) patients had dyspeptic symptoms, three (13.6%) patients had dyspeptic symptoms, and only two (9.1%) patients had esophageal symptoms.

Endoscopic and pathologic characteristics

The endoscopic and pathological characteristics of these lesions are summarized in Table 2. The mean size of tumors was 33.7 ± 21.7 mm (range, 8–80 mm). Overall, four

Table 2  Endoscopic and pathologic characteristics of early esophageal neoplastic lesions.

<table>
<thead>
<tr>
<th>Total lesions (n = 26) a</th>
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<tbody>
<tr>
<td>Tumor location</td>
</tr>
<tr>
<td>Upper third esophagus</td>
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<tr>
<td>Middle third esophagus</td>
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<tr>
<td>Lower third esophagus</td>
</tr>
<tr>
<td>Esophagocardial junction</td>
</tr>
<tr>
<td>Tumor morphology</td>
</tr>
<tr>
<td>Type-0 IIa</td>
</tr>
<tr>
<td>Type-0 IIb</td>
</tr>
<tr>
<td>Type-0 IIc</td>
</tr>
<tr>
<td>Tumor size in mm, mean</td>
</tr>
<tr>
<td>Circumferential extension of tumor</td>
</tr>
<tr>
<td>&lt;1/2</td>
</tr>
<tr>
<td>&lt;3/4</td>
</tr>
<tr>
<td>≥3/4</td>
</tr>
<tr>
<td>Final pathology</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Depth of tumor invasion</td>
</tr>
<tr>
<td>Mucosa</td>
</tr>
<tr>
<td>m1</td>
</tr>
<tr>
<td>m2</td>
</tr>
<tr>
<td>m3</td>
</tr>
<tr>
<td>Submucosa</td>
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<tr>
<td>sm-minor</td>
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<td>sm-massive</td>
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</table>

SD = standard deviation.

a 26 lesions detected in 22 patients.
were located in the upper esophagus, 15 (57.7%) in the middle third, six (32.1%) in the lower third, and one (3.8%) in the esophagocardial junction. The macroscopic type was IIa in three (11.5%) lesions, IIb in 12 (46.2%), and IIc in the remaining 11 (42.3%) lesions. Fourteen (53.8%) lesions extended less than one-half of the circumference of the esophageal lumen, but two (7.7%) extended more than three-fourths of the circumference.

Regarding depth of invasion, intraepithelial cancer (m1) was diagnosed in 18 (69.2%) lesions, cancer invading the lamina propria mucosae (m2) in two (7.7%), cancer invading the muscularis mucosae (m3) in two (7.7%), and cancer invading superficial submucosa (sm-minor) in two (7.7%), whereas deep submucosal invasion (sm-major) was reported in the remaining two (7.7%) patients.

**Endoscopic submucosal dissection**

ESD was performed for 24 lesions in 20 patients, except for two patients with bleeding tendency. The mean procedure time was 92.7 \pm 69 minutes (range, 30–310 minutes). The mean size of resected specimens was 43.1 \pm 19.2 mm (range, 15–90 mm). At endoscopy, en bloc resection of the lesion was successful in 23 (95.8%) lesions. Resection-free margins (R0 resection) were achieved in 21 (87.5%) lesions. Only two lesions presented with incomplete resection due to deep submucosal invasion, and ESD was stopped in one patient due to severe subcutaneous emphysema during the procedure.

There were three (12.5%) ESD-related complications: one with delayed bleeding, one with perforation during ESD, and one with mediastinal/subcutaneous emphysema during the procedure. Regarding patients with ESD-related complications, one with delayed bleeding received successful endoscopic hemostasis, one with mediastinal/subcutaneous emphysema received supportive treatment, and the remaining patient with perforation during ESD received urgent operation due to unstable vital signs. All three patients were discharged without sequela. Additional esophagectomies were performed in two patients due to deep submucosal invasion by the cancer. Three lesions (12.5%) in two patients developed post-ESD esophageal stricture who needed repeated endoscopic bouginage (Fig. 2). There was no procedure-related mortality. No local recurrence was found during the follow-up period (mean, 11.5 months). These results are shown in Table 3.

**Figure 2** (A) Chromoendoscopy with Lugol staining revealed a IIb Lugol-voiding area with extension more than one-half of the circumference of the esophageal lumen; (B) postoperative stricture developed 3 months after ESD; (C) balloon dilation performed for esophageal stricture; (D) stricture resolved after balloon dilation. ESD = endoscopic submucosal dissection.
Discussion

ESD is increasingly gaining acceptance and is currently the treatment of choice for superficial esophageal neoplasia in Japan. However, most of these preliminary applications of ESD have been exclusively performed in Japan. Our study shows that ESD is also a greatly effective, technically feasible, and relatively safe treatment for selected early esophageal neoplasia in Taiwan. The 87.5% rate of en bloc R0 resection of our study is in-line with the rates of 78%–93% reported by previous Japanese series. Similarly, the 12.5% major complication rate is also comparable with the rates of the 13%–22% range extrapolated from the Japanese studies.

When dealing with large lesions, ESD allows en bloc resection in the majority of the patients and represents a substantial improvement compared with standard EMR, in which en bloc resection of neoplasia 20 mm or larger was feasible in only 4%–43% of the cases. In this study, the mean size of the tumors was 33.7 mm in diameter and the mean size of resected specimens obtained was 43.1 mm in diameter. The higher efficacy of ESD compared with that of EMR is also confirmed by the net difference of local recurrence rates. Post-EMR local recurrence rate has been consistently shown to be as high as 26%–43% of the cases. On the other hand, only 0%–3% rates of local recurrence were reported with a R0 ESD in previous studies. In our study, there was no local recurrence during the follow-up period.

Esophageal cancer is highly aggressive with a low survival rate worldwide. This disappointingly low survival rate can be attributed, at least in part, to ineffective screening tools and guidelines such that most patients have late stage or unresectable diseases at presentation. For these reasons, we have conducted a prospective screening project by using NBI followed by high magnification in patients with head and neck cancers, and betel nut users since April 2008. In this study, the majority (72.7%) of patients had a history of head and neck cancer and one-half involved high-grade dysplasia of the esophagus. Most patients were diagnosed with early-stage esophageal neoplasia after screening. In fact, our previous work had demonstrated that NBI followed by high magnification significantly increases the accuracy of detection of esophageal neoplasia, especially at an early stage of the disease and patients with alcohol consumption, oropharynx or hypopharynx cancer were associated with the development of synchronous esophageal neoplasia.

This strongly implicated routine screening of esophageal neoplasia is beneficial and mandatory for such high-risk patients.

From a technical point of view, ESD appears to be a demanding procedure, especially for the esophagus. The esophageal wall is thinner than that of the stomach. It will move with respiratory motion and heart beat, which will interfere adequate examination and therapeutics. Moreover, the esophageal lumen is narrow, precluding knife maneuverability and endoscope retroflexion. For these reasons, esophageal ESD seemed to be a more time-consuming and risky procedure. Besides, esophageal ESD seems to be associated with a relatively high risk of major complications, such as emphysema, stricture, and perforation. Most series reported a 4%–7% rate of perforation during ESD, which was similar to our result. Although perforation can be temporarily clipped by hemoclips, our patient with perforation developed unstable vital signs during the procedure this resulted in an urgent operation. Fortunately, there was no sequela after operation.

In a recent study from Japan, up to 31% patient developed pneumomediastinum after ESD by chest CT scan. The authors mentioned that endoscopic muscle exposure during ESD is a significant risk factor and all patients recovered well after conservative treatment without any clinically significant complications. There was one patient with severe subcutaneous emphysema resulting postponed ESD in our series. He recovered well under supportive treatment.

Bleeding during ESD is inevitable and can be managed with coagulation forceps and hemoclipping. Delayed bleeding may occur, especially in patients with early gastric cancer after ESD. A recent, retrospective study concluded that a second-look endoscopy after gastric ESD may contribute little to the prevention of delayed bleeding. There was no solid evidence supporting the role of a second-look endoscopy after esophageal ESD yet. Since limited experience, we performed a second-look endoscopy for all patients after ESD. One patient suffered delayed bleeding and endoscopic hemostasis was performed successfully.

Postoperative stricture after esophageal ESD is a major complication in long-term follow-up. Esophageal stricture can evoke severe dysphagia, and results in a decrease in quality of life or, occasionally, aspiration pneumonia. There were three (12.5%) lesions that developed post-ESD stricture that required endoscopic balloon dilatation in our study. This result is within the 6.8%–18% range reported by

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Table 3: ESD for 24 esophageal neoplastic lesions: Procedures and complications.

<table>
<thead>
<tr>
<th>Total lesions in 20 patients</th>
<th>Procedure time in min, mean ± SD (range)</th>
<th>Diameter of resected specimen in mm, mean ± SD (range)</th>
<th>En-bloc resection</th>
<th>R0 resection</th>
<th>ESD-related complications</th>
<th>Massive bleeding during ESD</th>
<th>Delayed bleeding</th>
<th>Perforation during ESD</th>
<th>Subcutaneous emphysema</th>
<th>Blood transfusion</th>
<th>Emergent surgery</th>
<th>Additional surgery</th>
<th>Esophageal stricture need</th>
<th>Bougination after ESD</th>
<th>Local recurrence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>92.7 ± 69.0 (30–310)</td>
<td>43.1 ± 19.2 (15–90)</td>
<td>23 lesions (95.8%)</td>
<td>21 lesions (87.5%)</td>
<td>3 (12.5%)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0 (0%)</td>
<td>1 (4.2%)</td>
<td>2 (8.3%)</td>
<td>3 (12.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

ESD = endoscopic submucosal dissection; SD = standard deviation.

a Two with confirmed deep submucosal invasion.

b Mean follow-up period was 11.5 months (range, 0–28 months).
previous series.11, 12, 23, 26–28 Mizata and colleagues26 reported that a lesion more than one-half of the circumference of the esophageal lumen was a predictive factor for esophageal stenosis after ESD. Ono and others27 also described that a more than three-fourths of the circumferential extension of tumor and tumor invasion depth more than lamina propria (m2) were two major predictive factors. Once esophageal stricture developed after ESD, repeated endoscopic balloon dilatation remains the most effective treatment method. Although there are no solid criteria, some endoscopists perform preventive balloon dilatation. Further large-scale studies would be needed to address this issue.

The current study raises some concerns. First, we only performed PET for patients with biopsy-proved carcinoma or those with dysplasia but questionable regional lymph node detected by EUS or CT. Previous studies had showing PET to have a relatively low accuracy for tumor depth and regional lymph node staging in early-stage esophageal cancer as compared with EUS alone or EUS combined with CT.29–31 Accordingly, EUS and CT provide better information for regional staging in early-stage esophageal cancer. In our series, patients were not considered to receive ESD if regional lymph node metastasis suspected by any image studies. Secondly, our result indicated that pre-ESD EUS or CT.29 regional lymph node staging in early-stage esophageal cancer. This finding was in concordance with other reports that the sensitivity of EUS for tumor invasion was about 80% for early-stage lesions.32 Since the rate of lymph node metastasis increases in cancers with submucosal invasion, further adjuvant therapy (such as esophagectomy, radiotherapy, or chemotherapy) will be needed in these patients. Finally, in spite of no local recurrence during follow-up period in our patients, longer observation needed to make such conclusion. Local recurrence and distal metastasis after ESD had been demonstrated in previous studies.33, 34, 35 Therefore, regular follow-up for these patients may be warranted.

In conclusion, ESD is a promising local curative treatment option for early esophageal neoplasia in Taiwan, but it still carries the risks of perforation and bleeding. Esophageal stricture is an important concern to be aware of in the postoperative review of patients undergoing this procedure. Education regarding this procedure and more hands-on training will facilitate endoscopists to improve the outcome of this procedure.

References


