Applying Endoscopic Submucosal Dissection for Treating Early Gastric Cancer

José Galindo¹, Jorge Rodríguez², Enrique Norero¹, Gloria Aguayo⁴, Martha Pruyas⁴, Eva Nilsen⁴, Cristián Martínez³, Sergio Báez³, Alfonso Díaz³, Alfonso Calvo²,³,⁵*

¹Department of Digestive Surgery, Pontificia Universidad Católica de Chile, Santiago, Chile
²Therapeutic Endoscopy Unit, Hospital Dr. Sótero del Río, Santiago, Chile
³Department of Surgery, Hospital Dr. Sótero del Río, Santiago, Chile
⁴Department of Pathology, Hospital Dr. Sótero del Río, Santiago, Chile
⁵Endoscopy Unit, CRS San Rafael, La Florida, Santiago, Chile

Abstract: Introduction: Endoscopic submucosal dissection (ESD) is a standard method for the treatment of early gastric cancer and low risk of lymph node metastasis. Its advantage is to obtain a higher negative edge rate than mucosal resection and less trauma than surgery. Objectives: The short-term prognosis, pathological anatomy and long-term survival of ESD patients in our center were analyzed. Methods: Descriptive research. The clinical records of patients with early gastric injury treated with ESD from January 2008 to June 2012 were reviewed. Results: There were 15 patients included, 8 males and 7 females. The median age was 70 years (45–88). Tumor location: 2 cases in the upper third, 5 cases in the middle third and 8 cases in the lower third. The median tumor size was 13.5 mm (6–21). Most injuries are IIc. Among the postoperative complications, 1 case of gastrointestinal bleeding was treated by endoscopy and 3 cases of gastric perforation (gastric anastomosis) were treated by surgery. The average hospitalization was 3 days (1–23). There was no death record after operation. 86.7% of the cases had a negative edge. One case was positive at the deep edge after subtotal gastrectomy, and the other case was positive at the lateral edge. A new ESD treatment was used. The median follow-up was 16 months (7–61), and there was no pathological death of tumor. One case of tumor recurrence (51 months) was treated surgically. Conclusion: ESD is an alternative to the treatment of early gastric injury, allowing a high proportion of negative edges.

Keywords: Early gastric cancer, Endoscopic dissection, Endoscopy

1 Introduction

Gastric cancer is the second leading cause of cancer death[1]. Its prognosis remains poor due to the fact that in most cases the diagnosis is late. According to population records, the five-year survival rate in western countries is no more than 15%[2,3].

In 1962, the Japanese Society of Gastrointestinal Endoscopy defined early gastric cancer as infiltrating mucosa or submucosa, with or without
lymph node infiltration, and is curative if detected at this stage.

Traditionally, radical surgery is the first choice for the treatment of early and advanced gastric cancer, with 5-year survival rates of 92.2% and 89.1% in mucinous cancer and submucosal cancer, respectively, and low locoregional recurrence rate\textsuperscript{[4,5]}. These patients have a risk of lymphatic spread of 3% for mucosal tumors and 18% for submucosal tumors\textsuperscript{[6]}. Therefore, a considerable number of patients with early gastric cancer can be treated with more invasive methods than radical gastrectomy.

The first case of endoscopic polypectomy was published in 1974. In the 1980s, various endoscopic mucosal resection (EMR) techniques were published, using different types of attachments. In the 1990s, the characteristics of lesions amenable to endoscopic resection were defined\textsuperscript{[7,8]}. However, EMR has several disadvantages, such as obtaining eccentric parts, increasing local recurrence rate, difficulty in histological analysis, and only allowing resection of small tumors.

At present, endoscopic submucosal dissection (ESD) is the first choice for the treatment of early gastric cancer, and expands the standard of endoscopic resection\textsuperscript{[9-12]}. The purpose of this study was to describe the short-term results, histological analysis, and overall and disease-free survival of patients with early gastric tumors treated with ESD in our center.

2 Materials and methods

2.1 Design

Retrospective study. These data were obtained through a review of all endoscopic operations at Hospital Dr. Sótero del Río. From January 2008 to June 2012, all patients with early gastric tumors treated with ESD were continuously included in the study.

Most candidates for ESD were selected through the early gastric cancer screening program in San Diego, Florida\textsuperscript{[13]}. According to the classification of early gastric cancer in Japan, the main characteristics of gastric tumors (size, location, type, etc.) were reviewed\textsuperscript{[14]}. All ESD were performed according to the extended standard of submucosal resection proposed by Gotoda et al.\textsuperscript{[11]}

2.2 Technique

After obtaining informed consent, the operation was performed in the endoscopy room. The operation was performed under propofol sedation and cardiopulmonary monitoring. Preoperative evaluation included ECG and laboratory examination. Dissemination studies were performed by abdominal ultrasound or computed tomography.

An Olympus Exera II 180™ single channel video endoscope was used in all cases. Indigo Carmine or Narrow Band Imaging (NBI) was used to identify and divide the tumor. There is a freezing point of about 5 mm at the edge of the tumor. In recent cases, the submucosa was infiltrated with normal saline plus adrenaline or hydroxyethyl starch. Then, a circular incision was made on the mucosa outside the freezing point, followed by dissection of the submucosa away from the muscular plane, preferably using a circular or triangular IT Knife. After resection, stop bleeding and check the integrity of the gastric wall. Figures 1 and 2 show the surgical scheme and endoscopic images of ESD in this series of patients.

The excised part extends to a surface, and its edge is fixed with pins to prevent shrinkage and facilitate histopathological analysis. Consult with at least two pathologists to analyze the results of endoscopy and biopsy. The histological report of the section includes the diameter of the lesion, gross grade, histological type and degree of differentiation, lateral and deep edge conditions, and vascular or lymphatic invasion. According to the standards proposed by the Japanese Gastric Cancer Association, the operation is considered to be curative\textsuperscript{[14]}. After the operation, the patient was sent to the short-term rehabilitation center and then to the general ward. All patients were immediately treated with omeprazole and sucralfate for 6–8 weeks. Feeding began at 48 or 72 hours.
2.3 Statistical analysis

The biological demographic variables, clinical characteristics, surgical techniques, surgical related morbidity, histological results of surgical sites and follow-up were analyzed. Data included age, gender, ASA classification\textsuperscript{15}, tumor characteristics (location, classification, size), preoperative and postoperative histology, intraoperative complications, postoperative morbidity, length of hospital stay, postoperative mortality, tumor recurrence, overall survival and disease-free survival.

Categorical variables are expressed in numbers and percentages. Continuous variables are expressed in median and range. The statistical analysis was carried out with SPSS ver. 2.0 and GraphPadPrism ver. 5.0.

2.4 Follow up

Follow-up was based on outpatient endoscopy and routine scar biopsy at 3, 6 and 12 months, and annually thereafter.

2.5 Ethical aspects

The analysis of the study, clinical, endoscopic and pathoanatomical records was approved by the hospital ethics committee.

3 Results

During the study period, 15 ESD tests were performed on 15 eligible patients with early gastric injury. The median age was 70 years (extreme: 45–88). There were 8 males (53.3%). 73.3% of patients were classified as ASA II (Table 1).

According to the classification of early gastric cancer in Japan, all lesions were divided into type II. 4 cases were type IIa lesions, 3 cases were type IIb lesions and 10 cases were type IIc lesions (Table 1).

According to the anatomical division of the stomach, the lesions were located in 2 cases in the upper third, 5 cases in the middle third and 8 cases in the lower third. Relative to the gastric circumference, most lesions were located at minor curvature (8 cases), 4 at major curvature, 2 at the anterior surface and 1 at the posterior surface (Table 1).

Preoperative biopsy was consistent with adenocarcinoma in 12 cases and high-grade dysplasia (HGD) in 3 cases. Due to the endoscopic manifestations of the lesions, ESD was performed after repeated biopsy and diagnosis of HGD (Table 2).

With regard to surgical related complications,
Table 1. Preoperative characteristics of ESD patients

<table>
<thead>
<tr>
<th>n</th>
<th>Gender</th>
<th>Age</th>
<th>ASA score</th>
<th>Classification</th>
<th>Tumor localization</th>
<th>Tumor localization (circumferential)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>70</td>
<td>II</td>
<td>II b + II c</td>
<td>S</td>
<td>Cme</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>79</td>
<td>II</td>
<td>II c</td>
<td>M</td>
<td>Cma</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>53</td>
<td>II</td>
<td>II c</td>
<td>S</td>
<td>Post</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>67</td>
<td>I</td>
<td>II c</td>
<td>I</td>
<td>Cma</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>64</td>
<td>II</td>
<td>II b</td>
<td>I</td>
<td>Ant</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>88</td>
<td>II</td>
<td>II c</td>
<td>I</td>
<td>Cma</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>45</td>
<td>I</td>
<td>II</td>
<td>I</td>
<td>Cme</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>85</td>
<td>II</td>
<td>II a + II c</td>
<td>I</td>
<td>Cme</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>64</td>
<td>II</td>
<td>II c</td>
<td>I</td>
<td>Ant</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>80</td>
<td>II</td>
<td>II</td>
<td>I</td>
<td>Cme</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>56</td>
<td>II</td>
<td>II b</td>
<td>M</td>
<td>Cme</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>85</td>
<td>I</td>
<td>II</td>
<td>M</td>
<td>Cma</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>75</td>
<td>II</td>
<td>II c</td>
<td>M</td>
<td>Cme</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>56</td>
<td>II</td>
<td>II c</td>
<td>M</td>
<td>Cme</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>75</td>
<td>I</td>
<td>II c</td>
<td>I</td>
<td>Cme</td>
</tr>
</tbody>
</table>

S: Upper Third; M: Middle Third; I: Lower Third; Cma: Major Curvature; Cme: Minor Curvature; Ant: Anterior Surface; Post: Posterior Surface.

Table 2. Histological analysis of ESD sections

<table>
<thead>
<tr>
<th>N</th>
<th>Preoperative endoscopic tumor size (mm)</th>
<th>Preoperative histology</th>
<th>Final histology</th>
<th>ESD tumor size (mm)</th>
<th>Positive margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>AC</td>
<td>AC</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>AC</td>
<td>AC</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>AC</td>
<td>AC</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
<td>AC</td>
<td>AC</td>
<td>18</td>
<td>Vertical</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>AC</td>
<td>HGD</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>AC</td>
<td>AC</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>HGD</td>
<td>HGD</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>AC</td>
<td>HGD</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>12</td>
<td>AC</td>
<td>AC</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>HGD</td>
<td>AC</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>AC</td>
<td>AC</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>HGD</td>
<td>AC</td>
<td>15</td>
<td>Lateral</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>AC</td>
<td>AC</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>AC</td>
<td>AC</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>AC</td>
<td>AC</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

AC: Adenocarcinoma; HGD: High-grade Dysplasia; ND: Not Available.
three gastric perforations were diagnosed, two of which were the first case in this series and were surgically treated by gastric repair. On the other hand, gastrointestinal bleeding occurred at the anatomical site, and endoscopy was performed by paper clip. The incidence curve is shown in Figure 3. The average length of stay was 3 days (extreme: 1–23). There was no surgery related mortality.

Postoperative pathology confirmed 12 cases of adenocarcinoma and 3 cases of HGD. Adenocarcinoma was found at the resection site in 2 cases (66.7%) diagnosed as HGD before operation. According to the degree of differentiation, 3 cases were highly differentiated, 8 cases were moderately differentiated and 1 case was poorly differentiated (7 mm lesions). The median lesion was 13.5 mm (end: 6–21). Lymphatic, vascular or perineural infiltration was not reported in any patients. Submucosal infiltration was reported in 1 case (8.3%). Two patients had positive margins (16.6%) (Table 2). In the first case, we treated the deep margin (submucosal infiltration), which was treated by laparoscopic subtotal gastrectomy, and no malignant tumor was found in the biopsy. The second case was a positive lateral margin patient who underwent a new endoscopic resection. Subsequent examinations did not show tumor recurrence (Figure 4). Overall, 85.7% of the operations were considered effective.

All patients were followed up for an average
of 16 months (extreme: 7–61). During this period, there was only one tumor recurrence, diagnosed 51 months after resection. The patient refused to accept the new endoscopic resection and accepted the subtotal gastrectomy with classical surgery. The postoperative progress was good, the tumor was well controlled, and there were no new signs of recurrence. At the end of this study, no patients died of tumor pathology during follow-up.

4 Discussion
Radical surgery is the first choice for the treatment of early gastric cancer. Laparotomy and laparoscopy are used for the first time in recent years. However, it is not without morbidity and mortality and distant complications, such as post gastrectomy syndrome, which affect the quality of life of patients. The advantage of endoscopic resection is to completely preserve the stomach and reduce the incidence, operation time, hospital stay and related costs[16].

Preoperative evaluation of gastric cancer is an important content to determine the correct treatment. In this sense, endosonography has become a useful tool for assessing tumor depth and ganglion involvement[17]. However, this is a surgical procedure that increases costs and is not without morbidity. In a recent meta-analysis, it had a diagnostic efficiency of 75% for wall depth and 64% for ganglion involvement, which was more accurate in the evaluation of advanced tumors (T3 and T4)[18]. In this series, endoscopy is not used as an auxiliary tool for endoscopic diagnosis, mainly due to the fact that the resources of our center are not available.

The first endoscopic resection technique for early lesions is REM; however, it is technically limited to well differentiated lesions, less than or equal to 20 mm in diameter, without ulcers or scars. Although this is a relatively simple technique with a low incidence of complications, the risk of local recurrence is higher due to the percentage of incomplete resection, edge damage, or histology that cannot be fully evaluated, mainly due to the removal of two or more fragments.

Based on a large number of patients undergoing surgery for early gastric cancer, it can be determined that there is a subgroup with the lowest risk of lymph node involvement, which enables the endoscopic resection standard to be extended to highly differentiated or moderately differentiated adenocarcinoma, without size limitation if they are intramucosal and without ulceration, or smaller than 30 mm if they present ulceration, submucosal infiltration of less than 500 µm (SM1), and undifferentiated cancers of less than 20 mm, without ulceration[11]. ESD has become the standard treatment for this subgroup of patients. Compared with EMR, this technique allows resection of larger lesions (mainly fragments), reduces local recurrence, and allows appropriate histological studies to determine whether surgery is effective or whether additional treatment is needed[19-21].

In recent years, ESD has replaced radical surgery in the treatment of early gastric cancer in countries with high cancer incidence such as Japan and South Korea[22,23]. In western countries, this technology is slowly adopted, with the number of patients increasing every year[24-26]. ESD is a technically more complex process than EMR, which requires higher skills and experience of endoscopy personnel and more accessories. The main complications are perforation and bleeding of gastric wall. In contrast, the perforation rate of ESD is higher than that of EMR, but bleeding is similar in both techniques[20].

In our series, the three cases associated with perforation were treated with laparotomy and suture perforation, with no surgery related morbidity and mortality. This higher proportion of the oriental series can be explained by the surgical technology learning curve, since two of the three cases (66.7%) correspond to the first and second cases in the series.

In our experience, we observed a gastrointestinal hemorrhage that occurred intraoperatively and was successfully treated by endoscopy.

The histological interpretation of early tumors is difficult in endoscopic biopsy and resection biopsy. In addition to the knowledge and experience required to correctly explain these lesions, there are differences in the definition of cancer between Japanese and western pathologists. On the other
hand, there may be differences between observers among pathologists with similar training\textsuperscript{[27]}. To avoid these differences, Japanese and western pathologists have reached a consensus called “Vienna Classification of Gastrointestinal Epithelial Tumors”, which divides lesions into 5 categories and allows clinicians to determine behavior based on biopsy results\textsuperscript{[28]}. In this series, patients in categories 4 and 5 have been resected according to this protocol. Among the 15 cases, 11 cases had positive correlation between endoscopic biopsy and surgical biopsy. 2 cases were diagnosed as tumor by HGD biopsy and 2 cases were diagnosed as HGD. Finally, one patient developed a lesion and underwent several biopsies to diagnose HGD; it was considered a neoplastic lesion according to the Vienna classification (according to Japanese standards, intramucosal carcinoma) and was removed.

In large series, the resection rate of one fragment is about 95%, and the negative edge rate is between 66% and 88%. In our study, 2 of the 14 patients finally diagnosed with gastric adenocarcinoma were found to be edge positive, and the cure rate was 85.7%. The two patients with non-curative resection received supplementary treatment (re-ESD for lateral margin resections and deep margin surgery). This indicates that detailed histopathological analysis is of great significance in evaluating the curability of resection.

These patients were followed up by endoscopic scar biopsy, even if there was no suspicion of recurrence. This allows early diagnosis of recurrence, of a synchronous cancer not found in preoperative study and the appearance of a methyl cancer in our series of patients. This supports sustained and long-term follow-up, which should also include the eradication of Helicobacter pylori, a treatment with evidence to reduce the risk of metachronous cancer\textsuperscript{[29]}

To the best of our knowledge, this study is the first national report of ESD in the treatment of early gastric injury. From this brief experience, it can be concluded that this is a feasible procedure to perform in our environment. This technique has been verified in thousands of cases in Japan and South Korea, and has obvious surgical advantages in a subgroup of early tumors. In view of the high incidence of gastric cancer in China, early detection is a challenge, which will increase the number of endoscopic surgeries in different centers and improve the survival rate of gastric cancer.

**Conflict of interest**

Authors declared no conflict of interest.

**Acknowledgements**

We thank the technicians María Alicia Correa, Claudia Velásquez and Patricía Verdugo, for their participation in preoperative evaluation, intraoperative care and follow-up.

**References**