

## Endoscopic Resection of Early Gastric Cancer: Review Article

**A Murillo-Zolezzi\*,  
H Mascareño-Ortega,  
J Martínez-López,  
D Vite-Mata and  
F Díaz-Castro**

General and Laparoscopic Surgery,  
Technologic De Monterrey School of  
Medicine, Mexico

\*Corresponding author: A Murillo-Zolezzi

✉ dradrianmurillo@gmail.com

General and Laparoscopic Surgery,  
Technologic De Monterrey School of  
Medicine, Mexico

Tel: +5215516793489

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### Abstract

Gastric cancer, which once was the most common type of cancer, still afflicts a great proportion of the population. There is a tendency towards improving outcomes in regards to mortality, through a greater understanding of tumor biology and particularly its association with *Helicobacter pylori* infection. However, 5-year survival, in general, is still poor (20%). One of the most important areas of opportunity in the treatment of this disease, particularly in high incidence countries and in at-risk individuals is early detection of the disease. If this is achieved the individual is a candidate for a diverse set of organ saving interventions which are minimally invasive and achieve excellent long term results. The purpose of this review article is to analyze endoscopic resection as a treatment for early gastric cancer, describing the two most common techniques: Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD), their characteristics and results. Both of them, alone or in a hybrid-modality could be curative in selected patients with low risk for nodal metastases, without the implications and complications of a gastrectomy. Albeit these are excellent treatment options, there are concerns regarding incomplete resections, lack of expertise, procedural complications and still lack of follow up surveillance criteria. Further research is needed before recommending endoscopic resection as the first line therapy for early gastric cancer.

**Keywords:** Early gastric cancer; Endoscopic resection; Endoscopic mucosal resection; Endoscopic submucosal dissection

### Abbreviations

Early Gastric Cancer (EGC); Endoscopic Mucosal Resection (EMR); Endoscopic Submucosal Dissection (ESD)

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### Introduction

Gastric cancer is the second cause of cancer deaths in both sexes worldwide, producing 738,000 deaths per year [1]. However, there is a trend that has been observed during the last 10 years towards a decrease in mortality from the disease [2]. The cumulative risk of the disease is 2.4% for males and 1.7% for females worldwide. It is currently the fourth most common malignancy in the world (although it was the most common in 1975), 70% of cases occur in developing countries, probably related with the higher prevalence of *Helicobacter pylori* (*H. pylori*), with the highest incidence (50% of the total) in Eastern Asia. The male-female ratio is 2:1 in non-cardiac cancer, but 5:1 in gastric cancer of the cardiac [3]. Most of the cases are related to *H. pylori* infection [4]. Dietary changes, where populations have better access to fresh fruits and vegetables are declined in the

prevalence of *H. pylori* is related to the decline in the incidence of gastric cancer [2]. Pathologically, cancer is classified in four stages: According to the Tumor Node Metastasis staging system. Where stage I is an early stage which has limited involvement of the wall of the stomach (mucosa, submucosa, muscular propria) with at most limited lymph node involvement. Stage II is marked by subserosal invasion or extension into visceral peritoneum with or without lymph node involvement. Stage III and IV are more extensive tumors with greater lymph node involvement and spread into adjacent viscera or with distant mets [5]. 5-year survival of 95% is expected if the disease is confined to the inner lining of the stomach wall, but few cancers are diagnosed at this stage [3]. In general, the 5 year survival for tumors in stage I is 70%, 30% for stage II, 10% for stage III and 0% for stage IV. Death is more often correlated with metastasis, obstruction, and malnutrition [5]. A study conducted in Japan in 2015 found a 57%

mortality reduction of gastric cancer with endoscopic screening, suggesting its effectiveness [6]. The opportune diagnosis and treatment of gastric cancer is associated with better prognosis, increased 5-year survival and better quality of life. Thus, this article aims to describe the characteristics of early gastric cancer, its screening, classification, and treatment with endoscopic resection comparing techniques and results. Of importance is the fact that gastric cancer screening is cost-effective only in areas of the high incidence of the disease. This article is a review article on the literature available on Early Gastric Cancer (EGC) management. With particular attention to the most prevalent modalities Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD), with a brief description of the technical differences, indications, and pitfalls.

## Screening

EGC is by definition a tumor that invades no more than the mucosal or submucosal layers, with or without lymph node involvement [7]. Two main modalities for screening for gastric cancer are upper endoscopy and contrast radiography. Endoscopy has a reported accuracy 90%-96%; it allows for direct visualization of the margin of the lesion, visualization of the gastric mucosa, the horizontal extent, and depth of tumor also can be measured with standard endoscopic ultrasound and chromoendoscopy. Also, endoscopy permits tissue diagnosis permitting the identification of precancerous lesions in addition to gastric cancer which may appear as a subtle polypoid protrusion, a superficial plaque, mucosal discoloration, a depression, or an ulcer [8].

The second modality is contrasted radiography, double-contrast barium imaging with photofluorography can diagnose infiltrating lesions, malignant gastric ulcers, and early gastric cancer albeit with a low sensitivity of only 14%. Linitis plastica is the only scenario in which a barium study may be superior to upper endoscopy [9].

Other studies have been proposed, but their utility is still unclear. Low serum pepsinogen I and low serum pepsinogen I/II ratio are suggestive of the presence of atrophic gastritis, a risk factor for gastric cancer. Serum Trefoil Factor 3 (TFF3) a small protein in the small and large intestine and in gastric intestinal metaplasia, expressed in the goblet cells (sensitivity and specificity 81%), in combination with pepsinogen may provide even higher sensitivity for gastric cancer [10]. MicroRNAs: miRNA-421, miRNA 18a, and miR-106a, are detectable in gastric aspirates and in peripheral blood; further studies are needed to establish them as biomarkers for gastric cancer [11]. Screening for gastric cancer is controversial, population-based screening for gastric cancer has been implemented in some countries with a high incidence of gastric cancer such as Japan, Korea, Venezuela, and Chile, in this population, it is recommended for patients greater than 50 years old. In areas with low gastric cancer incidence, screening should be reserved for specific high-risk groups, those with gastric intestinal metaplasia, pernicious anemia, gastric adenomas, familial adenomatous polyposis, Lynch syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome. Those patients with hereditary diffuse gastric cancer are not good candidates for screening, because gastric tumors can arise beneath an

intact mucosa and elude endoscopic detection; prophylactic gastrectomy should be strongly considered [12-14].

## Classification

Gastric cancers are classified according to both histologic and macroscopic findings. There are important differences between Japanese and Western classifications because Japanese have based the diagnosis on cytological and architectural changes alone, without invasion of the lamina propria and western pathologies require an invasion of the lamina propria for the diagnosis. To close the gap, there are some international classifications, such as the Padova international classification of dysplasia and the Vienna classification of Gastrointestinal Epithelial Neoplasia [15,16] including V categories:

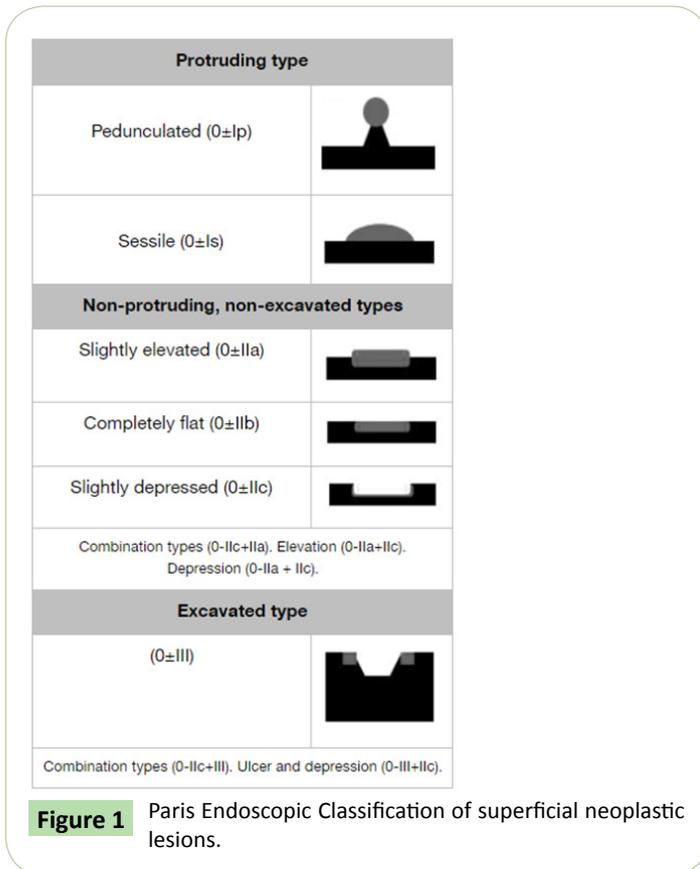
1. Negative for neoplasia/dysplasia
2. Indefinite for neoplasia/dysplasia
3. Non-invasive low-grade neoplasia
4. Non-invasive high-grade neoplasia
  - High-grade adenoma
  - Non-invasive carcinoma (*in situ*)
  - Suspicion of invasive carcinoma
5. Invasive neoplasia
  - Intramucosal carcinoma
  - Submucosal carcinoma or beyond

The Lauren classification includes the histopathological characteristics, dividing into two types of lesions: Intestinal Type- Tend to form glands, well differentiated, slow growth, and higher incidence in men and more often in older people. Diffuse Type- Poorly differentiated, very aggressive and tend to spread throughout the stomach. The same incidence in men and women, but at a younger age [17]. Macroscopically, one of the most common classification systems is the Borrmann system **Table 1**. Type I- polypoid, II- fungating, III- ulcerated and IV- diffusely infiltrating tumors. The Japanese Macroscopic Classification of Superficial Gastric Carcinoma is used in Eastern Asia, based on endosonographic features, in particular for indications and outcomes of endoscopic mucosal resection. This system includes four types of lesions **Table 1** [18].

Similar to Japanese classification, the Paris endoscopic classification of superficial neoplastic lesions **Figure 1**. Divided into three groups, Type 0 as polypoid, nonpolypoid or excavated. Type 0-I protruding types, pedunculated or sessile, type 0-II non-protruding and non-excavated types, subcategorized as nonpolypoid type, slightly elevated, flat and slightly depressed.

**Table 1:** Japanese macroscopic classification of superficial gastric carcinoma.

Type 1. Polypoid	Type 2. Flat Lesions
Ip: pedunculated	Ila: Superficial elevated
Ips/sp: sub pedunculated	Iib: Flat
Is: sessile	Iic: Flat Depressed
	Iic+Ila: elevated area with a depressed lesion
	Ila+Iic: depressed area with an elevated lesion
Type 3. Ulcerated Lesions	Type 4. Lateral Spreading



Type 0-III excavated lesions [19].

## Indications for Endoscopic Resection

Adequate selection of patients for endoscopic treatment of early gastric cancer is the most critical step in the process. Endoscopic Mucosal Resection (EMR) is the process where the lesion is elevated and removed. This technique is minimally invasive and safe. The criteria for selection of patients, who are appropriate for the endoscopic treatment, according to the Japanese Gastric Cancer Association are [20,21]:

- Well/moderately differentiated papillary carcinoma or adenocarcinoma
- Confined to the mucosa
- Elevated cancer less than 2 cm in diameter
- Smaller than 1cm for depressed and flat cancers
- Without ulcer or ulcer scar
- Without lymphatic or venous involvement

Endoscopic Submucosal Dissection (ESD) is for the complete removal of early gastric carcinoma regardless of its size. Is being used to achieve en bloc resection. Indications of ESD for EGC were expanded, for differentiated type cancers without evidence of lymphovascular invasion. An expansion of these criteria has been proposed from clinical observations, to avoid unnecessary surgery [21]

- Intramucosal cancer without ulceration and lymphovascular

invasion, irrespective of tumor size

- Intramucosal cancer with ulceration, without lymphovascular invasion, less than 3 cm in diameter
- Undifferentiated cancer without lymphovascular invasion, without ulceration, smaller than 2 cm
- Minimal (500 μm from the muscularis mucosa SM1) submucosal invasive cancer, without lymphovascular invasion, less than 3 cm in size

## Techniques

Endoscopic resection of early gastric cancer in two modalities: Endoscopic Submucosal Dissection (ESD) and Endoscopic Mucosal Resection (EMR). These techniques have been compared with gastrectomy in many meta-analyses. In selected patients who meet the general indications for endoscopic resection and who have a low risk for nodal metastases, endoscopic resection could be curative. The data suggest similar clinical outcomes when comparing gastrectomy versus endoscopic management in terms of death and recurrence with a 5-year overall survival of both over 90%. However, endoscopic management with ESD or EMR is preferred because of the lower medical costs and shorter hospital stay besides the better quality of life after the procedure if the stomach is preserved [22,23].

The development of metachronous gastric tumor (a second gastric adenocarcinoma or dysplasia detected more than 1 year after ESD or EMR), is one of the major concerns with endoscopic management. The incidence described with endoscopic resection after a long-term period range from 4.3% to 8.5%, compared with 2.4% of incidence after partial gastrectomy [23]. Surveillance after endoscopic resection is usually recommended at 6-month intervals during the first year and then annually thereafter. There is still no consensus on a standardized follow-up schedule for the detection of metachronous gastric tumors, but successful treatment of these secondary tumors is possible with repeated endoscopic resection [24]. Regardless of approach, it is important to treat *H. pylori* if there is evidence of infection because its eradication after endoscopic resection has demonstrated a protective effect against metachronous gastric tumors [23].

Endoscopic Submucosal Dissection (ESD) and Endoscopic Mucosal Resection (EMR) are the most studied modalities of endoscopic treatment of EGC. Other modalities include photodynamic therapy, Nd: YAG laser treatment and argon plasma coagulation but this article will focus on the first ones [25].

EMR consists of the removal of the mucosal lesion from its deeper layers with a snare instrument. Lesions <2 cm can be removed en bloc while larger lesions require piecemeal removal. There are three different methods, most of them described in the 1990s and still performed today. In the injection-assisted EMR, the neoplasia is lifted from the muscularis propria layer with submucosal injections of saline solution [26] or 50% dextrose (that lasts longer). Other substances such as: 10% glycerol, 5% fructose, a fibrinogen mixture, sodium hyaluronate and Hydroxypropyl Methylcellulose (HPMC), hydroxyethyl starch 6%, have been used. It is recommended that an injection of 20 to 40 cc of the solution be used to decrease the risk of perforation

Table 2: ESD versus EMR.

Feature	Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: a meta-analysis (30)	Long-term clinical efficacy and perioperative safety of endoscopic submucosal dissection versus endoscopic mucosal resection for early gastric cancer: an updated meta-analysis (34)
En bloc resection rate	Significantly higher for ESD with OR=9.69	Higher in the ESD group than in the EMR group (OR=0.10)
Histological complete resection rate	Significantly higher for ESD with OR=5.66	Higher in the ESD group than in the EMR group (OR=0.14)
Recurrence rate	Significantly higher for ESD with OR=0.09	Lower in the ESD group than in the EMR group (OR=37.83)
Operation time	Significantly higher for ESD with OR(SMD=1.73 vs SMD=1.58 for EMR)	ESD group was associated with longer operative times than the EMR group (OR=-49.86)
Perforation rate	Significantly higher for ESD with OR=4.67	Higher in the ESD group than in the EMR group (OR=0.37)
Bleeding rate	Slightly higher for ESD with OR=1.49	No statistical difference was seen in respect to postoperative bleeding rates between the two groups (OR=0.79)

OR: Odds Ratio; SMD: Standardized Mean Difference

[27]. After the injection, an electrocautery snare is used to cut the lesion.

The cap-assisted EMR uses a cap placed at the tip of the endoscope to suck the lesion. A snare loaded previously onto the rim of the cap is pulled after the suction, and the content is resected with the high-frequency current. Finally, ligation-assisted EMR uses a standard variceal band ligation device that captures the mucosa and submucosa without muscularis propria due to its contractile force, with subsequent resection with electrocautery snare [26].

ESD is a technique that allows en bloc removal of lesions greater than 2 cm or flat. The margins should be marked (preferably at 3 to 5 mm from the margin) by electrocautery and the lesion can be lifted with submucosal injection. Specialized endoscopic electrocautery knives are required to perform a circumferential incision around the lesion into the submucosa [27]. The lesion is then dissected from underlying deep layers with this knife carefully, avoiding incising the superficial dysplastic tissue and the deep layer of muscularis propria [28]. A hybrid technique has been described, in which ESD is performed with partial submucosal dissection, with subsequent EMR snare resection, decreasing the complications of ESD alone [29].

## Result

Different researchers have compared EMR versus ESD. Different meta-analysis has concluded that ESD has a superior efficacy but higher complication rate regarding EMR [30,31].

They have found that mean intervention time was longer for ESD but also the en bloc and histologically complete resection rates were significantly higher in this group, leading to lower recurrence rates, compared with the higher risk of recurrence with the piecemeal resection in EMR. However, the perforation rate was significantly higher after ESD with respect to EMR. Both

techniques had similar bleeding incidences **Table 2**. There are several retrospective cohort studies that have reported greater success when ESD is performed in early gastric cancer, likely to result in higher complete resection rates (93% versus 34%) with a recurrence-free survival at five years of 100 versus 83% respectively [32].

ESD treatment in early cancer showed a curative resection in 88.1% of patients and completed en bloc resection in 98.9%. Non-curative resection was associated with bigger lesions, localized in the upper half of the stomach and ulcerated lesions. Characteristics associated with successful resections where distal lesions, non-ulcerated, smaller than 20 mm. A lesser probability of successful treatment (up to 40% of failure) was found in a proximal, ulcerated and bigger than 30 mm [33]. Other factors related to non-curative endoscopic resection are female sex, lesion size greater than 2 cm, longer procedure time, nodularity, depression, and undifferentiated carcinoma. The identification of these factors may help in improving the efficacy of the endoscopic resection in the treatment of ECG with better patient selection [34].

## Discussion and Conclusion

The European Society of Gastrointestinal Endoscopy guideline of 2015 recommends ESD as a first treatment option for all early gastric cancers with an exception for small (<10 mm), Paris 0-IIa lesions in which EMR could be considered [23].

Today, the endoscopic resection is the first-line treatment for selected patients with early gastric cancer, with several advantages over total gastrectomy. However, the outcomes still depend on the expertise of the center [33], the accurate selection of patients, the thorough examination of specimen and process of endoscopy and a standardized follow-up strategy [25].

## References

- 1 Ferlay J, Shin HR, Forman D, Mathers C, Parkin DM, et al. (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 127: 2893-2917.
- 2 Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, et al. (2009) Recent patterns in gastric cancer: A global overview. *Int J Cancer* 125: 666-673.
- 3 Crew KD, Neugut AI (2006) Epidemiology of gastric cancer. *World J Gastroenterol* 12: 354-362.
- 4 González CA, Megraud F, Buissonniere A, Lujan L, Agudo A, et al. (2012) *Helicobacter pylori* infection assessed by ELISA and by immunoblot and noncardia gastric cancer risk in a prospective study: the Eurgast-EPIC project. *Ann Oncol* 23: 1320-1324.
- 5 Ajani JA, Bentrem DJ, Besh S, D'Amico TA, Das P, et al. (2013) Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 11: 531-546.
- 6 Hamashima C, Ogoshi K, Narisawa R, Kishi T, Kato T, et al. (2015) Impact of endoscopic screening on mortality reduction from gastric cancer. *World J Gastroenterol* 21: 2460-2466.
- 7 Ang TL, Khor CJ, Gotoda T (2010) Diagnosis and endoscopic resection of early gastric cancer. *Singapore Med J* 51: 93-100.
- 8 Longo WE, Zucker KA, Zdon MJ, Modlin IM (1989) Detection of early gastric cancer in an aggressive endoscopy unit. *Am Surg* 55: 100-104.
- 9 Dooley CP, Larson AW, Stace NH, Renner IG, Valenzuela JE, et al. (1984) Double-contrast barium meal and upper gastrointestinal endoscopy-A comparative study. *Ann Intern Med* 101: 538-545.
- 10 Aikou S, Ohmoto Y, Gunji T, Matsuhashi N, Ohtsu H, et al. (2011) Tests for serum levels of trefoil factor family proteins can improve gastric cancer screening. *Gastroenterology* 141: 837-845.
- 11 Cui L, Zhang X, Ye G, Zheng T, Song H, et al. (2013) Gastric juice microRNAs as potential biomarkers for the screening of gastric cancer. *Cancer* 119: 1618-1626.
- 12 Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, et al. (2008) The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 38: 259-267.
- 13 Choi IJ (2014) Endoscopic gastric cancer screening and surveillance in high-risk groups. *Clin Endosc* 47: 497-503.
- 14 Hamashima C, Kim Y, Choi KS (2015) Comparison of guidelines and management for gastric cancer screening between Korea and Japan. *Value Health* 18: A272.
- 15 Rugge M, Correa P, Dixon MF, Hattori T, Leandro G, et al. (2000) Gastric Dysplasia: The Padova International Classification. *Am J Surg Pathol* 24: 167-176.
- 16 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, et al. (2000) The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 47: 251-255.
- 17 Ma J, Shen H, Kapasa L, Zeng S (2016) Lauren classification and individualized chemotherapy in gastric cancer. *Oncol Lett* 11: 2959-2964.
- 18 Japanese Gastric Cancer Association (1998) Japanese Classification of Gastric Carcinoma, 2<sup>nd</sup> English Edition. *Gastric Cancer* 1: 10-24.
- 19 Participants in the Paris Workshop (2003) The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 58: S3-43.
- 20 Min YW, Min BH, Lee JH, Kim JJ (2014) Endoscopic treatment for early gastric cancer. *World J Gastroenterol* 20: 4566-4573.
- 21 Ko WJ, Song GW, Kim WH, Hong SP, Cho JY (2016) Endoscopic resection of early gastric cancer: status and new approaches. *Transl Gastroenterol Hepatol* 1: 24.
- 22 Choi KS, Jung HY, Choi KD, Lee GH, Song HJ, et al. (2011) EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. *Gastrointest Endosc* 73: 942-948.
- 23 Park JY, Kim SG, Kim J, Han SJ, Oh S, et al. (2017) Risk factors for early metachronous tumor development after endoscopic resection for early gastric cancer. *PLoS One* 12: e0185501.
- 24 Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, et al. (2015) Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 47: 829-854.
- 25 Jung HY (2017) Current status of endoscopic resection of early gastric cancer in Korea. *Korean J Gastroenterol* 70: 121-127.
- 26 ASGE CO, Kantsevoy SV, Adler DG, Conway JD, Diehl DL, et al. (2008) Endoscopic mucosal resection and endoscopic submucosal dissection. *Gastrointestinal Endosc* 68: 11-18.
- 27 Fujishiro M, Yahagi N, Kashimura K, Mizushima Y, Oka M, et al. (2004) Comparison of various submucosal injection solutions for maintaining mucosal elevation during endoscopic mucosal resection. *Endoscopy* 36: 579-583.
- 28 Bhatt A, Abe S, Kumaravel A, Vargo J, Saito Y (2015) Indications and techniques for endoscopic submucosal dissection. *Am J Gastroenterol* 110: 784-791.
- 29 Toyonaga T, Man-I M, Morita Y, Azuma T (2014) Endoscopic submucosal dissection (ESD) versus simplified/hybrid ESD. *Gastrointest Endosc Clin N Am* 24: 191-199.
- 30 Facciorusso A, Antonino M, Maso MD, Muscatiello N (2014) Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. *World J Gastrointest Endosc* 6: 555-563.
- 31 Zhao Y, Wang C (2018) Long-term clinical efficacy and perioperative safety of endoscopic submucosal dissection versus endoscopic mucosal resection for early gastric cancer: An updated meta-analysis. *Biomed Res Int* 3152346.
- 32 Ko WJ, Song GW, Kim WH, Hong SP, Cho JY (2016) Endoscopic resection of early gastric cancer: current status and new approaches. *Transl Gastroenterol Hepatol* 1: 24.
- 33 Forero-Piñeros EA, Arantes V, Toyonaga T (2012) Endoscopic dissection of the submucosa (DES) in early gastric cancer: State of the art. *Colombian Associations of Gastroenterology, Digestive Endoscopy, Coloproctology and Hepatology* 27: 200-221. (<http://www.scielo.org.co/pdf/rcg/v27n3/v27n3a07.pdf>)
- 34 Nam HS, Choi CW, Kim SJ, Kang DH, Kim HW, et al. (2018) Preprocedural prediction of non-curative endoscopic submucosal dissection for early gastric cancer. *PLoS One* 13: e0206179.