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Correlation between gastritis cystica profunda and the risk of lymph node metastasis in early gastric cancer

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In early gastric cancer (EGC) patients, lymph node metastasis (LNM) risk assessment is particularly important for the selection of surgical methods. In this study, we investigated the correlation between gastritis cystica profunda (GCP) and the risk of LNM in EGC. From January 2014 to December 2019, EGC patients who underwent curative radical gastrectomy were enrolled in this study. The clinicopathological features were analyzed, and the correlation between GCP and the risk of lymph node metastasis was assessed. Data for 180 EGC patients were analyzed, and 17.8% (32/180) had LNM. The incidence of LNM was 2.6% in the GCP-positive group and 21.8% in the GCP-negative group. Univariate analysis revealed that GCP, depth of tumor invasion, and lymphovascular invasion were the risk factors of LNM in EGC patients. Multiple regression analysis showed that GCP was associated with the risk of LNM in EGC patients (OR=0.097, 0.121, 0.100, $p<0.05$). The curve fitting results showed that there was a negative correlation between the GCP and LNM in EGC, which was consistent between different tumor sites, size, ulceration, differentiation types, depth of tumor invasion, lymphovascular invasion, and no significant interaction was found among these factors (p for interaction range 0.224–0.717). GCP is closely related to LNM in EGC. Preoperative assessment of whether EGC is combined with GCP is beneficial for the assessment of the risk of LNM.

Key words: early gastric cancer, gastritis cystica profunda, lymph node metastasis

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1]. According to Chinese cancer statistics, in 2015, the incidence and mortality of gastric cancer ranked second in all malignant tumors in China [2]. The prognosis of gastric cancer is closely related to the clinical stage of the disease. Early gastric cancer (EGC) refers to a gastric tumor that is confined to the mucosa or submucosa, no matter with or without lymph node metastasis. The 5-year overall survival (OS) of EGC patients can be above 90%, and the recurrence rate is less than 2–3%. In contrast, the 5-year OS of patients with advanced gastric cancer is only 20–25% [3].

In recent years, with the improvement of endoscopic technology, there are more options for early gastric cancer surgery. Although radical gastrectomy remains the mainstream treatment for early gastric cancer, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been readily accepted by patients because of their advantages such as small trauma, rapid recovery, high safety, short average hospitalization time, and less impact on postoperative quality of life, and thus is gradually becoming new treatment options for EGC. However, currently, EMR, ESD, and other endoscopic treatment techniques are unable to perform lymph node dissection. In EGC patients, lymph node metastasis (LNM) is an important factor affecting the prognosis, and the 5-year OS of gastric cancer patients with LNM is significantly lower than those without LNM [4]. Therefore, LNM risk assessment is particularly important for the selection of surgical methods in EGC patients.

Through systematic review and meta-analysis, Hatta et al. found that the incidence of LNM in early gastric cancer was about 8.1%, and the risk of LNM was correlated with lymphatic invasion, vascular invasion, positive margin, submucosal invasion (≥500 μm), and tumor size (>3 cm) [5]. Ding et al. found that the depth of tumor invasion, vascular invasion, and tumor differentiation type were independent risk factors for LNM in EGC patients [6]. Osumi et al. found that in pT1b EGC, the risk of LNM in EGC patients with

EBV infection was significantly reduced, suggesting that EBV-related EGC is a promising biomarker for endoscopic resection [7].

Gastritis cystica profunda (GCP) is a rare submucosal lesion of the stomach. Its pathogenesis involves the destruction of gastric mucosa caused by various causes, which lead to the growth of the glands in gastric mucosa through the muscularis mucosa and the formation of cystic hyperplasia. GCP lacks specific clinical manifestations and white light endoscopic manifestations, and most clinicians have a limited understanding of GCP. Choi et al. found that the depth of invasion and LNM in gastric cancer patients with GCP were mostly at the early stage [8]. However, the relationship between GCP, EGC, and LNM has not been fully investigated. Therefore, we retrospectively analyzed 180 cases of EGC patients and selected 38 cases of EGC with GCP for further analysis, as reported below.

Patients and methods

Patient population. In this study, we included 180 patients with EGC confirmed by pathology after curative radical gastrectomy in Changzhou Second Hospital Affiliated with Nanjing Medical University from January 2014 to December 2019 as the research objects. The following clinical and pathological data of the patients were collected: age, gender, tumor size, tumor location, gross classification of the tumor, ulceration, tumor differentiation type, depth of tumor invasion, vascular invasion, GCP, and LNM. The tumor size was recorded as the maximum diameter of the tumor. Based on the Paris classification [9], EGC can be divided into elevated, flat, and depressed types. According to the 2010 guidelines of the Japanese Gastric Cancer Society [10], gastric cancer can be divided into the differentiated type and the undifferentiated type. The differentiated type includes moderately-to-well differentiated tubular adenocarcinoma and papillary adenocarcinoma; and the undifferentiated type includes poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma. The location of the tumor is divided into three parts: cardia and gastric fundus (upper part, U), gastric corpus (middle part, M), and antrum and pylorus (lower part, L). The depth of tumor invasion is classified based on T classification of gastric cancer AJCC/UICC 8th Edition: T1a) tumor invasion of lamina propria or muscularis; T1b) tumor invasion of submucosa [11]. Ulceration, vascular invasion, and GCP were determined by postoperative pathology. The pathological features of GCP were as follows: the proper gastric glands infiltrated deep into mucosa or submucosa, and the glands were cystically expanded, accompanied by connective tissue hyperplasia and inflammatory cells.

Statistical analysis. The count data were expressed as a constituent ratio. χ^2-test or exact probability test was used to compare the rates between groups. The measurement data with normal distribution were expressed as the mean ± standard deviation. The mean values between the two groups were compared using a t-test (normal distribution variable) and the Kruskal-Wallis test (skew distribution variable).

Univariate logistic regression analysis was used to calculate the correlation between clinical and pathological features and lymph node metastasis of EGC (p-value was extended to 0.10). The generalized linear models with a logit link were used to evaluate the independent and comprehensive effects of GCP on LNM in EGC (binary variables). We adjusted gender, age, tumor size, location, ulceration, depth of invasion, vascular invasion, and differentiation type of tumor. After adding these characteristics to the model, the odds ratio of matching was changed by at least 10%.

In the stratified analysis, possible changes in the correlation between EGC lymph node metastasis risk and GCP were also evaluated for the following variables: location (cardia and fundus, U; gastric corpus, M; antrum and pylorus, L), tumor size grouping (≤2 cm or >2 cm), ulceration (absence or presence), differentiation type (undifferentiated or differentiated), depth of tumor invasion (0T1a or 0T1b), and vascular invasion (absence or presence). The generalized additive models (GAM) were used to determine the correlation between the probability of LNM in EGC and GCP.

All data were analyzed using R software (version 3.4.3, http://www.R-project.org). A p-value <0.05 was considered statistically significant.

Results

Baseline demographic characteristics. A total of 180 EGC patients were included in this study, including 38 patients with GCP and 142 patients without GCP. The average age of 38 EGC patients with GCP was 64.7 years old, including 32 males (84.2%) and 6 females. The lesions were located in the fundus of the cardia in 21 cases, in the gastric corpus in 10 cases, and in the antrum and pylorus in 7 cases. Under endoscopy, we found that 37 cases were roughly flat type and 1 case was compressed type. The diameter of the lesion was less than 2 cm in 32 cases and larger than 2 cm in 6 cases. Postoperative pathology revealed that there were 33 cases of differentiated tumor (86.8%), and 5 cases of undifferentiated tumor; 29 cases without ulceration, and 9 cases with ulceration; 37 cases (97.4%) without vascular invasion, and one case with vascular invasion; 23 cases (60.5%) of tumor invasion depth at T1a stage, and 15 cases at T1b stage; 37 cases (97.4%) without LNM and one case with LNM. The comparison of clinical and pathological features between EGC with the GCP group and EGC without the GCP group is shown in Table 1 and Figures 1A–1F. There was no significant difference in age, gender, tumor size, lesion morphology, depth of tumor invasion, and differentiation type between the two groups (p>0.05). There were significant differences in tumor location, ulceration, vascular invasion, and lymph node metastasis (LNM) between the two groups (p<0.05). Among 180 patients with GCP, 32 cases had LNM (17.8%).

Table 1. Comparison of clinicopathological features between GCP-EGC and non-GCP-EGC patients in this study.

Variable	Non-GCP-EGC	GCP-EGC	p-value
Total number of cases	142	38	
Age, years (mean ± SD)	63.2±9.8	64.7±8.0	0.363
Sex, n, %			0.204
Female	38 (26.8)	6 (15.8)	
Male	104 (73.2)	32 (84.2)	
Tumor size, n (%)			0.063
≤2 cm	98 (69.01)	32 (84.21)	
>2 cm	44 (30.99)	6 (15.79)	
Location of tumor, n (%)			0.031*
Cardia-fundus	47 (33.1)	21 (55.3)	
Corpus	67 (47.2)	10 (26.3)	
Gastric antrum	28 (19.7)	7 (18.4)	
Morphology, n (%)			0.266
Protrusion type	9 (6.3)	0 (0.0)	
Flat type	128 (90.1)	37 (97.4)	
Depressed type	5 (3.5)	1 (2.6)	
Ulcer, n (%)			0.035*
Absent	127 (89.4)	29 (76.3)	
Present	15 (10.6)	9 (23.7)	
LNM, n (%)			0.006*
Absent	111 (78.2)	37 (97.4)	
Present	31 (21.8)	1 (2.6)	
Vascular invasion, n (%)			0.018*
Absent	117 (82.4)	37 (97.4)	
Present	25 (17.6)	1 (2.6)	
Depth of invasion, n (%)			0.589
0T1a	79 (55.6)	23 (60.5)	
0T1b	63 (44.4)	15 (39.5)	
Histologic type, n (%)			0.068
Undifferentiated	39 (27.5)	5 (13.2)	
Differentiated	103 (72.5)	33 (86.8)	

Abbreviations: GCP-gastritis cystica profunda; EGC-early gastric cancer; LNM-lymph node metastasis; 0T1a-the tumor invades the lamina propria or muscularis mucosa; 0T1b-the tumor invades the submucosa

Table 2. Univariate analysis of clinicopathological and histological features for lymph node metastasis in patients with early gastric cancers.

Variable	No. of patients (%)	OR (95% CI)	p-value
Age, years (mean ± SD)	63.5±9. 5	1.007 (0.967, 1.050)	0.723
Sex, n (%)			
Female	44 (24.4)	Reference	
Male	136 (75.6)	0.964 (0.398, 2.334)	0.936
Tumor size, n (%)			
≤2 cm	130 (72.2)	Reference	
>2 cm	50 (27.8)	0.4 (0.2, 1.2)	0.098
Location of tumor, n (%)			
Cardia-fundus	68 (37.8)	Reference	
Corpus	77 (42.8)	1.719 (0.705, 4.194)	0.234
Gastric antrum	35 (19.4)	1.639 (0.554, 4.852)	0.372
Morphology, n (%)			
Protrusion type	9 (5.0)	Reference	
Flat type	165 (91.7)	0.391 (0.092, 1.662)	0.203
Depressed type	6 (3.3)	1.000 (0.112, 8.947)	1.000
Ulcer, n (%)			
Absent	156 (86.7)	Reference	
Present	24 (13.3)	0.914 (0.290, 2.884)	0.879
GCP, n (%)			
Absent	142 (78.9)	Reference	
Present	38 (21.1)	0.097 (0.013, 0.734)	0.024*
Histologic type, n (%)			
Undifferentiated	44 (24.4)	Reference	
Differentiated	136 (75.6)	0.548 (0.240, 1.251)	0.153
Vascular invasion, n (%)			
Absent	154 (85.6)	Reference	
Present	26 (14.4)	39.444 (13.314, 16.858)	<0.001*
Depth of invasion, n (%)			
0T1a	102 (56.7)	Reference	
0T1b	78 (43.3)	6.402 (2.595, 15.793)	<0.001*

The incidence of LNM was 2.6% in the GCP positive group, and 21.8% in the GCP negative group.

Univariate analysis of LNM. Univariate logistic regression analysis was performed using whether EGC is accompanied by LNM as the dependent variable (Y=1), and clinical and pathological characteristics including GCP parameters as independent variables. The results showed that GCP, depth of tumor invasion, and vascular invasion were possible risk factors for LNM ($p<0.05$, Table 2).

Multiple regression analysis of the correlation between GCP and the risk of LNM in EGC. Table 3 shows the results of univariate and multivariate logistic regression analysis. The initial adjusted covariates included age, tumor size, tumor location, and ulceration. Fully adjusted covariates included age, tumor size, tumor location, ulceration, depth of invasion, vascular invasion, and degree of differentiation. In the regression equation, regardless of whether the covariates were unadjusted, initially adjusted, or fully adjusted, GCP positive significantly reduced the risk of LNM in EGC patients, with OR values of 0.097, 0.121, and 0.100, respectively (all $p<0.05$).

Curve fitting. GAM test was performed to determine the correlation between GCP and LNM in EGC patients. The results showed that after adjusting for gender, age, tumor location, ulceration, depth of invasion, vascular invasion, and degree of differentiation, GCP positive reduced the average incidence of LNM in EGC patients from 21.83% (6.65–52.28%) to 1.55% (0.04–27.69%) (Figure 2).

Interaction. Hierarchical analysis was carried out to further evaluate the correlation between GCP and the risk of LNM in EGC patients. We found that no variable, including tumor location (cardiac fundus, gastric corpus, or antrum and pylorus), tumor size grouping (≤2 cm or >2 cm), ulceration (absence or presence), differentiation type (undifferentiated or differentiated), depth of tumor invasion (0T1a and

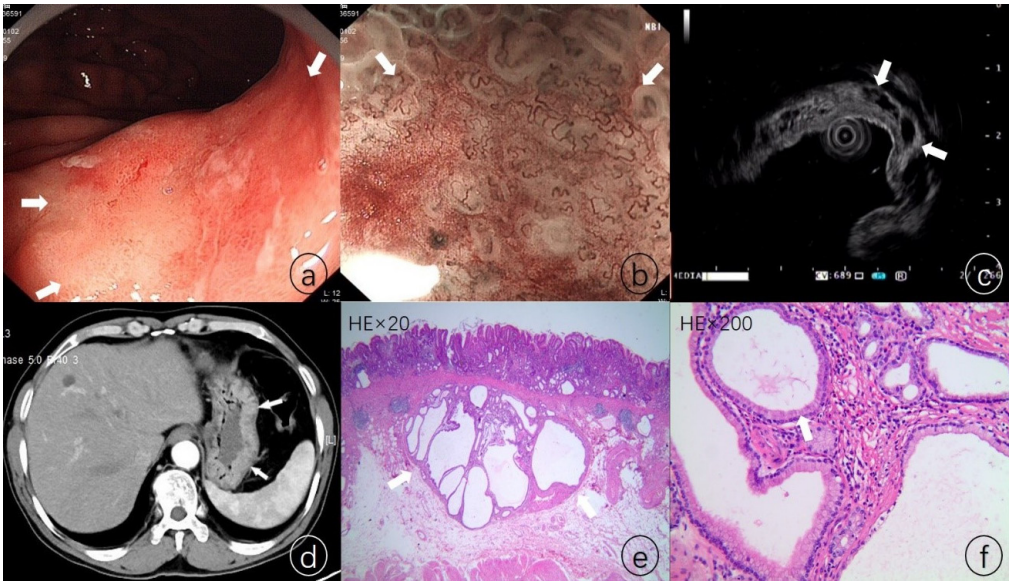

Figure 1. Endoscopy imaging and pathological features of early gastric cancer with GCP. a) Gastroscopy revealed a flat lesion with a reddish depressed area in the posterior wall of the cardia (indicated by the arrows); b) Magnified NBI observation revealed clear a demarcation line, disordered microvascular pattern, and different type micro-surface pattern (indicated by the arrows); c) Endoscopic ultrasonography (UM-2R) revealed a heterogeneous submucosal mass with internal cystic space (indicated by the arrows) d) CT imaging revealed slightly thickened cardiac wall (indicated by the arrows); e) Low power view of the H&E staining (H&E ×20) revealed cystically dilated gastric glands without dysplastic changes into the submucosa (indicated by the arrows); f) High power view of the H&E staining (H&E ×200) showed gastritis cystica profunda (indicated by the arrows).

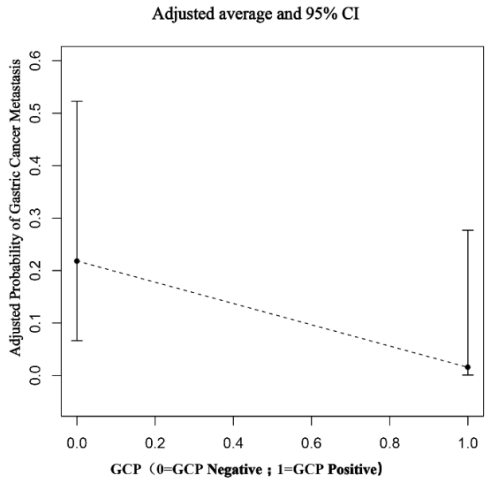

Figure. 2. Curve-fitting result showed GCP and the probability of metastasis in early gastric cancer after adjusting.

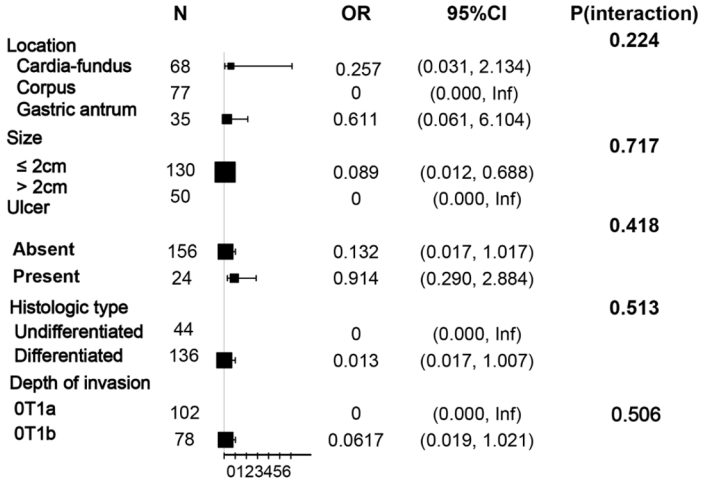

Figure. 3. Hierarchical analysis of the correlation between GCP and LNM in patients with early gastric cancer.

0T1b), significantly changed the correlation between GCP positive and the risk of LNM in EGC patients (p-value for interaction range, 0.224–0.717) (Figure 3).

Discussion

With the popularization of gastric cancer screening, more and more EGC patients are diagnosed. The therapeutic effect of EGC is much better than that of advanced gastric cancer. Therefore, while ensuring the treatment effect, the quality of life of patients after treatment has been increasingly emphasized. The incidence of LNM in EGC, especially intramucosal tumors, is very low. A large range of lymph node dissection will not only increase the risk of surgery but also reduce the quality of life after surgery [12]. With the extensive application and continuous improvement of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for EGC, endoscopic resection of the tumor has

Table 3. Multiple regression analysis of the value of GCP in early gastric cancer with lymph node metastasis.

Variable	Unadjusted model		Adjusted model 1		Adjusted model 2	
GCP	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Absent	1.0		1.0		1.0	
Present	0.097 (0.013, 0.734)	0.024	0.121 (0.015, 0.986)	0.048	0.100 (0.011, 0.876)	0.038

Notes: adjusted model 1-Sex, age, tumor size, location of tumor, ulcer; adjusted model 2-sex, age, tumor size, location of tumor, ulcer, depth of invasion, vascular invasion, histologic type

become the preferred treatment for EGC patients without the risk of LNM. It is particularly important to screen out patients with low risk of LNM through in-depth analysis of the clinical characteristics of patients and the biological behavior of the tumor before operation [13].

GCP was first discovered in 1972 by Lettler et al. [14] and was officially named by Franzin et al. in 1981 [15]. It was named because the changes in the gastric gland were similar to that of colitis cystica profunda. There is no large-scale clinical study on GCP so far. At present, pathological examination remains the gold standard for the diagnosis of GCP. The pathological feature of GCP is that gastric proper glands invade deep into the mucosa or submucosa of the stomach, and the glands were cystically dilated, accompanied by connective tissue hyperplasia and inflammatory cells. In well-differentiated gastric adenocarcinoma, the difference between the gland structure and the tumor cells is not significant, and it is difficult to distinguish well-differentiated gastric adenocarcinoma from GCP when the tumor breaks through muscularis mucosa and reaches submucosa. Therefore, in pathological diagnosis, caution should be used to differentiate GCP from well-differentiated gastric adenocarcinoma. The glands in the lamina propria of GCP are not heteromorphic, presenting as a cluster of glands extending from the lamina propria to the submucosa, while well-differentiated adenocarcinoma is characterized by the invasion of separated irregular glandular ducts into submucosa [16]. Through literature review and analysis, Machicado et al. found that GCP lacks characteristic endoscopic manifestations under an ordinary endoscope [17]. Endoscopic ultrasonography (EUS) can be used to observe deep lesions and provide important differential diagnostic information for the diagnosis of GCP. Multiple hypoechoic cystic areas in the submucosa are the most common manifestations of GCP on EUS. Deng et al. collected 17 cases of pathologically diagnosed GCP and found that all of the 17 GCP patients had no specific clinical symptoms [18]. Among these GCP patients, 16 received preoperative EUS examination, and cystic echo changes were found in 11 cases, with a diagnostic rate of 68.8% (11/16). Therefore, EUS is of guiding significance for the diagnosis of GCP.

The cause of GCP is unclear. It is generally believed that GCP may be caused by chronic inflammation, which leads to the loss of mucosal myometrium integrity, and the downward growth of gastric glandular epithelium through the muscularis mucosa into the submucosa to form cystically dilated hyperplasia. Chronic inflammation can come from peptic ulcer, iatrogenic ulcer (after endoscopic treatment), bile and intestinal fluid reflux after surgery, and *Helicobacter pylori* or EB virus infection [19]. From the perspective of biological behavior, GCP is more likely to be a benign lesion, but some scholars have reported that GCP often occurs along with high-grade intraepithelial neoplasia or even gastric cancer [20]. Therefore, some scholars believe that GCP is a precancerous state [21]. Kim et al. [22] found that in 39 patients who developed GCP after gastrointestinal anastomosis, 16 patients (41%) concomitantly had EGC, and 3 patients (8%) had advanced gastric cancer. The mechanism of GCP that is associated with gastric cancer is unclear. Immunohistochemical studies [23] have revealed that the expression of Ki-67, p53, and p21 in GCP mucosa was enhanced in GCP patients with gastric cancer, suggesting that DNA damage, epithelial cell proliferation, and p53-dependent p21 expression may be the potential mechanism of GCP that is related to carcinogenesis. Kuwahara et al. considered that GCP is associated with gastric cancer, and the selective deletion of KCNE2 expression is the factor leading to GCP and gastric cancer [24].

In this study, we explored the clinical and pathological characteristics of EGC patients with GCP and those without GCP. We found that the incidence of LNM in EGC patients with GCP was markedly lower than that in EGC patients without GCP. Next, we carried out univariate logistic regression analysis to identify possible risk factors of LNM in EGC patients. The results showed that GCP, depth of tumor invasion, and vascular invasion were correlated with LNM in EGC patients. Similar to our results, a number of studies have confirmed that the depth of tumor invasion and vascular invasion are important factors affecting LNM in EGC patients [25, 26]. We established multiple regression equations to further investigate the correlation between GCP and LNM in EGC. After fully adjusting for confounding factors, we finally confirmed that GCP was an independent risk factor for LNM in EGC patients. The incidence of LNM in EGC patients with GCP was significantly reduced compared with that in EGC patients without GCP. After adjusting for vascular invasion and other confounding factors, curve-fitting results also confirmed that the risk of lymph node metastasis in the GCP positive patients was reduced from 21.83% to 1.55%. Our study comprehensively analyzed the correlation between GCP and the risk of LNM in EGC patients and verified the independent negative correlation between them. There are only a few studies on the correlation between GCP and the

risk of LNM in EGC patients. Choi et al. [8] found that the depth of tumor invasion and LNM in gastric cancer patients with GCP were mostly at the early stage, which is similar to our finding. Choi et al. considered that GCP was related to EBV infection. EBV-related gastric cancer has different clinicopathological and molecular characteristics from conventional gastric cancer, while gastric cancer patients with GCP and patients with EBV-related gastric cancer had similar clinicopathological features, and the risk of LNM was low. The specific mechanism is unclear. EBV-related gastric cancer usually shows marked gastric wall thickening. It can be well distinguished on gastroscopic ultrasound, which improves diagnostic efficiency [27]. Yin et al. [28] showed that in EBV-related gastric cancer, rich lymphocyte in stroma is a good prognostic factor for EBV-related gastric cancer, suggesting that rich lymphocyte infiltration indicates that patients have better tumor immune function. EBV-positive gastric cancers are reported to be more likely to express PD-L1 and to be good candidates for immunotherapy targeting [29]. However, the exact mechanism of EBV in the risk of LNM in EGC combined with GCP needs further study.

Our study has some limitations. Firstly, this study is a retrospective study, and there may be a selective bias. Our next study is to establish a prediction model for prospective research. Secondly, this study preliminarily explored the phenomenon that EGC patients with GCP have a lower risk of LNM, and the specific mechanism needs further study. Finally, this study is a single-center study, and there are some limitations in data promotion. Multicenter studies are needed to further verify our findings.

In conclusion, a number of guidelines and consensus have recommended endoscopic resection as the preferred treatment for EGC [30, 31], but whether there is LNM in EGC is the primary factor determining the treatment option. Our study demonstrated that the risk of LNM in EGC patients with GCP is low. Therefore, performing preoperative endoscopic ultrasonography to assess whether EGC is accompanied by GCP is conducive to the comprehensive and accurate assessment of the risk factors of LNM. Standardized preoperative diagnosis can further improve the quality of EGC endoscopic resection, so as to truly improve the quality of life in patients after treatment.

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