ORIGINAL ARTICLE

Endoscopic Submucosal Dissection for Gastric Cancer: a Western Perspective

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Abstract

Ulcerative colitis is a long-lasting inflammatory bowel disease that is caused by an abnormal immune response. Selenium concentrations may influence the development of some human disorders, such as the severity of inflammatory bowel disease and the likelihood of developing colon cancer. The present research sought to examine the correlation between blood Selenium concentrations and ulcerative colitis flare-ups.

Gastric cancer is the fifth commonly diagnosed cancer worldwide. In comparison to the Asian countries, where population-based national gastric screening programs are implemented, most gastric cancers in Western countries are diagnosed at a later stage in the disease process. Endoscopic Submucosal Dissection (ESD) with curative resection is a well-established, effective, and safe technique for management of early gastric cancer. There is an overall agreement amongst all the major Asian, European and American Society guidelines regarding the indications for ESD of gastric cancerous lesions. ESD for early gastric cancer has been practiced for decades in the Asian Countries, however its adaptation in the Western countries has had a slower slope. Lack of training programs, fewer experts in the field, lower prevalence of gastric cancerous lesions, and lack of reimbursement code in the Western countries are amongst the major fundamental barriers that have hampered general adaptation of ESD for management of early gastric cancer in the West. The aim of this review is to compare incidence and risk factors for gastric cancer in the eastern and western countries and compare the outcomes of ESD between the two groups.

Keywords: Early gastric cancer, Endoscopic Submucosal Dissection, Gastric Cancer Screening

Introduction

Incidence

Gastric cancer is the fifth most commonly diagnosed cancer worldwide and accounts for 1.5% of all new cancers diagnosed in the United States each year1,2. Gastric cancer is the fourth leading cause of cancer-related death worldwide and estimated for 1.8% of cancer-related death in the United States in 20223,4]. Gastric cancer is the leading cause of cancer death in several South Central Asian countries, including Iran, Afghanistan, Turkmenistan, and Kyrgyzstan3.

According to GLOBOCAN 2020, incidence rates of gastric adenocarcinoma are the highest in Eastern Asia and Eastern Europe, while Northern America and Northern Europe have the lowest rates3. Incidence rate of gastric adenocarcinoma is particularly high in Japan and Korea, and China5. In the United States, the incidence of newly diagnosed gastric adenocarcinoma is higher amongst Blacks, Hispanics, Asian or Pacific Islander compared to Non-Hispanic Whites6.

There has been a decreasing trend in incidence of gastric adenocarcinoma in the last 50 years in the western population due to higher rate of detection and eradication of Helicobacter Pylori (H. Pylori). Globally, H. Pylori negative gastric cancer has had a higher prevalence in Asian and western countries in the recent decade. 7Worldwide, gastric cancer incidence is also decreasing, this could be attributed to the change in food processing and preservation, access to electricity and refrigeration as well as less tobacco use.8

Methods

We performed a systematic electronic literature search in PubMed and MESH central for all published literature pertaining to this review. The search term included: “endoscopic submucosal dissection”, “early gastric caner”, “gastric adenocarcinoma”, “intestinal metaplasia”, “ chronic atrophic gastritis. Each manuscript was reviewed in detailed and manual search of each publication references to identify pertaining references was also performed.

Risk factors

Risk factors for gastric adenocarcinoma are divided into modifiable and non-modifiable risk factors. The most important non-modifiable risk factors include older age, male sex, family history and race9,10. However, the effect of race appears to be influenced by environmental factors rather than genetic predisposition. Gastric cardia adenocarcinoma rate is predominantly higher in African-Americans and Hispanics, while non-cardia type in more common in the white population11.

The main modifiable risk factors for gastric adenocarcinoma are infection with Helicobacter Pylori bacteria (H. Pylori), diet enriched in salt-preserved food and low vegetable and fruit content, tobacco exposure, alcohol consumption and gastric intestinal metaplasia12. Various H. Pylori strains have different virulence potential and tissue damage capabilities. Expression of Vacuolating cytotoxin A (VacA) and cytotoxin associated gene A (CagA) are associated with higher risk of developing gastric cancer.13

Gastric cancer rate is considerably higher is males in comparison to females (ratio 2:1)2. The lower rates of gastric cancer in females could be due to the change in diet and chemical exposure in this group as well as the protective effect of estrogen14. The incidence of gastric cancer has a similar pattern in post-menopausal women to men, but with a 10- to 15-year lag period14.

INTESTINAL METAPLASIA

Intestinal type of gastric cancer have a stepwise progression from normal mucosa to non-atrophic gastritis to multifocal atrophic gastritis to intestinal metaplasia (complete and incomplete) to dysplasia and then adenocarcinoma15. Therefore, Intestinal metaplasia is a known risk factor for the development of gastric adenocarcinoma and its presence requires surveillance endoscopy in high risk population. Risk factors associated with gastric intestinal metaplasia include older age, smoking, and race. In the US, Asian, Hispanics and Black have higher risk of gastric metaplasia compared to non-Hispanic white patients16,17.

Intestinal metaplasia is a common histological finding during endoscopy. In a meta-analysis of 107 studies (n = 20 912), the worldwide prevalence of intestinal metaplasia was between 19-30%18. The risk of progression from intestinal metaplasia to gastric adenocarcinoma varies depends on the population. In an observational cohort study in a low risk Western population in Sweden, twenty-year risk of developing gastric adenocarcinoma in patients with intestinal metaplasia was approximately 2.56%19. In another study which included 61,707 patients with intestinal metaplasia in Netherland, the annual incidence of gastric adenocarcinoma was 0.25%20. The risk of progression from intestinal metaplasia to gastric adenocarcinoma varies according to ethnicity. In a US based study, the risk of progression from intestinal metaplasia to gastric adenocarcinoma was higher in Eastern Asian immigrants compared to other ethnicities (adjusted odds ratio: 15.9 vs. 2)21. Even in Asian countries, the annual incidence of gastric adenocarcinoma in the setting of intestinal metaplasia is proportionally higher compared to patients without intestinal metaplasia. In a study from Japan, the cumulative 5-year incidences of gastric cancer were 1.5% in patients without intestinal metaplasia in comparison to 5.3% in the setting of gastric intestinal metaplasia limited to the antrum and 9.8% when intestinal metaplasia involved the body of the stomach22.

In the West, there is no clear guidelines on how to manage patients who were found to have intestinal metaplasia.

Recently, the American Gastroenterological Association (AGA) released its recommendations regarding the management of gastric intestinal metaplasia in 2019. AGA guidelines recommended to screen for H. Pylori, followed by treatment and confirmation of eradication in all the patients with gastric intestinal metaplasia23. Considering the overall high prevalence of gastric intestinal metaplasia in western population with low incidence of progression to gastric adenocarcinoma in general population, AGA recommends against routine endoscopic surveillance except in patients at higher risk populations. AGA defines high-risk population as those with a family history of gastric cancer, especially in first-degree relatives, racial or ethnic minorities, immigrants from countries with a high incidence of gastric cancer, and an incomplete extensive histological subtype of intestinal metaplasia23. Despite this recommendation, AGA also emphasizes on share decision making in a multidisciplinary manner between the patient and the endoscopist addressing the long term risks and benefits23.

Similar to intestinal metaplasia, chronic atrophic gastritis is linked to higher incidence of gastric adenocarcinoma. In a prospective population based study of 9949 patients, presence and severity of chronic atrophic gastritis was associated with higher incidence of gastric cancer; (HR mild/moderate 2.33, 0.55–9.76, HR severe 3.83, 1.48–9.90).24 Endoscopic screening for gastric cancer, not only entails surveying for visible gastric lesions but also obtaining at least two separate biopsies from two distant geographic areas in the stomach, for identification of advanced stages of atrophic gastritis.25 In patients with advanced stages of atrophic gastritis, follow up with a high quality endoscopy in 3 years for surveillance is recommended. This interval is shortened to 1-2 years in patients with family history of gastric cancer.25

When screening for intestinal metaplasia and atrophic gastritis, careful examination of the mucosa with high definition while light endoscopy and virtual chromoendoscopy are very important. High definition white light endoscopy for detection of intestinal metaplasia has high specificity of 94-98% however has very low sensitivity of 53-75% in the published literature.26,27 virtual chromoendoscopy with narrow band imaging (NBI) and i-Scan provides higher diagnosis accuracy and has higher sensitivity for detection of intestinal metaplasia. The sensitivity of virtual chromoendoscopy for detection of intestinal metaplasia increased from 53% to 87% in a prospective multicenter study.27 In a systemic review of 38 studies, the pooled sensitivity and specificity of virtual chromoendoscopy for the diagnosis of intestinal metaplasia were 86 % and 77 %, respectively.28 However for adequate staging of gastric precancerous conditions such as intestinal metaplasia and gastric atrophy, obtaining tissue biopsies from various segments of the stomach in separate bottles is important. The degree and severity of intestinal metaplasia and gastric atrophy can be used as predictive measures for developing gastric cancer.

The Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastritis Assessment based on Intestinal Metaplasia (OLGIM) systems are proposed for staging of atrophy and IM, respectively. These two grading and staging systems are designed to demonstrate the degree and extent of intestinal metaplasia and atrophy is various geographical sections of the stomach. In a meta-analysis of six case-control studies and two cohort studies, including 2700 subjects, a 27.7-fold higher increased risk of gastric cancer was observed in those with OLGA stages III/IV (RR 27.70; 95% CI3.75–204.87; $P < 0.001$).29 Although not commonly practiced, these two classification systems are useful resources for gastric cancer progression risk stratification.

Classification of gastric adenocarcinoma

Gastric adenocarcinoma is classified based on anatomical location (cardia/proximal or non-cardia/distal) and histologic type (diffuse or intestinal)30. More than 90% of the gastric cancers are non-cardia type and related to H. Pylori infection31. The diffuse type gastric adenocarcinoma is more prevalent in low-risk areas and is mostly associated with heritable genetic conditions30. The intestinal type occurs more frequently in high-risk areas and often related to environmental factors such as H. Pylori infection, tobacco smoking, high salt intake30. The majority of gastric cancers in the United States are non-cardia gastric cancers, arising from the antrum, incisura, body, and/or fundus32.

A dramatic shift in the type and location of upper gastrointestinal tract tumors has occurred in North America and Europe in recent years. There has been a marked decline in intestinal type gastric cancers of the distal stomach in North American and Western European countries over the past several decades33. According to a national data base study in the United States, the rate of intestinal type gastric cancer regardless of the site, decreased by 44% from 1978 to 200534. During the same period, the rate of diffuse type gastric cancer increased from by 62%34.

Survival rate and prognosis

Five-year survival rate and overall prognosis is closely associated with the stage of diagnosis. Five year relative survival rate of gastric cancer is higher is localized cases without regional lymph node metastasis as opposed to cases with distant metastasis (71.8% vs. 5.9%)4. According to the United States National Cancer Institute, gastric adenocarcinoma is diagnosed as localized (confined to primary site), regional (spread to regional lymph nodes), distant metastasis and unknow stage in 28%, 25%, 37% and 10% of the cases in the United States respectively4.

Notably, the five-year survival rates are exceptionally high in South Korea and Japan, reported as 60.3% to 76.5%, compared with the worldwide range of around 20% to 40%35. One of the most important factors that can explain these differences is the implementation of population-based national screening program for detection of gastric cancer in these two

countries35. The two main modalities for gastric cancer screening are upper endoscopy and upper gastrointestinal series with a higher detection rate of early stage gastric cancer reported with the former modality36. South Korean biannual gastric cancer screening program for adults ≥40 years old was established in 2002. As a result, an exponential increase in the detection of early stage gastric cancer from 39% of all gastric cancer cases in 2001 to 73% of all cases in 2016 was noticed37. In the European and western countries with lower incidence of gastric cancer, cost-utility models suggest a population -based screening will not be cost-effective.38,39 There is no uniform recommendations for the adoption of a gastric cancer screening program in the western countries. The surveillance and screening programs are limited to patients with certain ethnic background and those with family history of gastric cancer without a consensus on the optimal surveillance interval.

From 1992 to 2019 in the United States, the proportion of localized gastric cancer remained stable from 18.4% to 20.3% (P = 0.90), and the regional cancer rate decreased from 35.1% to 28.8% (P < .01). At the same time, the distant gastric cancer rate increased steadily from 33.1% in 1992 to 44.7% in 2019, and the proportion of unstaged cancer decreased from 13.2% to 8.9% (P = 0.04)40. This is owed to the advance in diagnostic modalities; as the result more cases with distant metastasis are being discovered. There has been a trend of a change in the age of diagnosis of gastric cancer over years parallel to the shift of histological subtypes. In the United States, the incidence of early-onset gastric cancer (≤60 year-old) has increased steadily from 1973 to 2015 leading to >30% of all gastric cancer being diagnosed as early-onset gastric cancer41. It is believed that this increase in early gastric cancer diagnosis in the United States is due to the unique genomic profile of early-onset gastric cancer rather than environmental risk factors.

The prognosis of gastric cancer differs depending on tumor location and histological subtype. In a Surveillance, Epidemiology, and End Results database study of 5593 cases with early gastric cancer, diffuse and intestinal type gastric adenocarcinoma had similar lymph node metastasis and prognosis42. Similar results were found by Tang et al in T1 tumors less than 2 cm. However Diffuse-type gastric adenocarcinoma had an overall poorer prognosis compared to the intestinal type in higher stage and larger tumors43.

RISK OF LYMPH NODE METASTASIS IN EARLY GASTRIC CANCER

Lymph node metastasis is an important prognostic factor in early gastric cancer. The incidence of lymphovascular invasion is higher if the tumor invaded the submucosal layer. According to a study of 652 patients with early gastric cancer, the incidence of lymph node metastasis was 4.8% for mucosal tumors in comparison to 23.6% in tumors expanding into the submucosal layer44. The incidence of lymphovascular invasion in smaller T1a and T1b tumors ranges between 5-9% and 20-30%, respectively45.

The overall incidence of lymph node metastasis in T1a gastric cancers in large Asian series has been between 2% to 5%46-48. The risk of lymphovascular invasion has been reported slightly higher in western countries. According to a study of 86 patients with early gastric cancer from Canada, the incidence of lymph node metastasis was 30%49. In this study, all patients meeting the standard endoscopic guideline cut off for ESD were node negative in comparison to node negativity in 86% of patients meeting expanded criteria for endoscopic resection49. In another study of 923 surgically resected early gastric cancer from the United States, the overall incidence of lymph node positivity was 7.8%50. In another SEER based study of 1577 patients in the United States, the rate of lymph node metastasis for well-differentiated or moderately differentiated T1a adenocarcinomas had an exponential increase from 1.7% for tumors smaller than 2 cm to 20% for tumors ≥ 4 cm.51 The observed incidence of lymph node metastasis was even more dramatic in T1b tumors (8.4% in tumors <1 cm to 35.8% in tumors ≥ 4cm) 51.

The risk of lymph node metastasis not only depends on the size, depth of invasion and histopathology, but also race has been shown as a risk factor for lymph node metastasis. Choi et al described a variation in lymph node positivity according to race; highest rate seen in blacks (10.9%) and whites (9.7%) followed by 7% in Hispanics and 5.2% in Asian population50. Similarly Fukuhara et al in their study of 104 patients with early gastric cancer post gastrectomy in a diverse population in New York, demonstrated that non-Asian race/ethnicities can have up to 9.09 times the odds of having lymph node metastasis compared to those of Asian race/ethnicity (p = 0.038) 52.

The etiology beyond these differences has remained unclear so far. Thus, considering the variation noted in lymph node metastasis rate noted amongst different ethnicities in the United States the expanded criteria for ESD of early gastric cancer should be interpreted with caution in certain ethnicities.

DESCRIPTION OF GASTRIC ESD

Before endoscopic embark on performing ESD for early gastric cancer, proper staging is essential. According to National Comprehensive Cancer Network (NCCN) guideline obtaining computed tomography (CT) scan of chest, abdomen and pelvis in addition to endoscopic ultrasound can provide information in terms of depth of invasion and distant metastasis. 53 Yet , it is worth mentioning that the sensitivity and specificity of EUS for early-stage gastric cancer is suboptimal. In a meta-analysis of 20 studies (n = 3321), the sensitivity of EUS in differentiating between T1a versus T1b gastric cancers was 0.87 (95% confidence interval [CI] 0.81–0.92) with associated specificity of 0.75 (95% CI 0.62–0.84).54 The details of ESD procedure has been explained in previous publications55,56. The first step entails of careful examination of the lesion with while light endoscopy and enhanced narrow band imaging for visualization of microvascular and microsurface patterns. Conventional ESD, pocket method and tunneling method are three major approaches for endoscopic submucosal dissection of the gastric

cancerous and precancerous lesions. The stepwise approach in conventional gastric ESD starts with mucosal marking, followed by submucosal injection of a lifting agent. Then a circumferential or semi-circumferential mucosal incision is made around the lesion using an electrosurgical knife. The next step is dissection within the submucosal layer to separate the lesion from the deeper muscle layer. This step is performed by series of submucosal injections to maintain submucosal cushion and dissecting the submucosal layer and underlying fibrotic tissue utilizing the electrocautery knife.

In order to facilitate dissection, endoscopists have adopted various traction devices such as clip-with-thread, rubber-band clip traction, and multi-loop traction device57. Careful continuous examination of the dissection field for detection of any visible blood vessel and pre-emptive coagulation is essential to prevent bleeding. Data regarding the role of closure post gastric ESD has remained controversial at large. According to the European Society of Gastrointestinal Endoscopy (ESGE) guideline the current evidence does not support routine closure of the gastric ESD site as a preventive measure for delayed bleeding.58 According to a recent review of 9 studies including 349 patients, adverse events and delayed bleeding rates were significantly lower in patients with post ESD defect closure (5.4% [19/349] vs. 12.4% [54/435], $P < 0.001$).59 Considering high cost of closure, perhaps closure should be considered in patients with higher risk of delayed bleeding such as those on anti-platelet and anti-thrombotic agents, lesions ≥ 40mm, patient with history of renal disease. Closure of the defect post gastric ESD should be considered decrease the risk of delayed bleeding and perforation on a case-by-case basis based on the size and location of the lesion as well as patient comorbidities. Closure could be achieved with through the scope hemostatic clips, over the scope hemostatic clips, over the scope endoscopic suturing and through the scope endoscopic suturing.

Depending on the final pathology results and curative resection status, follow up endoscopic surveillance is paramount. Endoscopic surveillance is not only indicated after resection of early gastric lesion but also after removal of dysplastic lesion. According to a recent study of 190 patients, the annual incidence of metachronous gastric neoplasm rate was 5.36%, 6.47% and 2.74% in patients with initial low grade dysplasia, high grade dysplasia and early gastric cancer, respectively.[60] Thus, endoscopic surveillance is a crucial step to consider in management of gastric neoplastic lesions. Step-by-step demonstration of two separate gastric lesions removed via conventional ESD can be found in figure 1 and figure 2.

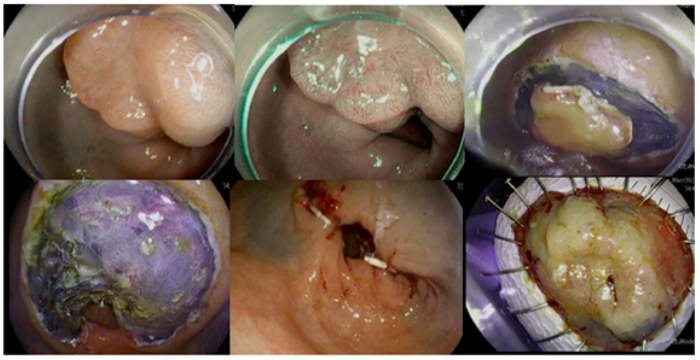

Figure 1- A 3cm raised lesions with central depression in the peripyloric area (white light and i-scan evaluation). The lesion was resected en bloc via conventional ESD technique and defect was closed with OverStitch endoscopic suturing. Final pathology showed moderately differentiated adenocarcinoma invading into the submucosa with a negative lateral and deep margins. Depth of invasion was 417 micrometer with a positive lymphovascular invasion. Patient refused surgery and elected for observation and has had no tumor recurrence since 2021.

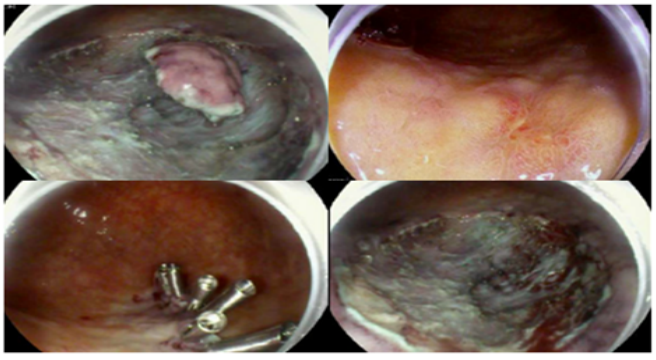

Figure 2- A 20 mm early gastric cancer with ulcerated feature resected via conventional ESD. Final pathology remarkable for moderately differentiated adenocarcinoma with negative lateral and radial margins.

INDICATION FOR ENDOSCOPIC SUBMUCOSAL DISSECTION IN EARLY GASTRIC CANCER

According to the most recent Japanese Gastric Cancer Association (JGCA) guideline in 2021 the absolute indications for ESD of early gastric cancer includes[61]:

- T1a, differentiated-type adenocarcinoma without ulcerative findings, > 2 cm.

- T1a, differentiated-type adenocarcinoma with ulcerative findings, ≤ 3 cm.
- T1a, undifferentiated-type adenocarcinoma without ulcerative findings, ≤ 2 cm.

Besides the absolute indications for early gastric cancer ESD, the guideline expanded the indication for ESD of early gastric cancer to include T1b(SM1) tumors (< 500 μm from the muscularis mucosae), ≤ 3cm in diameter, and histologically differentiated type61. In this scenario endoscopic curability is achieved only if the resection is en bloc with negative horizontal and vertical margins as well as negative lymphovascular invasion61.

Considering the lower incidence of gastric cancer in general in the Western countries, there is no clear guideline in terms of indications for ESD in early gastric cancer in this population. In 2019, AGA released their recommendations for endoscopic management of early gastric cancer in the United States62. According to the this clinical practice update recommendation, non-ulcerated lesions ≤ 2cm, moderately and well-differentiated lesions are absolute indication for ESD62. The experts expanded the recommendation for ESD to include larger than 2 cm lesions with moderately and well-differentiated histology, lesions ≤ 3 cm with ulceration or with early submucosal invasion, and ≤ 2 cm lesions with poorly differentiated histology.62

Similarly, the updated ESGE guideline in 2022 recommended ESD for management of gastric adenocarcinomas in cases without ulcerative findings either with well-differentiated morphology limited to sm1 and ≤ 30mm, or ≤ 20mm poorly differentiated intramucosal tumors63. A summary of recommendations in different guidelines can be found in table-1.

Table 1- Summary of absolute and relative indications for ESD of early gastric cancer

	Absolute indications	Relative indications
GJCA	-T1a, differentiated-type without ulceration, > 2 cm. -T1a, differentiated-type with ulceration, ≤ 3 cm. -T1a, undifferentiated-type without ulceration ≤ 2 cm.	-T1b, differentiated type, ≤ 3cm
AGA	-T1a, moderately to well-differentiated without ulcerations, ≤ 2cm.	-Moderately and well-differentiated histology, >2 cm lesions - Lesions ≤ 3 cm with ulceration or with early submucosal invasion -Poorly differentiated lesions and ≤ 2 cm.
ESGE	-Well-differentiated without ulcerative findings either with morphology limited to sm1 and ≤ 30mm. -Poorly differentiated intramucosal tumors ≤ 20mm.	

The incidence of lymph node metastasis in cases meeting the expanded criteria for ESD has remained controversial at large depending on the geographical area. Although most Japanese studies reported zero percent lymph node metastasis, the incidence of lymph node metastasis has been reported as high as 15% in the literature64. According to a recent meta-analysis including 19 studies, 1507 patients with T1b1 submucosal invasion (<500 μm), lymph node metastasis was noted in 3% of the patients65. In this meta-analysis, excluding studies from Japan, the risk of lymph node metastasis was increased to 4%65. In another multi-center study including 176 patients with early gastric cancer in the United States, the frequency of lymph node metastases among patients fulfilling standard and expanded Japanese criteria for endoscopic resection were 0 and 7.5%, respectively66. Thus, encountering patients with early gastric cancer meeting the expanded criteria, the risk of lymph node metastasis should be discussed with the patient in a multidisciplinary fashion and ESD curative resection intend could be considered for selected case.

In a systematic review comparing long term outcomes in patients with early gastric cancer with expanded indications for ESD in eastern countries, 1737 patients from six studies, there was no statistically significant difference in 5-year overall survival rate between patients undergoing ESD versus surgical resection (HR=1.22, p=0.53)67. However, 5-year disease-free survival was slightly higher is patients undergoing surgical resection (HR=3.29, p=0.001)67.

It is essential to remember the discordance between pathological assessment of initial biopsy and final resected specimen. This could be explained by the possibility of harboring neoplastic foci within the non-biopsied gastric dysplastic lesion. In a study of 411 malignant and premalignant gastric ESD cases, the endoscopical forceps biopsies had 66% concordance with final ESD specimen pathology.68 In this study the final diagnosis was upgraded by 29.8% and downgraded by 4.2% after final assessment.68 In another study of 2,150 cases of low grade dysplasia gastric lesions and 1,534 cases of high grade dysplastic gastric lesions, 27.4% of low grade dysplasia group and 72.7% of high grade dysplasia group noted to have gastric cancer in the resected specimen.69 Previous history of gastric cancer, H. pylori infection, smoking history, depressed ulcerated lesions >10 mm, were risk factors for presence of gastric cancer is patients with high grade dysplastic gastric lesions.69) Thus, careful examination of the entire gastric mucosa and detection of premalignant lesions and endoscopic removal of such lesions is as important as removing

the intended lesion via ESD. Although not mentioned in the guideline, our recommendation is to perform en bloc resection of gastric lesions with high grade dysplasia due to the high potential of occult malignancy.

Historically, endoscopic mucosal resection (EMR) was the method of choice for endoscopic resection of early gastric cancer lesions. It has been shown previously that EMR has a lower en bloc and curative resection rate for gastric cancerous lesions >1cm. 70,71 However, gastric thickness and endoscopic access varies in different segments of the stomach and limit the efficacy of EMR in en bloc resection of gastric cancerous lesions. Considering the high chance of hidden concordance malignancy is dysplastic lesions, EMR should also only be performed selectively to ensure achieving clean margins and curative resection.

OUTCOMES OF ESD FOR THE TREATMENT OF EARLY GASTRIC CANCER

Historically, the only method to achieve curative resection in early gastric cancer was partial gastrectomy and lymphadenectomy. ESD has provided an optimal alternative for curative resection of early gastric cancer, associated with less morbidity and mortality.

The majority of published outcome studies regarding the role of ESD in management of early gastric cancer are from the eastern countries considering the higher prevalence of gastric cancer in these countries. Overall higher curative resection rate has been reported in studies from South Asian region in comparison to the Western world.

In one of the recent meta-analysis comparing the ESD outcome of gastric lesions in 59966 patients between the eastern (n=59173) and western countries (n=793), similar en bloc resection (94.83% vs. 91.89%, p=0.289) and R0 resection rates (91.2% vs. 91.39%, p=0.95) were observed72. However, the average curative resection was comparably higher in the eastern countries (82.3%) than the western countries (71.3%)72. As the result, pooled local recurrent rate after gastric ESD in the Western countries was significantly higher than the Eastern Countries (1.34% vs. 4.07%, p=0.002)72. Pooled reported bleeding (4.13% vs. 6.6%, p=0.056) and perforation (2.63% vs 2.14%, p=0.7) were similar in Eastern and Western countries in this analysis72.

In another recent systematic review focusing on early gastric cancer ESD outcome in the Western populations exclusively, including 22 studies from Europe (n = 15), Latina America (n= 6), and Canada (n= 1) with 1210 lesions; en bloc resection and R0 resection were achieved in 96% and 84% of the cases, respectively73. Curative resection rate for early gastric cancer was observed in 72% of patients in this review73. In the same study, lesion recurrence rate was 3.5% (95% CI 2.3-4.4) over 23.2 ± 12.6 months in 1079 patients with available follow up information; pathology remarkable for 21 cases with early gastric cancer and 17 cases with dysplasia73. Pooled bleeding and perforation were 5.8% and 3.4%, respectively73.

Considering the lower prevalence of gastric cancer in North America, most published studies are limited to single center reported studies. To this date, there are two large multicenter trials in North America discussing ESD outcomes. In a recent multicenter retrospective chart review trial from North America including 347 patients with 139 patients with early gastric cancer, en bloc and R0 resection with ESD were achieved in 94% and 75% of patients, respectively74. In this study, ESD with curative resection was associated with zero local recurrence in follow up endoscopy [0 of 43] vs 18.5% [5 of 27] after noncurative resection; (P = 007)74. In another large multicenter prospective study in North America, 101 patients underwent ESD for gastric lesions (40 patients with adenocarcinoma)75. En bloc and R0 resection rates were achieved in 98% and 82.2% of cases, respectively75. Adverse events including bleeding and perforation were noted in 2.6-3% and 1-6.6% of patients in these two major trials, respectively74,75. These two major North American trials demonstrated similar overall risk of bleeding and perforation, comparable to Asian counter partners.

With improvement of techniques and devices in the field of third space endoscopy, the curative resection rate has been steadily increasing. Although in certain situations, surgery is inevitable after non-curative resection, salvage ESD and salvage laparoscopic lymph node dissection are alternative to surgery in special circumstances. A 6mm lateral margin positivity has been suggested as an independent risk factor for 5-year local recurrence after non-curative ESD76. Early salvage ESD before the fibrosis settles in, would be beneficial with optimal reported results in the literature and is associated with less morbidity77,78. Early salvage ESD has been shown to have higher curative resection in comparison to late salvage ESD when the tumor recurrence has occurred (100% vs. 86.7%)79.

Combined ESD with laparoscopic lymphadenectomy encountering early gastric cancer lesions with higher risk of lymph node metastasis (expanded criteria) has been shown to carry survival benefits and eliminated the need for morbid surgery such as gastrectomy80-82.

Although chemotherapy has been proven beneficial in stage II-II gastric cancer with R0 resection, the role of adjuvant chemotherapy after non-curative ESD of early gastric cancer has been controversial83-85. In cases with high risk of lymph node metastasis and on selective basis patients should be considered for adjuvant chemotherapy.

WESTERN CONSIDERATIONS IN MANAGEMENT OF EGC

ESD has been adapted for removal of early gastric cancer lesions for decades in the Asian countries. However, there is a slow adaptation of this technique in the Western countries and the United States as the result of magnitude of issues including limited training opportunities and lack of payer re-imbursement codes.

ESD is a technically challenging procedure, thus the learning curve to achieve proficiency and efficiency is quite steep. In the Japanese countries, the Master-Apprentice model for ESD training is applied from early on during training, entailing dedicated learning modules (conferences, animal labs, etc.) followed by extensive gradual involvement in human cases starting from simple antral cases to complex lesions till proficiency is achieved[67].86The training for ESD starts during fellowship in Japanese countries, allowing for dedicated time for supervised practice in human cases before independent practice. In comparison, in Western countries, not only there is no built-in ESD training modules during fellowship training, but also the curriculum and design of the training in the western countries would not allow time for implementing such training. Thus, most physicians will start exposure and training in ESD after graduation while building their practice as a novice endoscopist. Subsequently, the learning curve is longer.

Another advantage in ESD training in Asian countries is due to the higher prevalence of gastric cancerous and precancerous lesions, which allow for more practice in removal of feasible and safer lesions. With implementation of national screening programs in Asian countries, higher number of precancerous and cancerous cases are diagnosed annually, providing a larger pool of opportunities for training and practice. As the result of these barriers and fundamental differences between the West and the East, there are far less fewer experts in endoscopic submucosal dissection in the West. This serves as another limiting factor for universal adaptation of ESD.

Another obstacle in adapting ESD in west and specifically United States is the lack of reimbursement code. In comparison to other endoscopic interventions such as endoscopic mucosal resection, ESD takes longer and is associated with a controversially larger adverse event profile. Thus, endoscopists are only reimbursed for basic tissue resection techniques with available reimbursement codes as such a more complex and lengthier procedure. In a recent study by Othman et al evaluating the reimbursement data from a tertiary referral center in the United States from 2017 to 2019, ESD was found to be an under-reimbursed endoscopic procedure by governmental and private insurance companies87.

In most Asian countries, patients routinely get admitted to the hospital for ESD for observation often up to 4 days. Due to the different design of health care system in the Western countries and the United States, this approach is not cost-effective and most studies pertaining to practicing ESD in the Western countries recently are focused on outpatient and ambulatory setting practice with outpatient follow up75. In a recent multicenter prospective study including 831 patients (median lesion size, 44 mm), 71% of the patients were discharge the same day; the observed adverse events entailed delayed bleeding in 2% and delayed perforation in 0.7% of the cohort88. In spite of the above limitations, ESD continues to be an area of expansion in every major academic center in the US. However, the focus of ESD practice in the west is more related to benign colonic polyps management and early esophageal adenocarcinoma within Barrett's esophagus rather than early gastric cancer.

CONCLUSION

ESD is safe and effective in management of early gastric cancer. Despite inherited limitations in learning and practicing ESD in the western countries, ESD utilization in western countries has been slowly expanding. Recent studies have shown significant improvement in curative resection rates and lower rates of procedure related adverse events similar to the Asian countries. Perhaps with further innovations and device advancement in the field of third space endoscopy, in addition to more accessible and readily available ESD training programs, ESD in the Western world will reach the efficacy of the East.

References

1. Society AC. Key Statistics about Stomach Cancer https://www.cancer.org/cancer/stomach-cancer/about/key-statistics.html. Published 2023. Accessed January 3rd, 2023.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA* Cancer J Clin. 2018;68(6):394-424.
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.
4. Institute NC. Cancer Stat Facst: Stomach Cancer https://seer.cancer.gov/statfacts/html/stomach.html. Published 2022. Accessed January 3rd, 2023.
5. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(2):167-192.
6. Pabla BS, Shah SC, Corral JE, Morgan DR. Increased Incidence and Mortality of Gastric Cancer in Immigrant Populations from High to Low Regions of Incidence: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2020;18(2):347-359.e345.
7. Nguyen TH, Mallepally N, Hammad T, et al. Prevalence of Helicobacter pylori Positive Non-cardia Gastric Adenocarcinoma Is Low and Decreasing in a US Population. Dig Dis Sci. 2020;65(8):2403-2411.
8. Balakrishnan M, George R, Sharma A, Graham DY. Changing Trends in Stomach Cancer Throughout the World. Curr Gastroenterol Rep. 2017;19(8):36.
9. Norwood DA, Montalvan EE, Dominguez RL, Morgan DR. Gastric Cancer: Emerging Trends in Prevention, Diagnosis, and Treatment. Gastroenterol Clin North Am. 2022;51(3):501-518.
10. Shah D, Bentrem D. Environmental and genetic risk factors for gastric cancer. J Surg Oncol. 2022;125(7):1096-1103.

11. Kumar S, Metz DC, Ellenberg S, Kaplan DE, Goldberg DS. Risk Factors and Incidence of Gastric Cancer After Detection of Helicobacter pylori Infection: A Large Cohort Study. Gastroenterology. 2020;158(3):527-536.e527.
12. (WCRF/AICR) WCRFAIfCR. Continuous Update Project Report: Diet, Nutrition, Physical Activity and Stomach Cancer 2016. Revised 2018. https://acsjournals.onlinelibrary.wiley.com/doi/pdfdirect/10.3322/caac.21492. Published 2018. Accessed January 3rd, 2023.
13. Toh JWT, Wilson RB. Pathways of Gastric Carcinogenesis, Helicobacter pylori Virulence and Interactions with Antioxidant Systems, Vitamin C and Phytochemicals. Int J Mol Sci. 2020;21(17).
14. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012;21(1):20-38.
15. Correa P. Gastric cancer: overview. Gastroenterol Clin North Am. 2013;42(2):211-217.
16. Kligman E, Ali H, Chen E, et al. Ethnicity Is an Important Consideration in Screening for Gastric Intestinal Metaplasia. Dig Dis Sci. 2022;67(9):4509-4517.
17. Xing J, Min L, Zhu S, et al. Factors associated with gastric adenocarcinoma and dysplasia in patients with chronic gastritis: a population-based study. Chin J Cancer Res. 2017;29(4):341-350.
18. Marques-Silva L, Areia M, Elvas L, Dinis-Ribeiro M. Prevalence of gastric precancerous conditions: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2014;26(4):378-387.
19. Song H, Ekheden IG, Zheng Z, Ericsson J, Nyrén O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. Bmj. 2015;351:h3867.
20. de Vries AC, van Grieken NC, Looman CW, et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. Gastroenterology. 2008;134(4):945-952.
21. Choi AY, Strate LL, Fix MC, et al. Association of gastric intestinal metaplasia and East Asian ethnicity with the risk of gastric adenocarcinoma in a U.S. population. Gastrointest Endosc. 2018;87(4):1023-1028.
22. Shichijo S, Hirata Y, Niikura R, et al. Histologic intestinal metaplasia and endoscopic atrophy are predictors of gastric cancer development after Helicobacter pylori eradication. Gastrointest Endosc. 2016;84(4):618-624.
23. Gupta S, Li D, El Serag HB, et al. AGA Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia. Gastroenterology. 2020;158(3):693-702.
24. Holleczek B, Schöttker B, Brenner H. Helicobacter pylori infection, chronic atrophic gastritis and risk of stomach and esophagus cancer: Results from the prospective population-based ESTHER cohort study. Int J Cancer. 2020;146(10):2773-2783.
25. Pimentel-Nunes P, Libânio D, Marcos-Pinto R, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019;51(4):365-388.
26. Panteris V, Nikolopoulou S, Lountou A, Triantafillidis JK. Diagnostic capabilities of high-definition white light endoscopy for the diagnosis of gastric intestinal metaplasia and correlation with histologic and clinical data. Eur J Gastroenterol Hepatol. 2014;26(6):594-601.
27. Pimentel-Nunes P, Libânio D, Lage J, et al. A multicenter prospective study of the real-time use of narrow-band imaging in the diagnosis of premalignant gastric conditions and lesions. Endoscopy. 2016;48(8):723-730.
28. Kikuste I, Marques-Pereira R, Monteiro-Soares M, et al. Systematic review of the diagnosis of gastric premalignant conditions and neoplasia with high-resolution endoscopic technologies. Scand J Gastroenterol. 2013;48(10):1108-1117.
29. Yue H, Shan L, Bin L. The significance of OLGA and OLGIM staging systems in the risk assessment of gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2018;21(4):579-587.
30. Ma J, Shen H, Kapesa L, Zeng S. Lauren classification and individualized chemotherapy in gastric cancer. Oncol Lett. 2016;11(5):2959-2964.
31. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. Global burden of gastric cancer attributable to Helicobacter pylori. Int J Cancer. 2015;136(2):487-490.
32. Gupta S, Tao L, Murphy JD, et al. Race/Ethnicity-, Socioeconomic Status-, and Anatomic Subsite-Specific Risks for Gastric Cancer. Gastroenterology. 2019;156(1):59-62.e54.
33. Falk J, Carstens H, Lundell L, Albertsson M. Incidence of carcinoma of the oesophagus and gastric cardia. Changes over time and geographical differences. Acta Oncol. 2007;46(8):1070-1074.
34. Wu H, Rusiecki JA, Zhu K, Potter J, Devesa SS. Stomach carcinoma incidence patterns in the United States by histologic type and anatomic site. Cancer Epidemiol Biomarkers Prev. 2009;18(7):1945-1952.
35. Kim B, Cho SJ. Endoscopic Screening and Surveillance for Gastric Cancer. Gastrointest Endosc Clin N Am. 2021;31(3):489-501.

36. Choi KS, Jun JK, Park EC, et al. Performance of different gastric cancer screening methods in Korea: a population-based study. PLoS One. 2012;7(11):e50041.
37. Huang RJ, Koh H, Hwang JH. A Summary of the 2020 Gastric Cancer Summit at Stanford University. Gastroenterology. 2020;159(4):1221-1226.
38. Yeh JM, Hur C, Ward Z, Schrag D, Goldie SJ. Gastric adenocarcinoma screening and prevention in the era of new biomarker and endoscopic technologies: a cost-effectiveness analysis. Gut. 2016;65(4):563-574.
39. Gupta N, Bansal A, Wani SB, Gaddam S, Rastogi A, Sharma P. Endoscopy for upper GI cancer screening in the general population: a cost-utility analysis. Gastrointest Endosc. 2011;74(3):610-624.e612.
40. Chen M, Chen K, Hou H, et al. Incidence and mortality trends in gastric cancer in the United States, 1992-2019. Int J Cancer. 2022.
41. Bergquist JR, Leiting JL, Habermann EB, et al. Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features. Surgery. 2019;166(4):547-555.
42. Li ZY, Zhang QW, Teng LM, Zhang CH, Huang Y. Comparable rates of lymph node metastasis and survival between diffuse type and intestinal type early gastric cancer patients: a large population-based study. Gastrointest Endosc. 2019;90(1):84-95.e10.
43. Tang D, Ni M, Zhu H, et al. Differential prognostic implications of gastric adenocarcinoma based on Lauren's classification: a Surveillance, Epidemiology, and End Results (SEER)-based cohort study. Ann Transl Med. 2021;9(8):646.
44. Roviello F, Rossi S, Marrelli D, et al. Number of lymph node metastases and its prognostic significance in early gastric cancer: a multicenter Italian study. J Surg Oncol. 2006;94(4):275-280; discussion 274.
45. Akagi T, Shiraishi N, Kitano S. Lymph node metastasis of gastric cancer. Cancers (Basel). 2011;3(2):2141-2159.
46. Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer. 2000;3(4):219-225.
47. Nam MJ, Oh SJ, Oh CA, et al. Frequency and predictive factors of lymph node metastasis in mucosal cancer. J Gastric Cancer. 2010;10(4):162-167.
48. Fang WL, Huang KH, Lan YT, et al. The Risk Factors of Lymph Node Metastasis in Early Gastric Cancer. Pathol Oncol Res. 2015;21(4):941-946.
49. Watanabe A, McKendry GJ, Yip L, Donnellan F, Hamilton TD. Risk of lymph node metastasis in early gastric cancer for a Western population. J Surg Oncol. 2022.
50. Choi AH, Nelson RA, Merchant SJ, Kim JY, Chao J, Kim J. Rates of lymph node metastasis and survival in T1a gastric adenocarcinoma in Western populations. Gastrointest Endosc. 2016;83(6):1184-1192.e1181.
51. Pokala SK, Zhang C, Chen Z, et al. Lymph node metastasis in early gastric adenocarcinoma in the United States of America. Endoscopy. 2018;50(5):479-486.
52. Fukuhara S, Yabe M, Montgomery MM, Itagaki S, Brower ST, Karpeh MS, Jr. Race/Ethnicity is predictive of lymph node status in patients with early gastric cancer. J Gastrointest Surg. 2014;18(10):1744-1751.
53. Gastric Cancer. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Published 2023. Accessed May 14th, 2023.
54. Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. Gastrointest Endosc. 2011;73(6):1122-1134.
55. Ahmed Y, Othman M. EMR/ESD: Techniques, Complications, and Evidence. Curr Gastroenterol Rep. 2020;22(8):39.
56. Gotoda T, Ho KY, Soetikno R, Kaltenbach T, Draganov P. Gastric ESD: current status and future directions of devices and training. Gastrointest Endosc Clin N Am. 2014;24(2):213-233.
57. Esaki M, Ihara E, Gotoda T. Endoscopic instruments and techniques in endoscopic submucosal dissection for early gastric cancer. Expert Rev Gastroenterol Hepatol. 2021;15(9):1009-1020.
58. Libânio D, Pimentel-Nunes P, Bastiaansen B, et al. Endoscopic submucosal dissection techniques and technology: European Society of Gastrointestinal Endoscopy (ESGE) Technical Review. Endoscopy. 2023;55(4):361-389.
59. Kobara H, Tada N, Fujihara S, Nishiyama N, Masaki T. Clinical and technical outcomes of endoscopic closure of postendoscopic submucosal dissection defects: Literature review over one decade. Dig Endosc. 2023;35(2):216-231.
60. Suk S, Seo YJ, Cheung DY, Lee HH, Kim JI, Park SH. The pattern of metachronous recurrence after endoscopic submucosal dissection for gastric adenocarcinoma and dysplasias. Clin Endosc. 2023.
61. Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). Gastric Cancer. 2023;26(1):1-25.
62. Draganov PV, Wang AY, Othman MO, Fukami N. AGA Institute Clinical Practice Update: Endoscopic Submucosal Dissection in the United States. Clin Gastroenterol Hepatol. 2019;17(1):16-25.e11.
63. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of

Gastrointestinal Endoscopy (ESGE) Guideline - Update 2022. Endoscopy. 2022;54(6):591-622.
64. Kang HJ, Kim DH, Jeon TY, et al. Lymph node metastasis from intestinal-type early gastric cancer: experience in a single institution and reassessment of the extended criteria for endoscopic submucosal dissection. Gastrointest Endosc. 2010;72(3):508-515.
65. Abdelfatah MM, Barakat M, Othman MO, Grimm IS, Uedo N. The incidence of lymph node metastasis in submucosal early gastric cancer according to the expanded criteria: a systematic review. Surg Endosc. 2019;33(1):26-32.
66. Hanada Y, Choi AY, Hwang JH, et al. Low Frequency of Lymph Node Metastases in Patients in the United States With Early-stage Gastric Cancers That Fulfill Japanese Endoscopic Resection Criteria. Clin Gastroenterol Hepatol. 2019;17(9):1763-1769.
67. Xu X, Zheng G, Gao N, Zheng Z. Long-term outcomes and clinical safety of expanded indication early gastric cancer treated with endoscopic submucosal dissection versus surgical resection: a meta-analysis. BMJ Open. 2022;12(12):e055406.
68. Liu JM, Liang L, Zhang JX, et al. [Pathological evaluation of endoscopic submucosal dissection for early gastric cancer and precancerous lesion in 411 cases]. Beijing Da Xue Xue Bao Yi Xue Ban. 2023;55(2):299-307.
69. Jeon JW, Kim SJ, Jang JY, et al. Clinical Outcomes of Endoscopic Resection for Low-Grade Dysplasia and High-Grade Dysplasia on Gastric Pretreatment Biopsy: Korea ESD Study Group. Gut Liver. 2021;15(2):225-231.
70. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc. 2016;28(1):3-15.
71. Banks M, Uedo N, Bhandari P, Gotoda T. EMR achieves similar oncological outcomes as ESD for gastric neoplasia of <1cm, requiring less expertise, training and time. Gut. 2020;69(9):1.
72. Daoud DC, Suter N, Durand M, Bouin M, Faulques B, von Renteln D. Comparing outcomes for endoscopic submucosal dissection between Eastern and Western countries: A systematic review and meta-analysis. World J Gastroenterol. 2018;24(23):2518-2536.
73. Zullo A, Manta R, De Francesco V, et al. Endoscopic submucosal dissection of gastric neoplastic lesions in Western countries: systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2021;33(11):e1-e6.
74. Ngamruengphong S, Ferri L, Aihara H, et al. Efficacy of Endoscopic Submucosal Dissection for Superficial Gastric Neoplasia in a Large Cohort in North America. Clin Gastroenterol Hepatol. 2021;19(8):1611-1619.e1611.
75. Draganov PV, Aihara H, Karasik MS, et al. Endoscopic Submucosal Dissection in North America: A Large Prospective Multicenter Study. Gastroenterology. 2021;160(7):2317-2327.e2312.
76. Sekiguchi M, Suzuki H, Oda I, et al. Risk of recurrent gastric cancer after endoscopic resection with a positive lateral margin. Endoscopy. 2014;46(4):273-278.
77. Kinoshita S, Nishizawa T, Ochiai Y, et al. Salvage endoscopic submucosal dissection for incompletely resected esophageal or gastric neoplasms (case series). Endosc Int Open. 2020;8(1):E20-e24.
78. Kim TS, Min BH, Min YW, et al. Long-term Outcomes of Additional Endoscopic Treatments for Patients with Positive Lateral Margins after Endoscopic Submucosal Dissection for Early Gastric Cancer. Gut Liver. 2022;16(4):547-554.
79. Hoteya S, Iizuka T, Kikuchi D, et al. Secondary endoscopic submucosal dissection for residual or recurrent tumors after gastric endoscopic submucosal dissection. Gastric Cancer. 2014;17(4):697-702.
80. Li H, Huo ZB, Kong FT, et al. Predictive factors for lymph node metastasis and defining a subgroup treatable for laparoscopic lymph node dissection after endoscopic submucosal dissection in poorly differentiated early gastric cancer. World J Gastrointest Oncol. 2018;10(10):360-366.
81. Abe N, Mori T, Takeuchi H, et al. Successful treatment of early stage gastric cancer by laparoscopy-assisted endoscopic full-thickness resection with lymphadenectomy. Gastrointest Endosc. 2008;68(6):1220-1224.
82. Abe N, Mori T, Takeuchi H, et al. Laparoscopic lymph node dissection after endoscopic submucosal dissection: a novel and minimally invasive approach to treating early-stage gastric cancer. Am J Surg. 2005;190(3):496-503.
83. Di Costanzo F, Gasperoni S, Manzione L, et al. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. J Natl Cancer Inst. 2008;100(6):388-398.
84. Li J. Safety and effectiveness of endoscopic mucosal resection combined with chemotherapy for early gastric cancer. Eur Rev Med Pharmacol Sci. 2016;20(11):2265-2270.
85. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315-321.
86. Kotzev AI, Yang D, Draganov PV. How to master endoscopic submucosal dissection in the USA. Dig Endosc. 2019;31(1):94-100.
87. Gajula P JH, Tabash A., Barrett MR, Ahmed Y, Rungta M, El-Serag HB, Othman MO. Physician Reimbursement for Endoscopic Submucosal Dissection: A Single Center

Analysis.. Techniques and innovations in gastrointestinal endoscopy. 2020;24(2):153–158.
88. King W, Draganov P, Gorrepati VS, et al. Safety and feasibility of same-day discharge after endoscopic submucosal dissection: a Western multicenter prospective cohort study. Gastrointest Endosc. 2023.