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EDITORIAL

Gastric cystica profunda: Another indication for minimally invasive endoscopic resection techniques?

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Abstract

Gastric cancer presents a significant global health burden, as it is the fifth most common malignancy and fourth leading cause of cancer mortality worldwide. Variations in incidence rates across regions underscores the multifactorial etiology of this disease. The overall 5-year survival rate remains low despite advances in its diagnosis and treatment. Although surgical gastrectomy was previously standard-of-care, endoscopic resection techniques, including endoscopic mucosal resection and endoscopic submucosal dissection (ESD) have emerged as effective alternatives for early lesions. Compared to surgical resection, endoscopic resection techniques have comparable 5-year survival rates, reduced treatment-related adverse events, shorter hospital stays and lower costs. ESD also enables *en bloc* resection, thus affording organ-sparing curative endoscopic resection for early cancers. In this editorial, we comment on the recent publication by Geng *et al* regarding gastric cystica profunda (GCP). GCP is a rare gastric pseudotumour with the potential for malignant progression. GCP presents a diagnostic challenge due to its nonspecific clinical manifestations and varied endoscopic appearance. There are several gaps in the literature regarding the diagnosis and management of GCP which warrants further research to standardize patient management. Advances in endoscopic resection techniques offer promising avenues for GCP and early gastric cancers.

Key Words: Early gastric cancer; Endoscopy; Endoscopic submucosal dissection; Gastric cystica profunda

Core Tip: Gastric cystica profunda is a rare pseudotumour with risk of progression to gastric cancer. In addition to endoscopic visual assessment, endoscopic ultrasound and computed tomography of the abdomen should be used to investigate the depth and lymph node invasion depending on the lesion morphology. Endoscopic resection, specifically endoscopic submucosal dissection, can be an effective management strategy.

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INTRODUCTION

Gastric cancer represents a significant global health challenge, ranking as the fifth most common malignancy and the fourth leading cause of cancer deaths worldwide in 2020[1,2]. The International Agency for Research on Cancer projected a rise in the annual burden of gastric cancer to 1.8 million new cases and approximately 1.3 million deaths by 2040 globally[3]. There exists considerable global variation in gastric cancer incidence, with the highest rates observed in Asia and Eastern Europe, and a predilection for men over women. Sung *et al*[1] suggested a 40-fold difference in gastric cancer incidence between Eastern Asia (*e.g.* Japan and Mongolia, which have the highest incidence) and North America and North Europe (which have the lowest incidence). This variability is likely influenced by multiple factors, including environmental, genetic, dietary, and infectious elements, such as variations in *Helicobacter pylori* (*H. pylori*) prevalence and virulence[1].

The overall 5-year survival rate for gastric cancer patients globally stands at approximately 20%-30%[4]. However, notably higher survival rates, such as 67% in Japan and 69% in Korea, have been observed, largely attributed to robust screening programs facilitating detection of early gastric cancer (EGC) and their treatment[5,6]. Gastric cancers can be categorized based on their topography, with the majority occurring in the distal stomach (non-cardia), often associated with *H. pylori*, while those located in the proximal stomach (cardia) tend to correlate with increased alcohol consumption, smoking, and obesity[7-9].

The Japanese Society for Gastroenterological Endoscopy defines EGC as cancer that does not invade gastric layers deeper than the submucosa, regardless of lymph node involvement[10]. Histopathological exam is the gold standard for diagnosis of early EGC[11]. However, with improved endoscopic technologies, including white light endoscopy, magnifying endoscopy with narrow band imaging, and chromoendoscopy, the detection, optical analysis, and diagnosis of EGCs has improved[12]. Computed tomography (CT) or endoscopic ultrasound (EUS) are used for staging and determination of presence of lymph nodes. Gastrectomy with lymph node dissection was the standard of treatment for EGC with a 5-year overall survival rate of > 97%[13]. However, endoscopic resection techniques, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have emerged as accepted standards, particularly for patients without lymph node involvement or those meeting absolute indications per Japanese guidelines[13,14].

ENDOSCOPIC RESECTION TECHNIQUES

EMR, pioneered in Japan in the 1990s, initially targeted early gastric lesions detected through screening efforts and community awareness, proving effective as an *en bloc* resection technique for lesions under 15 mm[15]. However, larger lesions necessitated piecemeal resection, hindering margin evaluation. Thus, ESD was developed in the early 2000s and enabled *en bloc* resection of larger lesions (≥ 20 mm) by using an electrosurgical knife facilitating dissection in the submucosal plane[15]. A retrospective cohort study comparing ESD and gastrectomy for EGC or severely dysplastic lesions found that gastrectomy was associated with significantly longer operative time (265 minutes *vs* 89.6 minutes, $P < 0.001$) and length of hospital stay (9.9 days *vs* 3.0 days, $P < 0.001$)[16]. There was no difference in mortality, but gastrectomy was also associated with higher overall complication rate[16]. Jeon *et al*[17] compared ESD with surgery for EGC demonstrated similar 5-year overall survival rates (96.5% *vs* 99.1%, $P = 0.125$), and disease-specific survival rates (100% *vs* 99.1%). However, the disease-free survival rate (90.3% *vs* 98.0%, $P = 0.002$), and recurrence-free survival rates (95.1% *vs* 98.0%, $P < 0.001$) were lower in ESD compared to surgery[17]. A retrospective analysis comparing EMR *vs* gastrectomy for intramucosal gastric cancer found no difference in the risk of death (HR 1.30, 95%CI: 0.87-2.23) or recurrence (HR 1.18, 95%CI: 0.22-6.35)[18]. EMR was associated with shorter length of hospital stay (median 8 days *vs* 15 days, $P < 0.001$), and cost of care ($2049 *vs* $4042, $P < 0.001$), compared to surgery[18]. However, EMR was associated with a significantly higher risk of metachronous gastric cancers (HR 6.72, 95%CI: 2.00-22.58) which were also treated with EMR without any effect on overall survival[18]. Two additional retrospective studies comparing endoscopic resection *vs* surgery for patients with EGC found comparable 5-year overall survival[14,19]. There were higher rates of metachronous gastric cancers in patients treated with endoscopic resection which were successfully treated with endoscopic resection [14,18,19]. In summary, endoscopic resection techniques offer safe, effective, and minimally invasive alternatives to surgical resection, with comparable 5-year survival rates, lower adverse event rates, shorter hospital stays, and reduced costs[13,14,20].

Endoscopic resection techniques, including ESD and EMR, have different strengths in management of EGCs. In a meta-analysis comparing ESD and EMR for EGC, ESD was superior to EMR for "*en bloc*" and histological complete resection (OR = 9.69, $P < 0.001$ and OR = 5.66, $P < 0.001$, respectively)[21]. ESD is also associated with lower recurrence rates (OR = 9.69, $P < 0.001$[21]). However, ESD is also associated with higher complications, including higher perforation rates (OR = 0.09, $P < 0.001$) and a longer operating time (mean difference = 1.73, $P = 0.005$) with no difference in adverse events related to bleeding[21]. Additionally, a Japanese multicenter prospective cohort study compared 5-year overall survival in patients with EGC which were categorized by tumour differentiation, tumour staging, size, and ulceration and received endoscopic resection, with ESD in 99.6% and EMR in the remaining patients[22]. They reported a 5-year overall survival rates of 89% (95%CI: 88.3%-89.6%) in patients undergoing endoscopic resection which was similar to those who underwent surgical resection for EGC. Additionally, there was no difference in hazard ratio between the various characterizations of EGC, affirming the efficacy of these techniques[22]. A prospective study evaluated ESD of gastrointestinal lesions in 10 centers from the United States of America and Canada and found high proportions of *en bloc*, R0 and curative resections in 91.5%, 84.2%, and 78.3%, respectively[23]. These proportions are similar to proportions identified in a meta-analysis and systematic review, of 95%, 89%, and 82% for *en bloc*, R0 and curative resections, respectively, in Eastern studies[24]. Daoud *et al*[24] did report lower proportions of all resection markers in studies from Western countries. However, all included studies pre-dated the prospective study by Draganov *et al*[23], likely representing an improvement in ESD techniques after its adoption in Western countries. In a recent article, Kim[25] proposed that quality indicators, such as *en bloc*, complete, and curative resection rates of > 95%, > 90% and > 80%, respectively, should be implemented by all endoscopists for ESD for EGC to improve patient outcomes.

Recognizing the effectiveness of endoscopic resection, the Japanese Gastroenterological Endoscopy Society (JGES) established it as a safe and effective strategy, outlining absolute and expanded criteria for ESD[26]. Both the absolute and expanded indication lesions are presumed to have a < 1% risk of lymph node metastasis. This approach has been adopted by the American Society of Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) for managing EGC in Western populations[27,28].

GASTRIC CYSTICA PROFUNDA: WORKUP AND MANAGEMENT

In this issue, Geng *et al*[29] described their outcomes for the endoscopic management of gastric cystica profunda (GCP); which is a rare, gastric lesion initially identified by SCOTT and Payne[30]. The etiology of GCP remains unclear, with some studies suggesting associations with prior gastric insults, such as surgery or endoscopic procedures, with others finding no such correlation[31-34]. Only 12.5% of patients were noted to have a previous endoscopic or surgical treatment, suggesting a lack of association between previous gastric insults with GCP development[29]. In addition, geographic variation of GCPs is heterogenous worldwide, with most reports of GCP diagnosis and management from China[29,31,35], and only a few reports from Japan[36,37], Turkey[34], Pakistan[38], and United States[39,40]. Clinical presentations also vary and may include epigastric abdominal pain, belching, regurgitation, gastrointestinal bleeding, weight loss, or anorexia, though many patients remain asymptomatic and are diagnosed incidentally during endoscopy; such as in 63.5% of patients in Geng *et al*[29] study. They performed a single-center retrospective review of 104 patients with GCP who underwent endoscopic resection[29]. Endoscopically, GCP manifests as a tumour-like gastric lesion or polyp, characterized histologically by cystic dilations of the gastric glands and hyperplasia of connective tissue extending into the submucosa of the stomach[41]. Geng *et al*[29] demonstrated that 99% of GCP exhibited intraluminal growth and 74% had regular morphology. Most studies report GCP presenting as submucosal lesions, mimicking gastrointestinal stromal tumour[42], with fewer reports of GCP presenting with gastrointestinal bleeding[43] or malignancy[44].

Diagnosing GCP can be challenging, as biopsies obtained during endoscopy generally capture only the superficial mucosa. EUS may aid in identifying GCPs and determining their depth of invasion, with multiple anechoic cysts in the submucosa being a consistent EUS finding[39]. Although EUS is reliable for investigation of depth of most small and non-ulcerated gastric lesions, it has been shown to have poor accuracy determining the depth of gastric lesions greater than 20mm, those with ulceration, and/or non-flat morphology, which usually make up the expanded criteria outlined by JGES[45,46]. CT of the abdomen can assist in identifying associated lymph nodes and metastasis[47]. Despite the availability of various diagnostic techniques, there are no clear guidelines on the approach to diagnosing GCP. It is, therefore, reasonable that in a patient where GCP is suspected, EUS should be performed, for histopathology and depth of invasion evaluation. Moreover, CT should be performed, specifically in the presence of high-risk lesions, such as those with ulceration, irregular morphology, diameter > 20 mm, or IIc morphology. Although the role of optical assessment has not been established for GCP, Geng *et al*[29] found that irregular and ulcerated lesions in the cardia, IIa + IIc morphology were shown to be significantly associated with GCP with EGC compared to those without gastric cancer. Multidisciplinary team discussion, ideally at centers with expertise in minimally invasive endoscopic resection techniques and involving endoscopists, surgeons, radiologists, and pathologists, is recommended to optimize patient management.

Despite their benign nature, GCPs harbour malignant potential. Geng *et al*[29] reported a 59.6% association between GCP and EGC, consistent with 66.67% reported in a previous study[48]. Consequently, resection is warranted, with endoscopic resection preferred over surgical gastrectomy, particularly for benign lesions lacking deeper invasion. While no trials have compared various endoscopic resection techniques specifically for GCPs, ESD likely supersedes EMR due to its high rate of *en bloc* and histologically complete resection, especially given the risk of malignant potential[14,20]. Jiang *et al*[49] compared curative resection rates, rates of local recurrence, metachronous gastric cancers, and mortality in patients who underwent gastric ESD for GCP compared to gastric ESD for other indications and did not find any difference in their retrospective review. Almost 77% of patients in the aforementioned study underwent ESD. They

reported *en bloc* and complete resection in 91.3% of cases. Five cases had recurrence, although the initial resection modality was not specified. We suggest ESD for resection of GCP, especially larger lesions with irregular morphology or lateral spreading, as ESD facilitates more thorough post-resection assessment of surrounding and deeper layers to ensure complete resection, making it preferable despite its longer procedural time and higher risk of perforation compared to EMR. ESD can also enable resections of gastric lesions in patients who are comorbid or too frail for surgery, therefore, expanding its role in management of GCP and EGC[50].

CONCLUSION

A dearth of literature exists regarding the diagnosis and management of GCPs, likely attributed to their low incidence, with the majority of reported cases and series originating from the Eastern regions. This discrepancy could reflect underdiagnosis in Western populations rather than geographic prevalence variations. Consequently, additional studies elucidating endoscopic appearances and features on EUS or CT would enhance diagnostic accuracy. ESD should be the management of choice for EGCs given their superiority in *en bloc*, complete and curative resection over EMR, and equivalent success in both Eastern and Western settings. Moreover, centralizing endoscopic GCP management in expert centers could optimize patient outcomes. Integrating GCP management into the endoscopic resection criteria for gastric lesions outlined by ASGE, ESGE, and JGES would promote standardized management protocols.

FOOTNOTES

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