Heliyon 10 (2024) e29349

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

# Endoscopic submucosal dissection (ESD) for gastritis cystica profunda (GCP) with early gastric cancer: A propensity score matching analysis

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ARTICLE INFO

*Keywords:*
Early gastric cancer
Gastritis cystica profunda
Endoscopic submucosal dissection

ABSTRACT

*Background and aim:* Cystic dilatation of the gastric glands within the mucosal layer is the hallmark of the rare condition known as gastritis cystica profunda (GCP). Although it has been proved that GCP is the precursor lesion for early gastric cancer (EGC), the management strategy of GCP-related EGC is not well established.The purpose of this research was to determine if ESD is effective and safe for GCP-related EGC.

*Methods:* Patients with EGC who had ESD at Beijing Friendship Hospital between January 2015 and May 2023 were retrospectively included. All patients were divided into two groups: those with GCP-related EGC, and those with EGC alone. The two groups were matched 1:1 using the propensity score matching (PSM) method. Curative resection rate, postoperative adverse outcome rate (bleeding, perforation, stricture), and recurrence rate were the primary measures used to evaluate the efficacy and safety of ESD.

*Results:* There were a total of 386 participants (44 with GCP and 342 with EGC alone). Following PSM, 44 patients were paired and analyzed separately. Except for the presence of cysts in EUS (multiple/single/none cyst: 12/2/5 versus 1/0/25, $P < 0.0001$), there was no change in baseline characteristics, EUS appearance, or histology results between groups. Overall, there was no significant difference in curative resection rates between the GCP group (70.5 %) and the control group (81.8 %) ($P = 0.211$). Postoperative complications were comparative (9/44 vs 5/44, $P = 0.244$), as were rates of local recurrence (1/44 vs 0/44, $P = 1.0$), metachronous gastric cancer (1/44 vs 0/44, $P = 1.0$), and mortality (0/44 vs 0/44, $P = 1.0$).

*Conclusions:* Existence of cysts in EUS is a characteristic presentation to distinguish GCP-related EGC from EGC-alone lesions. ESD might be a safe and effective therapy for patients with GCP-related EGC.

## 1. Introduction

Gastritis cystica profunda (GCP) is an uncommon lesion featuring submucosal hyperplastic and cystic dilation of the stomach

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https://doi.org/10.1016/j.heliyon.2024.e29349
Received 11 December 2023; Received in revised form 4 April 2024; Accepted 5 April 2024

glands. Evidence suggests that chronic inflammation, ischemia, and foreign substances utilized during stomach anastomosis may contribute to these changes [1,2]. Despite its prevalence, GCP is frequently underdiagnosed due to its innocuous clinical presentation and inconspicuous endoscopic features.

Studies have uncovered evidence from both biological mechanisms and clinical manifestations suggesting that GCP are the precursor lesions for gastric cancer. A review of 10,728 patients who had surgery for gastric cancer revealed that the EBV-positive rate was significantly higher in the GCP group. It indicated that GCP was strongly associated with EBV-positive gastric cancers and was highly suspected as a premalignant lesion [3].What's more, primary gastric cancer, as well as secondary GCP, has been observed in experimental mice with a predisposition to Helicobacter infection [4].

Many pathological findings about GCP-related early gastric cancers have been documented in recent clinical investigations. Bogomoletz et al. described six cases of GCP coupled with primary gastric stump adenocarcinoma, demonstrating neoplastic gland intermingling with GCP and dysplastic alteration in the transitional area [5]. Furthermore, Mitomi et al. reported a case in which atypical or dysplastic epithelium was found in the deeper region of the GCP close to cancers [6]. A Korean study of 39 GCP patients found that 10,16 were related with early gastric cancers, 9 with adenoma, and 3 with advanced adenocarcinoma [7]. Early diagnosis and treatment of GCP is of paramount importance due to its propensity to exacerbate survival outcomes, metastasize to distant organs, and eventually result in mortality if not promptly addressed.

Previous evidence has demonstrated that endoscopic submucosal dissection (ESD) is a safe and effective therapeutic option for GCP in previously un-operated stomachs [8]. However, endoscopic manifestations and therapeutic options for GCP-related early gastric cancers have not been well studied. Certain characteristics of GCP-related gastric cancers set them apart from other malignancies diagnosed at an earlier stage. On one hand, the accurate assessment of lesions and their type using endoscopic ultrasound (EUS) is hindered by the unique cystic dilatation observed in GCP. On the other hand, the assessment of lesion extent through post-operative histology is more difficult in cases of polypoid cystic ectasia of benign gastric glands that involve the submucosa. Hence, these challenges may arise in the identification of malignancies at an early stage, evaluation of risk factors before surgical intervention, determination of suitable treatment approaches, and establishment of a coherent follow-up strategy (e.g., making decisions regarding the necessity of subsequent surgical procedures).

Sporadic case reports have addressed the efficacy of ESD in treating GCP-related early gastric cancers, however, no evidence from cohort studies has yet been found. This study aimed to evaluate the efficacy and safety of ESD in patients with GCP-related early gastric cancers through a propensity score matching (PSM) analysis. The results of this study will provide valuable insights into the application of ESD in the treatment of this rare and challenging condition.

## 2. Methods

### 2.1. Study design and subjects

We performed a propensity-score matching (PSM), retrospective cohort study in a tertiary center in Beijing from January 2015 to May 2023. Patients undergoing endoscopic resection for early gastric cancers accompanied with or without GCP confirmed by histopathology at Beijing Friendship Hospital, Capital Medical University between January 2015 and May 2023 were enrolled in the study. The exclusion criteria were as follows: 1) history of gastric surgery; 2) loss to follow-up; 3) underwent EMR only; 4) simultaneous ESD for multiple synchronous gastric neoplasms. All patients were assigned a unique identifier for the duration of the study to ensure confidentiality. Informed consent was waived because of its retrospective design.

### 2.2. Data collection

Clinical data were retrieved through the hospital information system (His), which is the electronic healthcare database under the management of Beijing Friendship Hospital, Capital Medical University. Clinical parameters were retrieved and analyzed, including demographics, medical comorbidities, procedure records, histopathology results, and post-procedural adverse events. We also manually reviewed the Medicare-I-Enenter system to extract data on endoscopic procedures. Details of OGD (the tumor location, morphology, the color of tumors, and coexistence of ulcers), EUS (the origin, extent, echo texture, and echo patterns of the lesion), and ESD/EMR were also collected.

The demographic characteristics (gender and age), and medical comorbidities including liver and renal diseases, hypertension (HT), ischemic heart diseases (IHD), cerebrovascular accidents (CVA), diabetes mellitus (DM), myocardial infarction (MI), peripheral vascular diseases (PVD), and congestive heart failure (CHF) were retrieved via an electronic database. We standardized the data by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Charlson comorbidity index was calculated based on the above factors.

### 2.3. Outcome measurements and definitions

In our study, we used a standardized ESD protocol employing the GIF-Q260J endoscope and VIO300D generator under general anesthesia. We marked lesions with APC or an ESD knife, then injected a saline-hyaluronate-indigo carmine mix into the submucosa. We made mucosal incisions outside the marked area and dissected the submucosa with an ESD knife. Post-dissection, we retrieved the specimen and performed preventive coagulation on visible vessels to prevent bleeding. We defined the tumor site as upper (cardia or fundus), middle (gastric body or gastric angle), or lower (gastric antrum and others). For morphological assessments, we utilized the

Paris endoscopic classification, distinguishing lesions as protruded (0-I), superficial (0-II, with subtypes IIa, IIa + IIc, IIb, IIc, IIc + IIa), or excavated (0-III), to ensure a consistent and universally understandable categorization [9]. Regarding EUS, we employed two devices tailored to lesion characteristics: the UM-3R, 20 MHz ultrasound probe for smaller or flatter lesions, and the EG-530UT/EG-530UR ultrasound endoscope for larger or more depressed lesions. EUS examinations were conducted by skilled endoscopists to determine the lesion's origin and full extent. Finally, we categorized the echo texture of GCP lesions as either homogeneous or heterogeneous, with echoic patterns classified into hypoechoic, hyperechoic, or mixed categories. For histopathology results, grade of differentiation (low/intermediate/high), tumor depth (laminae propria mucosae/muscularis mucosa/SM1/SM2), and lymphovascular invasion/horizontal or vertical margin invasion were followed. Tumor differentiation was classified according to the World Health Organization (WHO) histological grading system. Our pathologists assessed the degree of glandular differentiation within the tumor, categorizing them as well-differentiated, intermediately differentiated, or poorly differentiated based on the resemblance of tumor cells to normal gastric mucosal cells. The assessment of tumor depth involved examining the vertical extent of tumor invasion into the gastric layers. This was done by meticulously measuring the distance from the top of the tumor to the deepest point of invasion. We used established criteria to categorize the invasion into mucosa, submucosa, muscularis propria, or deeper layers. To determine margin involvement, we carefully examined the lateral and vertical resection margins of the excised specimens. The presence of tumor cells at or within a specific distance from the resection margin was noted. A margin was considered involved if tumor cells were found at the edge of the resected specimen, indicating incomplete resection. Histological diagnosis was established in accordance with the Japanese Classification of Colorectal Carcinoma and JGES guidelines as well as the Vienna classification [10,11].

## 3. Statistics

Data were analyzed by R software (4.1.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed in mean (±standard deviation). Categorical variables were presented as number (percentage). All statistical tests were 2-sided. Statistical significance was taken as $p < 0.05$.

We applied propensity score matching (PSM) to mitigate confounding factors, ensuring a robust causal inference framework. We utilized the 'matchit' package within the R statistical software (4.1.2; R Foundation for Statistical Computing, Vienna, Austria), adopting the nearest neighbor matching method. The matching criteria included patient demographics such as age and gender, along with clinical characteristics including degree of differentiation, vascular invasion, lesion size, and lesion location. We adhered to a 1:1 matching ratio, thereby aligning each treated subject with a corresponding control to diminish systematic disparities between groups.

## 4. Results

### 4.1. Patient characteristics

The flow chart for patient selection is depicted in Fig. 1. According to the post-ESD pathological results, a total of 342 patients who underwent ESD or endoscopic mucosal resection (EMR) for early gastric cancer, along with 44 patients who had early gastric cancer accompanied by GCP and underwent ESD/EMR, were found to meet the inclusion and exclusion criteria as previously stated. Following the implementation of 1:1 PSM, a total of 44 patients from the GCP group and 44 patients from the control group were selected to form the post-matching cohort.

For demographics, there was no difference in gender, age, or Charlson comorbidity index between the two groups. Table 1

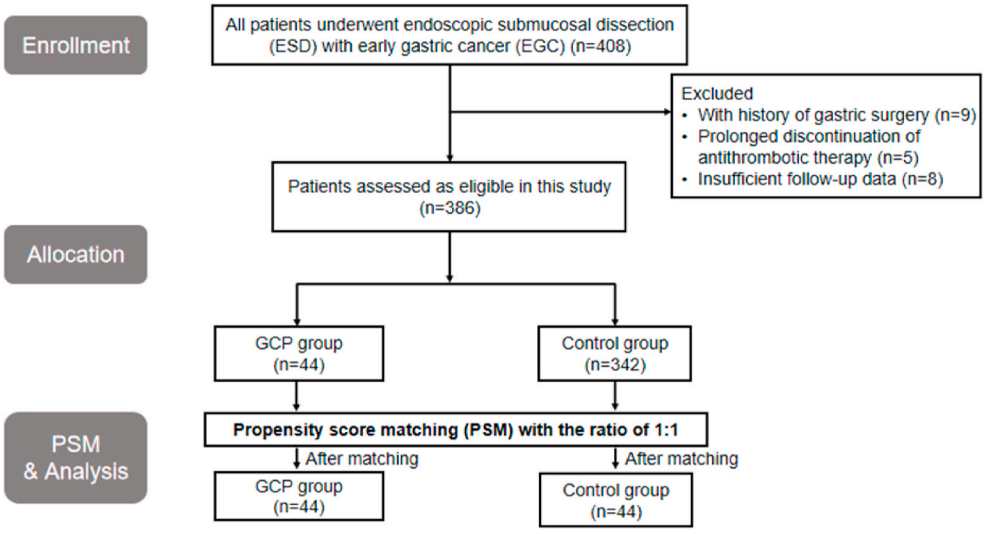


**Fig. 1.** Flow diagram showing selection of patients with EGC who underwent ESD.

demonstrates baseline characteristics of the patients in the two groups.

### 4.2. Endoscopic characteristics

In the context of white light endoscopy (WLE), it was observed that there were no substantial disparities in endoscopic characteristics between the two groups. According to the data shown in Table 1, the prevalence of GCP was highest in the upper gastrointestinal (GI) tract, accounting for 61.4 % (27 out of 44 cases). The middle GI tract had a lower prevalence of 27.3 % (3 out of 11 cases), while the lower GI tract had the lowest prevalence of 11.3 % (5 out of 44 cases). The majority of morphological types observed in both the GCP and control groups are Type 0-IIa, Type 0-IIb, and Type 0-IIc + IIa. There is no significant difference between the two groups in terms of these morphology types (P = 0.065). There were instances of surface mucosal ulcers observed in four patients in the GCP group and one patient in the control group, with no statistically significant difference between the two groups (P = 0.167).

43.2 % (19/44) and 59.1 % (26/44) of patients in GCP and control groups underwent EUS for further investigation. Fig. 2 showed the typical features of GCP with multiple cysts. 35.7 % (5/14) of lesions in GCP group and 44.4 % (8/18) in the control group originated from the basal mucosal layer and extended into the submucosal space (P = 0.745). In GCP group, 14 of 44 lesions were found to have cysts (Multiple cysts: n = 12; Single cyst: n = 2), while in control group only one was detected (Multiple cysts:n = 1) (P < 0.001). High, low and medium-low echo intensity were observed in 1, 14, and 4 patients in GCP group while as to that in control group, high, low, equal, and medium-low echo intensity were detected in 2, 12, 5 and 7 patients, respectively (P = 0.148). The EUS showed a homogeneous echo pattern in 8 patients in GCP group and 17 patients in control group (P = 0.121).

### 4.3. Procedure-related and histopathological outcomes

The overall treatment outcomes are detailed in Table 2. The endoscopic resection of early gastric cancer with or without GCP was carried out in all cases with ESD between two groups. The procedure time was 114.14 ± 114.198 in the GCP group and 136.48 ± 191.564 in the control group. The median procedure time for the GCP group was not significantly different from that for the control group (P = 0.508). The curative resection rate was 70.5 % in GCP group and 81.8 % in control group. There was no difference in the curative resection rate between the 2 groups (P = 0.211). Most of cases in both groups have an eCura score of 0–1. The average tumor size is 2.47 ± 1.469 in GCP group and 2.22 ± 1.082 in control group (P = 0.370). 3 lesions in GCP group and 4 lesions in control group were found to be poorly differentiated while others were low (GCP group:n = 16; Control group:n = 24)or intermediate grade of differentiation (GCP group:n = 25; Control group:n = 16). Positive horizontal/vertical resection margin involvement was not differently noted between two groups (P = 1.000; P = 0.078). The difference of lymphovascular invasion also failed to be observed.

### 4.4. Follow-up outcomes

The median follow-up period was 308.93 ± 116.424 days in the GCP group and 324.39 ± 114.827 days in the control group. The number of composite adverse outcomes (bleeding, perforation and stricture) was 9 in the GCP group and 5 in control group (P = 0.244). The occurrence of local recurrence (1/44 vs 0/44, P = 1.0), metachronous gastric cancer (1/44 vs 0/44, P = 1.0) and death (0/44 vs 0/44) was also not significantly different between the two groups.

## 5. Discussion

Our study enhances the current understanding of GCP and early gastric cancer by providing a comprehensive diagnostic approach

**Table 1**
Demographics, OGD and EUS characteristics after PSM.

| | GCP group | Control group | *P*-value |
|---|---|---|---|
| Gender, n (%) | | | 0.502 |
| Male | 40 | 38 | |
| Female | 4 | 6 | |
| Age (years, mean ± SD) | 68.82 ± 6.500 | 68.59 ± 7.813 | 0.811 |
| Charlson comorbidity index (mean ± SD) | 3.55 ± 1.470 | 3.48 ± 1.438 | 0.864 |
| Tumor location (upper/middle/lower), n (%) | 27/12/5 | 18/19/7 | 0.156 |
| Macroscopic type | | | 0.065 |
| Type 0–IIa | 12 | 12 | |
| Type 0–IIb | 13 | 12 | |
| Type 0–IIc | 0 | 6 | |
| Type 0–IIc + IIa | 11 | 12 | |
| Type 0–IIa + IIc | 5 | 2 | |
| Others | 3 | 0 | |
| Coexistence of ulceration (±), n (%) | 4 | 1 | 0.167 |
| Echo intensity (high/low/equal/medium-low), n (%) | 1/14/0/4 | 2/12/5/7 | 0.148 |
| Homogeneous echo pattern (y/n), n (%) | 8/11 | 17/9 | 0.121 |
| Submucosal invasion (y/n), n (%) | 5/14 | 8/18 | 0.745 |
| Existence of cysts (Multiple/Single/None) | 12/2/5 | 1/0/25 | <0.0001 |

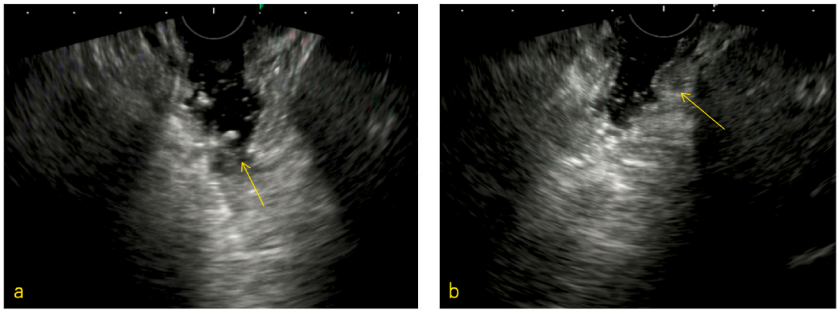


**Fig. 2.** Typical features of GCP with multiple cysts (a)multiple hypoechoic cysts of varying sizes (b)homogeneous hypoechoic cysts.

**Table 2**
Endoscopic resection results and long-term outcomes.

| | GCP group | Control group | *P*-value |
|---|---|---|---|
| Procedural time (minutes, mean ± SD) | 114.14 ± 114.198 | 136.48 ± 191.564 | 0.508 |
| Length of stay (days, mean ± SD) | 11.57 ± 4.948 | 11.18 ± 3.280 | 0.667 |
| Curative resection, n (%) | 31 (70.5) | 36 (81.8) | 0.211 |
| eCura score, n (%) | | | 0.534 |
| 0~1 | 37 (84.1) | 39 (88.6) | |
| 2~4 | 7 (15.9) | 5 (11.4) | |
| 5~7 | 0 | 0 | |
| Follow-up period (days, mean ± SD) | 308.93 ± 116.424 | 324.39 ± 114.827 | 0.532 |
| Follow-up outcomes, n (%) | | | |
| Composite adverse outcomes (bleeding, perforation, stricture) | 9 (20.5) | 5 (11.4) | 0.244 |
| Local recurrence | 1 (2.3) | 0 | 1 |
| Metachronous gastric cancer | 1 (2.3) | 0 | 1 |
| Death | 0 | 0 | NA |

that integrates WLE and EUS, offering more precise assessments compared to previous research. Additionally, we showcase the efficacy and safety of ESD as a superior, less invasive alternative to the traditional surgical treatment for GCP and early gastric cancer, marking a significant advancement in patient care. These methodological strengths, combined with our robust statistical analysis using propensity score matching, position our study as a pivotal reference in the field, contributing valuable insights and setting new benchmarks for future research.

GCP has been classified as a premalignant lesion in limited prior studies. As of now, there is no general agreement on how to address GCP, especially for its relationship with gastric cancer and the resection strategies. In this study, we found that ESD was a safe and feasible technique for early gastric cancer accompanied by GCP.

EUS is beneficial in displaying the shape, extent, and echoic patterns of GCP. The characteristic features of GCP such as echo intensity which were initially described by Xu et al. have been repeatedly observed in our study [8]. Additionally, we have found that the presence of cysts were specific in GCP-related EGC compared with EGC-alone. Hence, when confronted with a biopsy-confirmed EGC exhibiting numerous cystic structures during EUS, it is imperative for endoscopists to contemplate the potential presence of GCP-related EGC. Consequently, a more meticulous examination of the GCP lesion becomes necessary in order to establish a comprehensive diagnosis. Of note, histological testing is required for a conclusive diagnosis. In our study, no significant findings were detected under white-light endoscopy or EUS except the structure of cysts in GCP group compared with early gastric cancers. It has been claimed that EUS-guided FNA of the cystic fluid might differentiate GCP from a malignant tumor since tumor markers like CEA and CA19-9 could be evaluated in the cystic fluid. No individual EUS-guided FNA was performed in our study because all involved cases underwent ESD right after EUS.

Endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD) and total gastrectomy, have been investigated for GCP treatment despite the lack of data. In our study, we concur with earlier researchers that ESD was efficient for treating GCP or GCP with early gastric cancer. Additionally, ESD was used for diagnostic objectives. Endoscopic resection using EMR or ESD is superior to open surgery in many ways. The gastric function is more reliably and safely preserved after endoscopic resection. Endoscopic procedures were used successfully to remove GCP despite its location deep within the submucosal area, with only minimal bleeding noted. In our study, both cases in GCP and control groups have over 70 % of complete resection rate. Only one recurrence and sporadic cases of bleeding, perforation and stricture occurred during one-year follow-up period. Nevertheless, it is important to exercise caution when interpreting these findings due to the limited duration of the present study, which only followed up for a period of 1 year. Furthermore, it remains uncertain whether the margin-positive GCP tissues will undergo a recurrence of early cancers in the future. Therefore, additional fundamental research is necessary to validate the biological mechanisms underlying GCP-associated early cancers.

However, there were some limitations to this study. First, our study may exhibit selection bias due to its single-center design, limiting the generalizability and applicability of our findings. Also, the relatively small patient volume and short follow-up period may

limit the extrapolation of our findings to larger cohort. We attributed this reason to the scarcity of GCP. Despite efforts to minimize bias, the unique characteristics of our patient population could influence outcomes. Additionally, there were no established criteria for selecting either surgical or endoscopic treatment, with clinicians' preference and patient finances serving as the overriding considerations. These limitations need to be addressed by additional randomized controlled research based on multicenter experiences.

## 6. Conclusion

In summary, the identification of GCP-related early gastric cancer can be achieved through the utilization of EUS to detect the presence of cysts. Individuals diagnosed with early gastric cancer who also present with GCP may potentially experience favourable outcomes through the implementation of ESD as a therapeutic approach.

## Funding

This study was supported by the National Key Research Program (Grant number:2022YFC3600032).

## Ethics statement

This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Reference Number: YYYXYJ-2021-310). The informed consent was waived in terms of its retrospective design.

## Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## CRediT authorship contribution statement

**Wei Jiang:** Writing – original draft, Data curation, Conceptualization. **Liyi Bai:** Software, Data curation, Conceptualization. **Shutian Zhang:** Supervision. **Rui Cheng:** Writing – review & editing, Conceptualization.

## Declaration of competing interest

The authors have no conflicts of interest to declare. All the authors participated in review of the article and approved the final version of the manuscript.

## Acknowledgements

The authors thank all the patients and the hospital staff.

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