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Title

Quantifying early gastric cancer in Australia: What is the opportunity for gastric endoscopic submucosal dissection?

Running head

Incidence of early gastric cancer in an Australian cohort

Authors

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Abbreviations

EGC Early gastric cancer

EMR Endoscopic mucosal resection

ESD Endoscopic submucosal dissection

ESGE European society of gastrointestinal endoscopy

JSG Japanese society of gastroenterology

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Abstract

Background and Aims

Endoscopic submucosal dissection (ESD) is the recommended treatment for early gastric cancer (EGC). However, there are challenges in attaining expertise in ESD in countries where the incidence of gastric cancer, and proportion diagnosed at an early stage of disease is relatively low. This study aims to establish the proportion of gastric cancer meeting histological criteria for EGC which may be suitable for ESD, in a Western population.

Methods

Gastric cancers reported to the Victorian Cancer Registry between January 2011 and December 2016 were analysed. EGC was defined as tumour confined to mucosa (T1a) or submucosa (T1b). Histology reports were analysed using Japanese and European guidelines to identify potential ESD candidates. Criteria for extended ESD were based on grade of differentiation, tumour depth, lymphovascular and perineural invasion and ulceration.

Results

Twenty percent of 1217 gastric cancers was EGC (237 cases), with detailed histopathology reports suitable for evaluating ESD criteria recorded in 182 cases. Standard and extended ESD criteria were met in 46% (84/182) and 75% (132/182), respectively. Actual treatment of the 237 EGC was endoscopic in 14% (n=33) and surgery in 86% (n=204). Endoscopically treated EGCs were more likely to be stage T1a and located in the proximal stomach.

Conclusions

EGCs represented 20% of reported gastric adenocarcinomas with the majority fulfilling criteria for ESD. ESD should be considered in the management algorithm and discussed at tumour board meetings involving interventional endoscopists. To increase utilisation of ESD, systems need to be implemented to improve training, accreditation, and access to ESD.

Keywords

Multidisciplinary; intramucosal; submucosal; endoscopic resection

Background and Aims

Gastric cancer is the 14th leading cause of cancer-related mortality in Australia and the incidence is increasing.[1] Surgical resection is first line treatment for locally advanced, non-metastatic disease.[2] Gastric cancer which is limited to the mucosa (AJCC[3] stage T1a) or submucosa (stage T1b) is termed early gastric cancer (EGC), and curative resection can be achieved by Endoscopic Submucosal Dissection (ESD) if favorable histologic features are present (Table 1).[4] Short- and long-term outcomes of ESD are excellent, with disease-specific 5-year survival of up to 100% after complete resection.[5, 6] Advantages of ESD include lower morbidity and mortality compared to gastrectomy,[6] and it is recommended as first line treatment for EGC in international guidelines.[4, 7]

ESD is widely performed in Asia where gastric cancer has high prevalence.[8, 9] The proportion of gastric cancer diagnosed at an earlier stage amenable to ESD is larger in Asia with EGC accounting for up to 57% of all gastric cancer diagnoses in Japan compared to 15% to 21% in the United States and Europe.[10, 11] Lack of screening programs in Western countries and potential differences in tumor biology may contribute to this geographical variation.[12] Other barriers to ESD include the training required to achieve competency and lower case volume[13], and treating clinicians may not be aware of the utility and efficacy of ESD, and therefore cases suitable for ESD may be missed.

ESD is an advanced endoscopic procedure, analogous to complex surgical procedures that require high case volume to reach and maintain technical expertise and optimize operative and patient outcomes.[14] Centralization of such highly skilled procedures is especially necessary when the treating condition has low prevalence. While the complexity of the technique supports centralization, the potential case volume is unknown as the incidence of EGC in Australia has not been defined.

This study aims to establish the proportion of newly diagnosed gastric cancer that meet histological criteria for EGC and may be suitable for ESD in a Western population.

Methods

A retrospective analysis of all gastric cancers reported to Victorian Cancer Registry between January 2011 to December 2016 was performed. This is a mandatory reporting process for new cancer diagnoses in the State of Victoria, which includes 26% of the Australian population.[15] The Victorian Cancer Registry does not mandate reporting of gastric carcinoma in-situ or high-grade dysplasia. The institutional review board at Victorian Cancer Registry approved the collection and analysis of data (St Vincent's Hospital, Melbourne, HREC 036/18).

Definition of EGC

EGC was defined as adenocarcinoma restricted to mucosa (T1a) or submucosa (T1b) (see Figure 1).[7]

Histopathologic assessment and identification of EGC

Histopathology reports of all gastric cancers were manually reviewed to identify EGCs. Histopathologic assessment for surgical resection specimens were reported in accordance with the Royal College of Pathologists Australia guidelines, based on the International Collaboration on Cancer Reporting, and included specimen dimensions, tumor site and dimensions, macroscopic and histologic tumor type, distance to margins, involvement of lymph nodes or adjacent organs and response to adjuvant therapy if applicable.[16] There were no standardized protocol for the reporting of endoscopic resection specimens.

Where surgical resection specimens were available in addition to biopsy and/or endoscopic specimens, tumor staging from the surgical specimen was used. Where only biopsy specimen was available, the tumor was defined as EGC if confined to the lamina propria or muscularis mucosae, and/or the pathologist reported definite intramucosal or early gastric adenocarcinoma. Tumors described as "invasive" and/or "infiltrating" the muscularis propria were classified as T2 or greater. Records were excluded from analysis if tumor invasion beyond the muscularis mucosae was unable to be determined.

Data on type of resection (surgical or endoscopic), tumor size, morphology, presence of ulceration, differentiation, lymphovascular and perineural invasion were collected. Nodal involvement was recorded from the surgical specimen report. Pre-operative imaging and results of tumor board meetings were not available. Patient demographics and survival at last censorship in December 2017 were collected.

Assessing EGC for suitability for ESD

The Japanese and European guidelines for suitability for ESD were used to assess suitability for ESD in EGCs identified (Table 1). [4, 7]

Statistical analysis

All statistical tests were done using SPSS version 21(IBM Corp, NY). Chi-square and Fisher's exact test were used for categorical variables. T-test and non-parametric test were used for normally distributed and non-normally distributed continuous variables, respectively.

Role of the funding source

There was no external funding or study sponsors for this study.

Results

Over a 6-year period between 2011 and 2016, 1779 gastric adenocarcinomas were reported to the Victorian Cancer Registry, of which 1217 (68%) had complete histology reports where T staging was able to be determined (Figure 2).

237 EGCs were identified, comprising 20% of all gastric adenocarcinomas (237/1217). 182 EGCs had detailed histology reports for resection specimens; 33 endoscopic and 149 surgical. 46% (84 of 182) met standard criteria for ESD and 73% (132 of 182) met extended criteria for ESD (Figure 3). Of the 132 EGCs fulfilling the extended criteria for ESD, 26 (20%) were treated endoscopically and 106 (80%) by surgery. Endoscopic resections were performed using snare-based technique and ESD in 24 (93%) and 2 (7%), respectively. Both ESD cases achieved *en bloc* and R0 resections without intra- or post-procedural complications. One patient declined surveillance endoscopy due to advanced age. There was no cancer recurrence in the second patient at 5 years post-ESD. Positive lymph nodes were found in 10 of 106 (9%) of EGCs that met extended criteria for ESD and treated by surgery. Data on pre-operative lymph node stage was not available.

55 EGCs had gastric biopsy specimens only and did not have resection specimens available; 20 had death reported, 23 had no documentation of further treatment and 12 had no follow-up records at the Registry or the hospital where the diagnosis of gastric cancer was made.

Comparison of surgically versus endoscopically treated EGC (Table 2)

EGCs were treated at 17 hospitals in the State of Victoria (9 academic hospitals, 8 community or rural hospitals). Patient characteristics, tumor size and grade of differentiation were similar between surgically versus endoscopically resected EGC. Survival rate, as documented by Registry censorship on 31st December 2017, was similar between the two groups.

Tumor location, depth and involvement of pathologic margins was significantly different between surgical and endoscopic treatment groups (Table 2). More endoscopically treated tumors were located at the gastro-esophageal junction (GOJ) and cardia compared to surgically resected tumors (49% vs 28%, $p < 0.005$). More surgically resected tumors were in the antrum compared to endoscopically resected tumors (52% vs 2%, $p < 0.005$). The proportion of patients who had surgically resected EGCs with T1a and T1b stage was 37% and 61%, respectively, compared to endoscopically resected EGCs where 61% and 27% were T1a and T1b, respectively ($p<0.005$). Three in-situ EGCs were surgically resected. Resection margins were clear in 96% (n=143) of surgically resected specimens. Both ESD specimens had clear vertical and lateral margins. Lateral margins were involved in five snare-based endoscopic resections, which were all piecemeal resections.

Endoscopically resected EGCs that had subsequent surgery

Nine EGCs had surgery following initial piecemeal endoscopic resection. Seven of these cases had not met criteria for endoscopic resection; lymphovascular invasion (n=2), large tumor (>30mm) with ulceration (n=1), T1b tumors (n=4). Two cases that met ESD criteria underwent surgical resection for extensive intestinal metaplasia with multifocal dysplasia (n=1) and unknown reason (n=1). In the latter, the surgical resection specimen showed a 15mm well differentiated in-situ tumor with extensive intestinal metaplasia.

Five of the nine cases underwent surgery within 4 months of the endoscopic resection including the 2 meeting ESD criteria; all 5 surgical resection specimens showed T1a disease. Four of the nine cases had surgery more than 12 months after initial endoscopic resection, and the surgical specimens showed T2 or greater stage cancers in all cases.

Discussion

In this six-year Cancer Registry study, 20% of gastric adenocarcinoma with complete histology reports and T staging were classified as EGC, with 46% and 73% meeting the standard and extended criteria for ESD. The state-wide mean annual incidence in this Australian cohort study was 10 per million persons (0.01 per 1000 person-years). On application of the ESD criteria, our results would represent an average of 5 to 7 cases per million population per year that are potentially suitable for ESD in the state of Victoria. The true number of suitable cases for gastric ESD would likely be higher, as the Registry data does not include gastric high-grade dysplasia or in-situ carcinoma.

ESD has several advantages compared to surgery for treatment of EGC. ESD is associated with shorter hospital stay (mean difference -2.02 days, 95% confidence interval -2.64 to -1.39)[17], lower complication rates[18] and medical costs compared to gastrectomy.[19] Quality of life after ESD is greater, with less fatigue, nausea, vomiting and eating restrictions.[18] Complete resection rates and the 5-year and recurrence-free survival rates are similar between the two treatments, including EGC cases meeting the extended criteria.[20]

Prior to ESD availability, endoscopic mucosal resection (EMR) was the endoscopic treatment of choice for EGC. However, complete (R0) resection, which is critical to prevent recurrence, is not reliably achieved with piecemeal resection technique and is significantly affected by lesion size. The reported rates of R0 EMR are 33%-69% for sub-centimeter lesions and lower for larger lesions.[21] In contrast, ESD is significantly more efficacious for both R0 and *en bloc* resection, with a lower local recurrence rate.[21] *En bloc* resection with ESD also allows complete histologic assessment of the lateral and vertical margins for prognostication. Although there risk of perforation is higher with ESD (OR 4.7, 95% CI 2.8-7.9), the bleeding risk and all-cause mortality are not significantly

different to EMR.[22] The choice of endoscopic resection approach should therefore be tailored to lesion size, and gastric EMR can be considered for sub-centimeter lesions with dysplasia where *en bloc* resection is achievable.[23]

All patients who have an ESD should be discussed at tumor board meetings and those with EGC at higher risk of lymph node metastases should be considered for surgery if suitable. Risk factors for lymph node metastasis include lymphovascular invasion, poorly differentiated histology and increasing depth of tumor invasion.[24].The risk of lymph node metastasis in intramucosal (T1a) adenocarcinoma is <3%.[24] As the submucosal invasion depth extends into the first 500 micrometers (SM1), the risk increases to 10%.[25] Invasion to 500-1000 micrometers of submucosa is termed SM2 and beyond 1000 micrometers is termed SM3, with respective lymph node metastasis risks of 15% and 40%.[25, 26] Patients who have an ESD and dysplasia identified at the specimen margins on histopathology review (R1 resection), need careful consideration of further endoscopic or surgical approach, taking into account the degree of dysplasia present, and whether the dysplasia was at the lateral or vertical margin. In patients with R1 resection, disease-free and cancer-specific survival have been shown to be longer with subsequent gastrectomy compared to repeat ESD or observation. [27, 28]

With the accumulation of efficacy and safety data, indications for ESD as treatment of gastric cancer have also expanded, as recommended by the Japanese Gastric Cancer Association (Table 3).[29-31] In summary, endoscopic resection should be considered for tumors with low risk of lymph node metastasis that are suitable for *en bloc* resection. The new guidelines also recommend ESD in elderly or high-operative-risk patients where surgery cannot be undertaken due to various clinical circumstances, yet endoscopic resection may have the potential for cure. In these cases, endoscopic resection may still improve quality of life even if cure may not be achieved. In a retrospective multicenter study examining the association between advanced age and

additional surgery, majority of patients over the age of 80 did not undergo additional surgery but the difference in overall survival with or without additional surgery was not significant.[32] ESD is an increasingly versatile and important treatment option for EGC with the potential to offer both cure and care, and there may be more clinically appropriate candidates for ESD than strict application of the ESD criteria only. Multidisciplinary approach with informed discussion with the patient is critical in finding the balance between permanent cure and long-term quality of life.[33]

The incidence of EGC in this cohort is similar to that seen in other Western countries,[11, 34] which is lower than in Asia.[12] Subsequently, the volume of gastric ESD performed in the West is lower. ESD is an advanced endoscopic technique with a steep learning curve and the volume of procedures required to achieve mastery is between 40-80 cases.[13] This is harder to attain in the West with lower case volume. The overall prevalence of gastric cancer is higher in Asia and therefore, screening programs have been implemented, and gastroscopies are performed with a detailed approach to endoscopic examination aiming for detection of early gastric lesions. In Japan and Korea, 2-yearly gastroscopy is performed for screening of gastric cancer in adults greater than 40 years of age,[35] with routine use of advanced imaging techniques, meticulous examination and photo-documentation of normal and abnormal mucosa. This approach to gastroscopy can be applied in the West, especially in patients with risk factors for gastric dysplasia, to improve the rate of earlier detection of gastric cancer which is integral to improving gastric cancer survival.

Other reasons for lower uptake of ESD in the West may include an established referral pathway to surgical resection in the absence of awareness of ESD as a valid curative treatment for EGC. Consideration and referral for ESD may also be influenced by the location of the tumor and the risks and benefits of an alternative treatment option. In this study, despite similar grades of dysplasia at each anatomical location, most endoscopically resected EGCs were in the proximal stomach and GOJ, whereas most

that had surgical resection were in the distal stomach. We postulate that a lower proportion of proximal lesions were referred for surgery due to the morbidity associated with an Ivor-Lewis esophagectomy and/or total gastrectomy, compared to a greater proportion of distal lesions surgically treated given lower surgical morbidity associated with a distal gastrectomy.[36]

There are several ways to improve the uptake of ESD in the treatment of EGC. Dissemination of information on EGC and its management algorithm would increase awareness of referring clinicians. In Australia, short-term outcomes of gastric ESD for EGC are favourable with a recent single-centre experience of 135 EGCs reporting *en bloc* and Ro resection rates of 95% and 87% respectively.[37, 38] Accumulating more Australian data on the efficacy and safety of ESD will be important in validating and promoting ESD in the treatment of EGC. At an administrative level, this would involve centralization of ESD to quaternary centers and creating a streamlined referral pathway from all tertiary and community hospitals. At the institution offering ESD, endoscopic evaluation, staging and management of EGC can be included in institutional performance measures with discussions at tumor board meetings.

The limitations of this study lie in its retrospective nature. The information is restricted to the registry data and the complete clinical and staging information at the time of diagnosis were not available. Data on risk factors for gastric cancer such as ethnicity and Helicobacter pylori infection were unavailable. This would be a valuable information in analyzing patterns of EGC incidence in Australia which may reveal high-risk patient cohorts that may benefit from gastric cancer screening, EGCs were identified from histopathology report and the handling of the resection specimens and histologic reporting features that contribute to the ESD criteria was not standardized. Gastric carcinoma in-situ and high-grade dysplasia is likely underrepresented in this dataset, and it is also possible that some cases classified as EGC per the histology were more

advanced. However, it is the first study to elucidate the incidence of EGC in Australia and the potential need for gastric ESD in a Western population. This may assist in establishing the number of proceduralists and centers required to enable procedures to be performed in a timely manner and facilitate development and maintenance of ESD expertise through high volume quaternary centers.

Conclusion

In this State Cancer Registry study, 237 EGCs were diagnosed over a 6-year period, representing 20% of gastric adenocarcinomas. Most EGCs fulfilled criteria for ESD. Advanced resection techniques should be considered part of the management algorithm for EGC, ideally after discussion at a tumor board meeting involving interventional endoscopists. To increase the utilization of ESD, patients should be referred to centers with expertise in lesion assessment and advanced endoscopic resection, and systems implemented to improve training, accreditation, and access to ESD.

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TABLE 1: Suitability criteria for endoscopic submucosal resection

- STANDARD -				
Differentiation	**Size**	**Ulcer**	**LVI**	**Tumour depth**
Well/Moderate	≤2cm	None	None	T1a
- EXTENDED -				
Differentiation	**Size**	**Ulcer**	**LVI**	**Tumour depth**
Well/Moderate	Any	None	None	T1a
Well/Moderate	≤2cm	None	None	T1b (<500μm)
Well/Moderate	≤3cm	Present	None	T1a
Poor	≤2cm	None	None	T1a

Adapted from Japan Gastroenterological Endoscopy Society, 2016 [7] LVI; lymphovascular invasion

TABLE 2: Comparison of EGCs treated with surgical resection versus endoscopic therapy

	Surgical, n = 149	**Endoscopic, n = 33**	**p value**
Age at diagnosis (median, range)	69 (26 – 93)	71 (51 – 88)	0.168
Male (n, %)	105 (71)	23 (70)	0.690
Cross-sectional location of tumour (n, %)			
Anterior wall	60 (40)	3 (10)	<0.005
Posterior wall	14 (9)	8 (24)	<0.005
Lesser curvature	6 (4)	4 (12)	<0.005
Greater curvature	27 (18)	2 (6)	<0.005
Longitudinal location of tumour (n,%)			
GOJ/cardia	42 (28)	11 (33)	<0.005
Upper third of stomach	5 (3)	1 (3)	<0.005

Middle third of stomach	14 (9)	5 (15)	<0.005
Lower third of stomach	28 (19)	16 (49)	<0.005
Depth of tumour (n, %)			
Tis	3 (2)	4 (12)	<0.005
T1a	55 (37)	20 (61)	<0.005
T1b	91 (61)	9 (27)	<0.005
Differentiation (n, %)			
Well/Moderate	64 (43)	15 (45)	0.205
Poor	37 (25)	3 (10)	0.205
Not reported	48 (32)	15 (46)	0.205
Diameter (mm, median, range)	21.2 (0.2 – 65)	17.6 (6 – 90)	0.179
Lymphovascular invasion (n, %)	24/146 (16)*	4/31 (13)*	0.346
Perineural invasion (n, %)	4/134 (3)*	0/24 (0)*	0.422
Ulceration (n, %)	11/139 (8)*	2/26 (8)*	0.062

Pathologic margins clear (n, %)	143 (96)	23/30 (77)*	<0.005

GOJ – gastro-oesophageal junction

Table 3: Absolute and expanded indications for endoscopic resection of gastric cancer

- ABSOLUTE INDICATIONS FOR EMR -			
Differentiation	**Size**	**Ulcer**	**Tumour depth**
Well/Moderate	≤2cm	None	T1a
- ABSOLUTE INDICATIONS FOR ESD -			
Differentiation	**Size**	**Ulcer**	**Tumour depth**
Well/Moderate	>2cm	None	T1a
Well/Moderate	≤3cm	Present	T1a
- EXPANDED INDICATIONS FOR ESD -			
Differentiation	**Size**	**Ulcer**	**Tumour depth**
Poor	≤2cm	None	T1a
- RELATIVE INDICATIONS FOR ESD -			
Elderly and high-operative-risk patients with severe comorbidities with tumors that do not fulfil above indications			

Adapted from Japanese Gastric Cancer Treatment guidelines 2018[31]

EMR; endoscopic mucosal resection, ESD; endoscopic submucosal dissection.

FIGURE 1: Layers involved in T1a and T1b early gastric cancer

Early gastric cancer involves the mucosa (T1a) or submucosa (T1b). T1a disease is further defined as involving the epithelium (M1), lamina propria (M2) or muscularis mucosae (M3). T1b disease is subclassified according to the micrometric depth of invasion into the submucosa, with depths of up to 500μm, 1000μm and 1500μm beyond the muscularis mucosae commonly referred to as SM1, SM2 and SM3, respectively.

EGC – early gastric cancer; SM – submucosa

*SM1<500μm meets extended criteria for ESD

Adapted from American Cancer Society. 2018

FIGURE 2: Gastric cancers reported to Victorian Cancer Registry between 2011 and 2016, divided into Early Gastric Cancer and Tumour Stage >IA

FIGURE 3: Early Gastric Cancer reported to Victorian Cancer Registry 2011-2016