

# Endoscopic Submucosal Dissection for Gastric Epithelial Tumors: A Multicenter Study in Taiwan

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**Background/Purpose:** Endoscopic submucosal dissection (ESD) is an advanced endoscopic procedure to resect early gastric cancer (EGC). The purpose of this study was to determine the effectiveness and complications of ESD for gastric epithelial tumors in Taiwan.

**Methods:** We retrospectively analyzed the efficacy and outcome of ESD in patients who received ESD for gastric epithelial tumors between June 2004 and August 2007.

**Results:** A total of 70 patients with gastric epithelial tumors were treated by ESD. The mean age was  $66.5 \pm 12.9$  years (range, 35–84 years). The mean size of the gastric epithelial tumors was  $1.85 \pm 0.81$  cm. The mean size of resected specimens was  $3.26 \pm 1.39$  cm. The one-piece resection rate was 91.4% (64/70). The median operation time was 92.4 minutes. The complicating bleeding and perforation rates were 5.7% (4/70) and 4.3% (3/70), respectively. Emergency surgery was performed for three patients with perforations. The local recurrence rate of gastric cancer was 2.8%. Except for one patient who died of congestive heart failure and another who died of stroke, the remaining 68 patients (97.1%) survived.

**Conclusion:** ESD is a promising local curative treatment option for EGC in Taiwan but it still carries risks of perforation and bleeding. The education and learning curve of endoscopists will improve the outcome of this procedure. [*J Formos Med Assoc* 2009;108(1):38–44]

**Key Words:** endoscopic submucosal dissection, gastric epithelial tumors

Endoscopic mucosal resection (EMR) is widely accepted as a standard and useful treatment for early gastric cancer (EGC).<sup>1,2</sup> The original strip biopsy technique was advocated by Tada et al in 1993.<sup>1</sup> Modification of EMR by using a transparent cap (EMR-C), which was later developed by Inoue et al, was commonly used for treatment of early gastroesophageal tumors.<sup>2</sup> By using the strip biopsy

method and EMR-C, however, it remains difficult to remove a gastroesophageal cancer with a diameter greater than 2 cm and/or with ulceration or submucosal fibrosis. Hosokawa et al developed a new endoscopic knife, an insulation-tipped diathermic knife (IT-knife), with a ceramic ball at the top of the incising needle to prevent leakage of electricity toward the deeper layer of the stomach.<sup>3</sup>

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Experiments with swine stomach have shown that the IT-knife resects only the mucosal and submucosal layers without histologically evident burning effects in the serosa, and it is also possible to resect canine gastric mucosa successfully *in vivo*. After these promising experimental results in animal models, the device was introduced into the clinic in 1994.<sup>3</sup> Miyamoto et al<sup>4</sup> and Ono et al<sup>5</sup> have provided a better method for *en bloc* resection of gastric neoplasms larger than 30 mm in size. The definition, indication and application of endoscopic submucosal dissection (ESD) of early gastric cancer (EGC) have been expanded by Gotoda et al, at the National Cancer Center Hospital in Japan.<sup>6</sup> Although utilization of ESD in the treatment of EGC has become very popular in Japan, clinical experience and preliminary results of ESD for gastric epithelial tumors have been reported rarely outside Japan. Here, we report 70 patients with gastric epithelial tumors that were resected by ESD in a multicenter study in Taiwan.

## Methods

### Patients

We enrolled a total of 70 patients who received ESD for gastric epithelial tumors between June 2004 and August 2007. The indications for ESD followed mainly the guidelines of Gotoda et al,<sup>6</sup> except for two patients with poorly differentiated adenocarcinoma who refused surgery. The diagnosis of EGC was based on histologic confirmation of cancer invasion limited within the mucosal and submucosal layers. Forty patients received endoscopic ultrasonography for staging work-up. The majority of ESD procedures were performed at three medical centers including Taipei Medical University Hospital (10 cases), Chiayi Chang Gung Memorial Hospital (32 cases) and Tri-Service General Hospital (16 cases). The rest of the ESD procedures were performed at Taipei Veterans General Hospital (four cases), E-Da Hospital (four cases), Changhua Christian Hospital (two cases), National Taiwan University Hospital (one case), and Kaohsiung Chang Gung Memorial Hospital (one case).

### Instruments

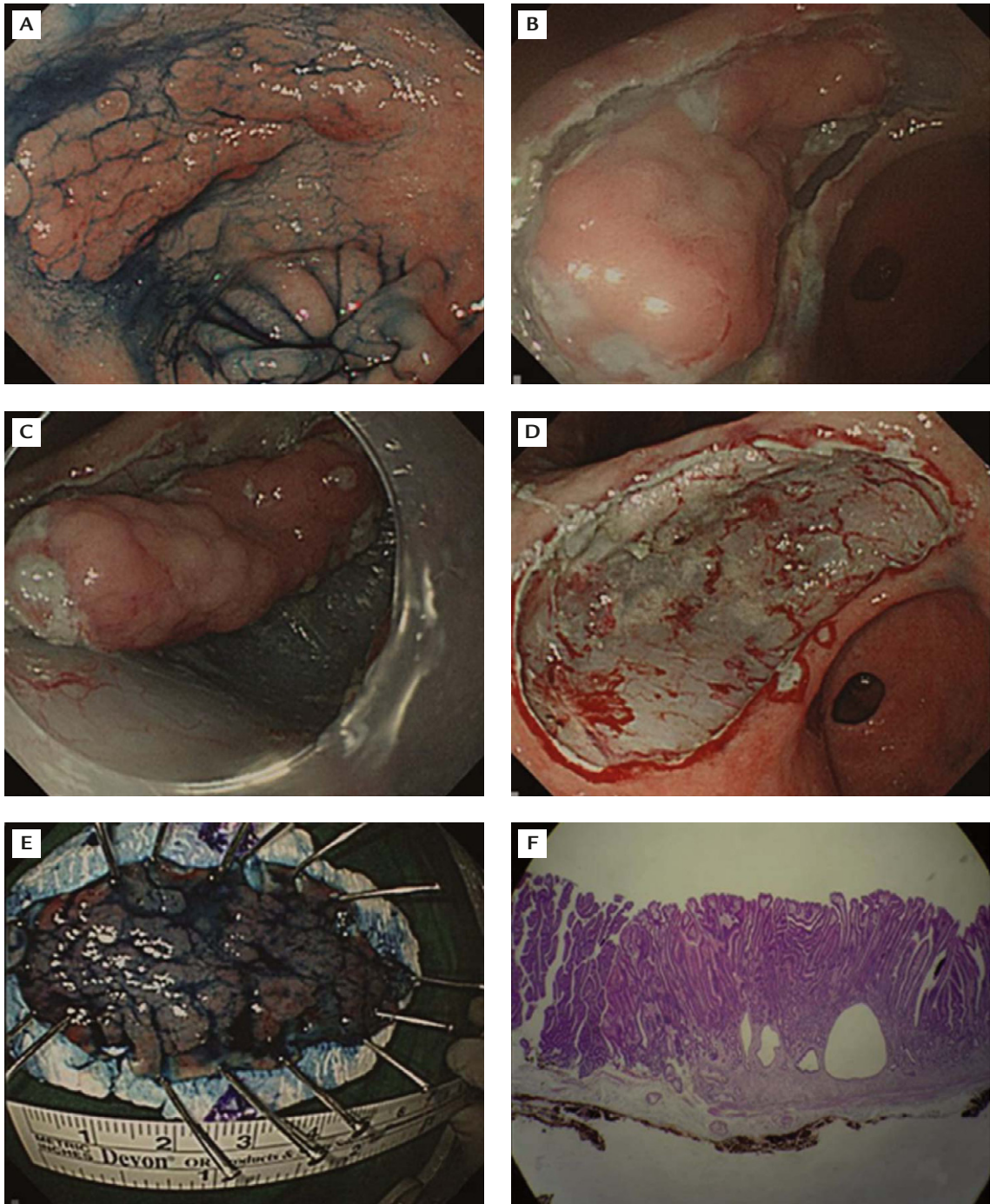
The instruments used for ESD included an endoscope and accessories, knife, and electrosurgical unit. The IT-knife and needle knife (KD 610L and KD-1L-1; Olympus Co. Ltd., Tokyo, Japan) were utilized most often. The PSD-60 (Olympus) or ICC-200 (ERBE, Tuebingen, Germany) were the two most commonly used electrosurgical units. The procedure was performed by using a conventional single-channel endoscope (GIF-Q240, GIF-Q260; Olympus). A hood (D-201-11802; Olympus) was attached to the tip of the endoscope for the submucosal dissection.

### Procedure

The procedure of ESD is similar in all institutes in Taiwan. A sample patient with EGC resected by ESD is described here. Prior to ESD, chromoendoscopy with 0.2% indigo carmine was performed to demarcate the margin of the gastric epithelial tumor. Several spots were marked at 5–10 mm outside the margin of the gastric epithelial tumor by using a needle knife to ensure a cancer-free margin. Next, using a 23-gauge disposable injector, 1–4 mL normal saline plus indigo carmine with 0.0025% epinephrine were injected into the submucosa to lift the lesion. A circumferential incision was made initially, followed by submucosal dissection with the IT-knife (Figures A–D). After ESD, an intravenous proton pump inhibitor (PPI) with a regular dose was given to all patients for 3 days.

Tumor location was classified as being in the upper, middle or lower third of the stomach.<sup>7</sup> One-piece resection was defined as *en bloc* resection. Resection was considered to have a tumor-free margin when the vertical and horizontal margins were free of tumor cells.

Resected specimens were fixed on a board with pins and cut into 2-mm slices according to the Japanese Classification of Gastric Carcinoma.<sup>7</sup> All specimens were evaluated histologically as to whether tumorous glandular tissue was present at the margin of each slice. Histopathologic diagnosis was based on the World Health Organization (WHO) criteria (Figures E and F).



**Figure.** (A) 0.2% indigo carmine-aided chromoendoscopy demonstrated a 5 × 3 cm IIa gastric epithelial tumor at the anterior wall of the gastric antrum. (B) Circumferential incision for the gastric epithelial tumor. (C) ESD with a transparent hood. (D) A 6 × 4 cm<sup>2</sup> mucosal defect after ESD. (E) A 6 × 4 cm<sup>2</sup> resected specimen fixed on a board with pins. (F) Pathology showed a well-differentiated intramucosal cancer (hematoxylin & eosin, 40×).

### *Complications of ESD*

Complications including massive bleeding and perforation were recorded after ESD. Massive bleeding was defined as blood loss > 500 mL. Perforation was diagnosed when other organs,

extraluminal fat, or the extraluminal space were observed endoscopically through the muscle layer during ESD, irrespective of the presence of air accumulation in the abdomen, retroperitoneum or mediastinum.

### Residual and recurrent tumors after ESD

Endoscopic re-examination was carried out every 2–3 months during the first year after ESD, every 6 months during the second year, and annually thereafter. In each endoscopic follow-up session, endoscopic biopsies were routinely taken from the surrounding areas of previous ESD and any suspicious lesions nearby, and histologic examination was carried out to identify any residual or recurrent cancer.

## Results

A total of 70 patients received ESD for gastric epithelial tumors; their demographic characteristics are presented in Table 1. There were 45 men and 25 women with a mean age of 66.5 years. The majority of the tumors were located in the

middle ( $n = 14$ ) and lower ( $n = 51$ ) stomach. The majority of the tumors were classified as flat, elevated superficial cancer, type IIa ( $n = 33$ ) and IIa + IIc ( $n = 20$ ), by endoscopic morphologic classification. The mean diameter of the tumors was 1.85 cm and that of the resected specimens was 3.26 cm. The depth of the gastric epithelial tumors was evaluated after pathologic assessment: 64 tumors were limited to the mucosal layer, two to the submucosal superficial layer ( $< 500 \mu\text{m}$  to the muscular muscle layer) and four to the deep submucosal layer. According to the final pathologic classification, the majority of EGCs resected were high-grade dysplasia ( $n = 26$ ) and well-differentiated adenocarcinoma ( $n = 25$ ). However, there were 12 tumors with low-grade dysplasia and two with poorly differentiated adenocarcinoma resected by ESD.

The one-piece resection rate with tumor-free margins was 91.4% (64/70). There were six patients who failed to be resected by *en bloc* resection. There were three patients with perforation; one patient with the tumor located at the posterior wall of the gastric antrum, one with the tumor located at the posterior wall of the middle gastric body, and one with the tumor located near the cardia. The median operation time was 92.4 minutes (range, 25–210 minutes). The median length of stay was 8.7 days (range, 4–26 days).

The complications and local recurrence after ESD are shown in Table 2. Four (5.7%) patients had massive bleeding during ESD and only two (2.8%) needed blood transfusions. The amount of blood lost from these four patients was 600, 700, 1000 and 1200 mL, respectively. The last two patients received blood transfusion after ESD. There were three (4.3%) patients who had

**Table 1.** Demographic characteristics of 70 patients with gastric epithelial tumors who underwent endoscopic submucosal dissection\*

Age (yr)	66.5 ± 12.9 (35–84)
Gender (male/female)	45/25
Tumor location (upper third/middle third/lower third)	5/14/51
Tumor gross appearance (I/IIa/IIb/IIc/IIa + IIc)	5/33/2/10/20
Tumor size (cm)	1.85 ± 0.81 (0.8–4.0)
Resected specimen size (cm)	3.26 ± 1.39 (1.2–8.0)
Depth of tumor (mucosa/submucosa)	64/6
Tumor pathology	
Low-grade dysplasia	12
High-grade dysplasia	26
Well-differentiated adenocarcinoma	25
Moderately-differentiated adenocarcinoma	5
Poorly-differentiated adenocarcinoma	2

\*Data presented as mean ± standard deviation (range) or n.

**Table 2.** Complications and local recurrence after endoscopic submucosal dissection\*

Massive bleeding	4 (5.7)
Blood transfusion	2 (2.8)
Perforation	3 (4.3)
Emergent surgery	3 (4.3)
Local recurrent cancer	2 (2.8)

\*Data presented as n (%).

the complication of perforation during ESD and they were sent for emergent surgery. Among these, two patients with upper gastric tumors and one with a lower gastric tumor perforated after ESD. The two perforated upper gastric tumors were a 2.5-cm and a 1.5-cm intramucosal cancer. The one perforated lower gastric tumor was a 1.5-cm submucosal cancer.

Curative treatment was defined as tumor-free margins, including lateral and vertical margins, no lymphovascular involvement, and tumor depth limited to the submucosal superficial layer (<500  $\mu\text{m}$  to the muscular muscle layer) after pathologic assessment. Sixty-five (92.8%) patients had curative treatment with ESD for gastric epithelial tumors. Five (7.2%) patients had non-curative treatment with ESD. One of these five patients had a cancer-involved vertical margin and four had submucosal deep cancer. These five patients were advised to undergo additional surgery but they all refused because of comorbidity with major systemic diseases, such as congestive heart failure and chronic renal insufficiency. Unfortunately, two (2.8%) patients had local recurrence and then received surgery. None of the patients died of gastric cancer-associated diseases during the follow-up period. One patient died 8 months after ESD because of congestive heart failure and another died 2 years after ESD because of a stroke. All the other patients (97.1%) survived.

## Discussion

Endoscopic resection is currently the treatment of choice for EGC in Japan. Outside Japan, this technique is increasingly gaining acceptance.<sup>8,9</sup> Endoscopic resection offers similar efficacy to surgery, and it is also minimally invasive. Endoscopic resection for gastric tumors is superior to other treatments such as argon plasma coagulation therapy or photodynamic therapy because it allows complete pathologic staging of the cancer after the procedure.<sup>10</sup> This is critical as it allows stratification and refinement of further treatment.<sup>11</sup>

In comparison with the risk of morbidity and mortality from surgery, patients with EGC who are at no or lower risk for developing lymph node metastasis are ideal candidates for endoscopic resection.<sup>12</sup>

EMR is accepted as an effective treatment for EGC. However, the standard EMR technique is usually inadequate for cancerous lesions greater than 20 mm in diameter. The local recurrence rates associated with incomplete EMR reported to date have been high (9–18%).<sup>5,13,14</sup> Incomplete resection leading to recurrent cancer in the residual stomach therefore continues to be a difficult problem.

ESD is superior to standard EMR because it can be accomplished easily using a standard single-channel gastroscope. ESD also has the advantage of achieving large *en bloc* resection, which allows precise histologic staging and reduced disease recurrence compared with standard EMR methods. In this study, the mean size of the resected specimens obtained was 3.26 cm and the mean size of the tumors was 1.85 cm. We confirmed that ESD can be utilized effectively to resect small superficial gastric cancer with a diameter less than 2 cm.

One-piece resection of the gastric tumor is important. It had lower local recurrence rate than piecemeal resection for gastric cancer. The one-piece resection rate in this study was (91.4%), which is lower than that (94.2%) of Onozato et al.<sup>15</sup> The reason for a lower one-piece resection rate was possibly inexperience in dealing with difficult locations of the gastric tumors.

Twelve gastric tumors, initially diagnosed as EGC, turned out to be low-grade dysplasia after resection and final pathologic examination. This could be explained by the discrepancy between different degrees of dysplasia and carcinoma, especially among various pathologists in the different institutes. Second opinions from other pathologists and unified pathologic criteria to define the dysplasia and carcinoma *in situ* are therefore needed before performing ESD. There were two gastric tumors with poorly differentiated adenocarcinoma resected by ESD, which were contradictory to the guidelines from the Japanese Gastric

Cancer Association.<sup>7</sup> The indications of ESD should be re-emphasized and strictly followed by endoscopists and pathologists in Taiwan.

The perforation rate in this study was 4.3%, which is similar to that (4%) of Gotoda's study.<sup>16</sup> Perforation in our patients occurred more frequently in the tumors located in the upper stomach. This situation has also been reported by Gotoda.<sup>16</sup> Although perforations can be temporarily clipped by hemoclips, none of our endoscopists performed this procedure to rescue perforations because of inexperience and difficult tumor locations. The bleeding rate in this study was 5.7%, which is less than that (7%) of Gotoda's.<sup>16</sup> Whether intravenous proton pump inhibitors for the initial 3 days after ESD are beneficial in reducing the bleeding rate requires to be confirmed by a larger scale randomized study.

Apart from IT-ESD, there are other ESD techniques that have been described, including the hook knife,<sup>17</sup> flex knife<sup>18</sup> and the knife in a small cap technique.<sup>19</sup> Chiu et al have also reported safely combining the use of these knives in dissecting early neoplasia of the foregut.<sup>20</sup>

There were several limitations in the current retrospective study. First, the case number in this study was too small to make a final conclusion. Second, this was a multicenter study. Different skills, experience, learning curves, and attitudes of endoscopists will give heterogeneous results. The learning curve is crucial for endoscopists performing ESD. Gotoda et al have advised that a trainee requires at least 30 cases to gain early proficiency in this technique.<sup>21</sup> Inexperienced endoscopists may be associated with a higher risk of procedure-related complications such as bleeding and perforation, and also with a higher risk of incomplete resection. Moreover, the pre-existent differences in the interpretation of histologic results among different pathologists will also result in discrepancies before and after ESD.

In conclusion, ESD is a promising local curative treatment option for EGC in Taiwan, but it still carries risks of perforation and bleeding. The education and learning curve of endoscopists will improve the outcome of this procedure.

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