




The correlation between the main and minor lesions of synchronous multiple gastric neoplasms assessed gastroscopically and microscopically

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Abstract

Background Patients with early gastric cancer (EGC) are at high risk of developing synchronous multiple gastric neoplasms (SMGNs) after undergoing endoscopic submucosal dissection (ESD). However, most previous studies have had small sample sizes, and few have focused on association studies.

Aims This study aimed to analyze the associations between SMGN lesion data from patients with EGC treated with ESD and their correlation coefficients.

Methods The clinical ESD data from two hospitals from January 2008 to January 2021 were retrospectively analyzed. The main lesions were defined as those with a significant depth of infiltration. The larger tumor diameter was considered the main lesion if the lesions had the same infiltration depth.

Results Of the 1013 post-ESD cases examined, 95 cases (223 lesions) had SMGN, and 25 patients had more than three lesions. For the correlation analysis, 190 lesions were included. The study revealed a similarity in pathological type between main and minor lesions ($r_s=0.37$) and a positive correlation in infiltration depth ($r_s=0.58$). The mean diameter sizes of the main and minor lesions were 20.7 ± 8.3 mm and 13.1 ± 6.4 mm, respectively, with statistically significant differences ($P < 0.001$). A linear correlation was observed between the diameter size and a linear regression model was constructed, producing $r = 0.38$ [95% confidence interval (CI) 0.19–0.54], $b = 0.29$ (95% CI 0.14–0.44), $t = 3.94$, $P < 0.001$]. A correlation was identified between the vertical distribution of the main and minor lesions, the horizontal distribution, and the gross endoscopic morphology ($\phi_c = 0.25$, $P = 0.02$; $\phi_c = 0.32$, $P < 0.001$; $\phi_c = 0.60$, $P < 0.001$).

Conclusions The correlation coefficients for microscopic characteristics were higher than those for gastroscopy. There is a significant positive correlation between the main and minor lesions regarding pathological stage and depth of infiltration, respectively. The spatial distribution of the lesions and the gastroscopic morphology were similar.

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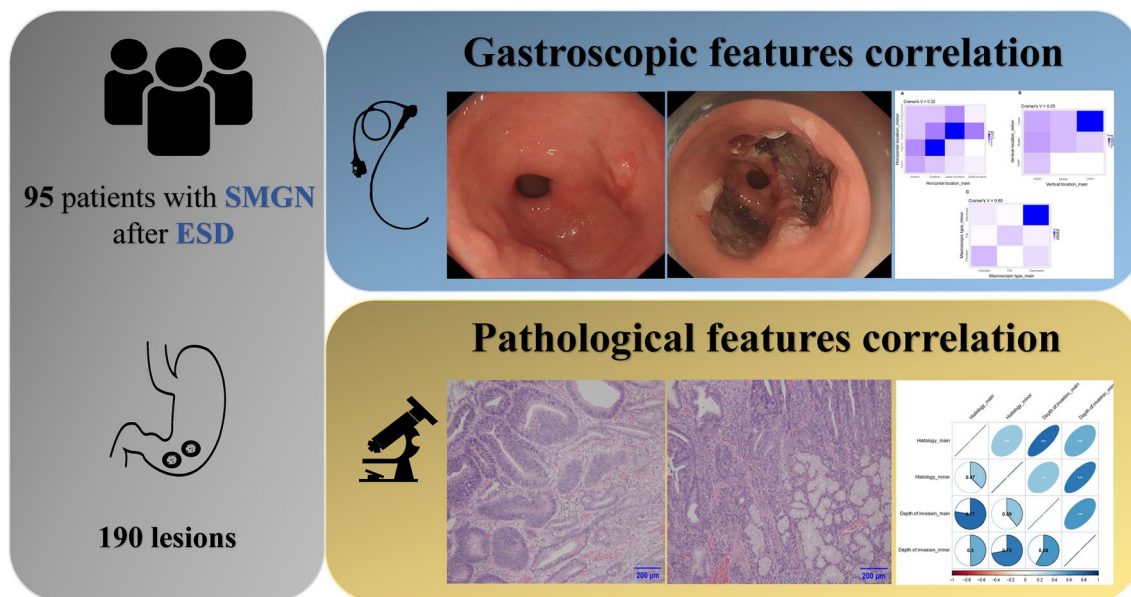
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Graphical abstract

SMGN synchronous multiple gastric neoplasms, ESD endoscopic submucosal dissection.



Keywords ESD · SMEGC · Morphology · Pathology · Intraepithelial neoplasia

Gastric cancer is one of the most common malignancies worldwide. Early gastric cancer (EGC) is cancer cells confined to the mucosal or submucosal layer, with or without lymph node metastases. Fortunately, the prognosis for EGC is generally favorable, with a 5-year survival rate of more than 90% [1]. Unlike surgery, endoscopic submucosal dissection (ESD) is a minimally invasive gastrointestinal endoscopic technique that preserves the normal physiological functioning of the entire stomach. ESD has shown a prognosis comparable to surgery and has become the standard for treating EGC [2]. However, researchers have identified multiple histopathological occurrences in postoperative cases of gastric cancer [3]. While preserving the entire gastric mucosa, ESD raises concerns about the event of postoperative synchronous tumors or the potential for missed synchronous tumors [1, 4]. Two or more EGC lesions detected either before the initial ESD or within 1 year after ESD are referred to as simultaneous multiple early gastric cancers (SMEGC).

Consequently, exploring SMEGC has become a prominent research topic in recent years. Various studies have been conducted to analyze risk factors contributing to missed diagnoses, risk of lymph node metastasis, pathological characteristics, prognosis of the disease, and genomic studies associated with SMEGC [5–7]. However, it should be noted that specific study cohorts have been derived from surgical cases rather than cases involving ESD. Furthermore, the incidence of SMEGC is low, accounting for approximately

9–14% of all gastric cancer cases [8]. Many existing studies focusing on SMEGC face limitations due to the small sample sizes ($n < 40$) and the limited availability of statistical data. It is worth noting that studies on multifocal correlations are rare. Early studies focused mainly on descriptive statistics [9]. Due to the limited sample size, there are several subgroups with a sample size of 0, which introduces bias and reduces the credibility of the findings [10]. Furthermore, the existing studies did not assess the strength of the correlation between the main and minor lesions, and the data on the correlation coefficient remain unknown. Consequently, the results of the previous studies are not comprehensive, highlighting the need for a larger sample size to validate the findings and obtain additional correlation coefficients.

There is a significant likelihood of intraepithelial neoplasia progressing to gastric cancer in the near term, thus justifying its inclusion as an indication for ESD [11]. Our study enrolled patients with synchronous multiple gastric neoplasms (SMGN), including SMEGC and intraepithelial neoplasia [5]. Expanding the sample size will allow for more robust analysis and validation of the findings. On the other hand, conducting more in-depth research on SMEGC and early lesions will provide a deeper understanding of the disease and its characteristics. This study aimed to analyze the correlation between SMGN lesions and summarize the association between various factors. Additionally, data on correlation coefficients between the main and minor lesions were

included in the study. These additional data provide valuable information on the relationship between these lesions in SMGN patients. By incorporating correlation coefficients, researchers can quantitatively assess the strength and direction of the correlation, improving the understanding of the disease.

Materials and methods

Study design and definitions

This retrospective analysis was conducted at two hospitals in China, the Fujian Provincial Hospital South Branch, and the Fujian Provincial Hospital, Fuzhou, from January 2008 to January 2021. Two or more lesions detected either before the initial ESD or within 1 year after ESD, including SMEGC and intraepithelial neoplasia, are called SMGN. The inclusion criteria were patients who received ESD and who were pathologically confirmed as SMGN. The diagnosis of SMGN was based on Moertel criteria [12]. These criteria consists of the following components: (1) pathological examination that confirmed each lesion as tumors or intraepithelial neoplasia, (2) microscopic observation of normal gastric mucosa between different lesions, and (3) exclusion of lesions resulting from local infiltration or metastasis. Basic information, endoscopic variables, and postoperative pathological variables were recorded for each case. Gastroscopy was performed using a visual gastroscope (GF-H260; Olympus Optical Co., Ltd., Tokyo, Japan). At least two endoscopists with at least 10 years of experience in endoscopy reviewed the gastroscopic findings. Gastroscopy reports were obtained from the hospital's endoscopy database. The study protocol was approved by the hospital's ethical review committee (approval number K2021-04-035, approval date April 15, 2021).

Moertel's criteria were used to classify major and minor lesions as follows: (1) in cases where two or more lesions had the same depth of infiltration, the lesion with the largest diameter was designated as the major lesion, while the remaining lesions were classified as minor lesions; and (2) if two or more lesions exhibited different depths of infiltration, the lesion with the highest depth of infiltration was classified as the major lesion, while the others were categorized as minor lesions. In cases with more than three EGC lesions, the secondary main lesion was considered a minor lesion.

The gross gastroscopic morphology of SMGN was classified into three groups according to the Paris typology [13]. Superficial gastric cancer (Type 0) is classified into three categories: elevated lesions (Type 0-I), flat lesions (Type 0-II), and depressed lesions (Type 0-III). Within Type 0-I, there are two subdivisions: pedunculated type (Type 0-Ip) and non-pedunculated type (Type 0-Is). Type 0-II is divided

into three subtypes: Type 0-IIa, Type 0-IIb, and Type 0-IIc, based on the degree of slight elevation, flatness, and slight depression of the lesions. The cutoff between Type 0-I and Type 0-IIa is a bulge height of 2.5 mm (measured as the closed thickness of the biopsy forceps), and the cutoff between Type 0-III and Type 0-IIc is a depression depth of 1.2 mm (measured as the open thickness of the biopsy forceps with a single clamp). The macroscopic type of tumor was divided into three types: elevated (0-I, 0-IIa), flat (0-IIb), and depressed (0-IIa+IIc, 0-IIc, 0-III).

Pathologically, the lesions were divided into three groups based on the WHO classification criteria [14]: precancerous lesions (intraepithelial neoplasia), differentiated adenocarcinoma (well and moderately differentiated tubular adenocarcinomas), and undifferentiated tubular adenocarcinomas (poorly differentiated tubular adenocarcinoma, signet-ring cell carcinoma, and poorly cohesive carcinoma). The depth of infiltration of the early lesions was categorized into three categories: mucosal lamina, mucosal muscularis, and submucosa. Based on the microscopic presentation, background mucosal atrophy and intestinal metaplasia were classified as mild, moderate, or severe. The horizontal distribution of the tumor was classified as the anterior wall, the lesser curvature, the posterior wall, and the greater curvature. The vertical distribution was divided into the upper (cardia, fundus), middle (gastric body), and lower (gastric angle, sinus, and pylorus) regions [14, 15].

Early ESD guidelines were differentiated-type adenocarcinoma without ulcerative findings, of which the depth of invasion is clinically diagnosed as T1a and the diameter is ≤ 2 cm [16]. The latest edition of the ESD guidelines integrates a significant portion of expanded indications into the category of absolute indications. The absolute indications for ESD were (1) differentiated mucosal endocarcinoma without ulcers, (2) differentiated mucosal endocarcinoma with ulcers and lesions ≤ 3 cm, (3) high-grade intraepithelial neoplasia of the gastric mucosa, and (4) undifferentiated mucosal endocarcinoma with lesions ≤ 2 cm and no ulcers [11]. Endoscopic examinations are conducted at 3 months, 6 months, and 1 year postoperatively.

Statistical analysis

Statistical analysis was conducted using R (version 4.2.3, R Foundation for Statistical Computing, Vienna, Austria, <https://www.r-project.org>) and SPSS 25.0 (SPSS Inc. Chicago, Illinois, USA). Normally distributed data are reported as mean \pm standard deviation, while count data are presented as frequencies and percentages (%). The Chi-square test or Fisher's exact test was used for group comparisons. The Spearman test was used to analyze the association of grade variables, while the Cramer *V* test was utilized to investigate the association of unordered multicategorical

variables. Linear regression analysis was employed to determine the correlation between the sizes of main and minor lesions in SMGN patients. *P* values < 0.05 were considered statistically significant.

Results

Clinical characteristics

A total of 1031 patients with EGC who were followed up 12 months after ESD, and 936 were excluded (899 cases of solitary cancer and 37 cases with various other types of gastric tumors). Among the 95 (9.4%) patients diagnosed with SMGN (223 lesions after surgery), 25 patients (26.3%) had more than three lesions. The median time to detection of the synchronous multiple lesions was 7.4 months (range 3.9–11.3). The analysis included the final data of 190 lesions. Thirty-three lesions other than the main and minor ones were excluded as they were the third or subsequent lesions within the same patient (Fig. 1). The mean age was 63.9 ± 7.4 years, and 74 (77.9%) were men. The *Helicobacter pylori* infection

rate was 52.6%. The baseline characteristics of the patients are shown in Table 1.

The gastroscopic similarity of the main and minor lesions

Table 2 presents the statistical analysis of the spatial distribution areas and endoscopic macrotypes of the main and minor lesions in SMGN. Most main and minor lesions exhibited significant similarity in spatial distribution areas and the endoscopic macrotypes. In particular, many main and minor lesions in SMGN were found in the distal stomach. Specifically, 55.1% of the minor lesions were also observed in the lower part of the stomach when the main lesion was located in the lower part. In the upper part of the stomach, 60% (9/15) of minor lesions were located in the same region as the main lesion. Similarly, when the lesions were located in the middle or lower area of the stomach, 32.3% (10/31), 55.1% (27/49) of the minor lesions were also located in the same region as the main lesion. Overall, 48.4% of the lesions were distributed in the same vertical position. Likewise, when the lesions were located in the anterior wall, posterior wall, lesser, and greater

Fig. 1 Flow chart showing the lesions selection process. *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer, *SMGN* synchronous multiple gastric neoplasms

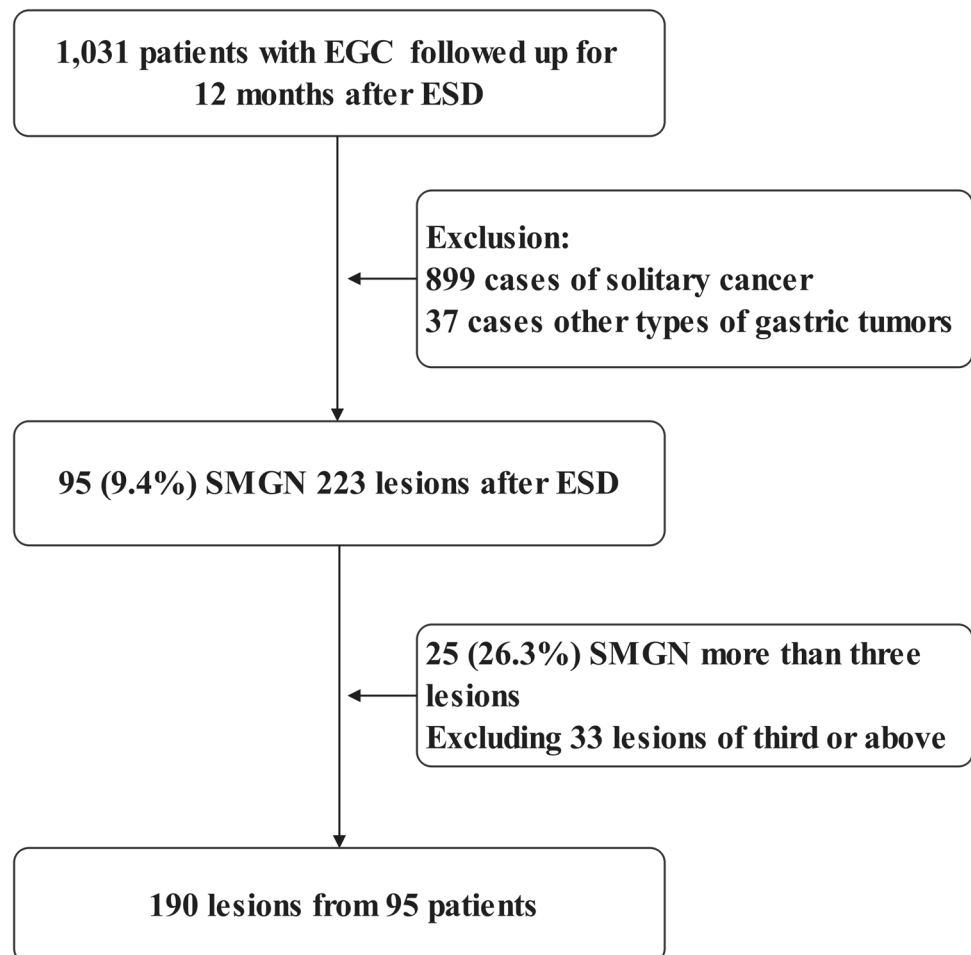


Table 1 Baseline characteristics of patients with SMGN

Characteristics	Patients (<i>n</i> = 95)
Age (year), mean ± SD	63.9 ± 7.4
Gender, <i>n</i> (%)	
Male	74 (77.9)
Female	21 (22.1)
Main lesion diameter (mm), mean ± SD	20.7 ± 8.3
Minor lesion diameter (mm), mean ± SD	13.1 ± 6.4
Mucosal atrophy, <i>n</i> (%)	
Mild	9 (9.5)
Moderate	44 (46.3)
Severe	42 (44.2)
Intestinal metaplasia, <i>n</i> (%)	
Mild	13 (13.7)
Moderate	67 (70.5)
Severe	15 (15.8)
Histology_main, <i>n</i> (%)	
Dysplasia	53 (55.8)
Differentiated	39 (41.1)
Undifferentiated	3 (3.2)
Histology_minor, <i>n</i> (%)	
Dysplasia	68 (71.6)
Differentiated	26 (27.4)
Undifferentiated	1 (1.1)
Depth of invasion_main, <i>n</i> (%)	
Mucosa	62 (65.3)
Muscularis mucosa	28 (29.5)
Submucosa	5 (5.3)
Depth of invasion_minor, <i>n</i> (%)	
Mucosa	79 (83.2)
Muscularis mucosa	16 (16.8)
Vertical location_main, <i>n</i> (%)	
Upper	34 (35.8)
Middle	23 (24.2)
Lower	38 (40.0)
Vertical location_minor, <i>n</i> (%)	
Upper	15 (15.8)
Middle	31 (32.6)
Lower	49 (51.6)
Horizontal location_main, <i>n</i> (%)	
Anterior	22 (23.2)
Posterior	33 (34.7)
Lesser curvature	29 (30.5)
Great curvature	11 (11.6)
Horizontal location_minor, <i>n</i> (%)	
Anterior	13 (13.7)
Posterior	27 (28.4)
Lesser curvature	38 (40.0)
Great curvature	17 (17.9)
Macroscopic type_main, <i>n</i> (%)	
Elevated	22 (23.2)
Flat	14 (14.7)

Table 1 (continued)

Characteristics	Patients (<i>n</i> = 95)
Depressed	59 (62.1)
Macroscopic type_minor, <i>n</i> (%)	
Elevated	24 (25.2)
Flat	17 (17.9)
Depressed	54 (56.8)
Tumor number at the first time of ESD, <i>n</i> (%)	
Single lesion	27 (28.4)
Multiple lesions	68 (71.6)
Helicobacter pylori infection, <i>n</i> (%)	
Yes	50 (52.6)
No	45 (47.4)

SMGN synchronous multiple gastric neoplasms, SD standard deviation, ESD endoscopic submucosal dissection

curvatures of the stomach, 46.2%, 59.3%, 42.1%, and 5.9% of the minor lesions were found in the same region as the main lesion, respectively, in the corresponding horizontal positions. Consequently, 41.1% of the lesions were distributed in the same horizontal position. Among the lesions analyzed, 62.5% were of the elevated type, 64.7% were of the flat type, and 87.0% were classified as depressed. This indicates that 76.8% of the lesions exhibited the same endoscopic macrotypes. The Cramer *V* test examined the correlation between the spatial distribution of the lesions and the endoscopic macrotypes. The results showed significant correlations between the horizontal distribution ($\chi^2 = 27.47$, $\phi_c = 0.32$, $P < 0.001$) (Fig. 2A), vertical distribution ($\chi^2 = 11.62$, $\phi_c = 0.25$, $P = 0.02$) (Fig. 2B), and endoscopic macrotypes ($\chi^2 = 53.80$, $\phi_c = 0.60$, $P < 0.001$) (Fig. 2C) of the main and minor lesions.

Correlation heat map

A positive correlation was observed between the diameters of the main and minor lesions and the depth of lesion infiltration ($r_s = 0.48$, $r_s = 0.58$). Furthermore, there was a similarity in the pathology type between the main and minor lesions ($r_s = 0.37$). A positive correlation was observed between the lesion size and the severity of the pathology type, the degree of mucosal background atrophy, and the degree of intestinal metaplasia ($r_s = 0.30$, $r_s = 0.33$). All these results were statistically significant. In contrast, no association was found between sex, age, gastric mucosal background, lesion characteristics, or pathological features (Fig. 3).

Linear regression analysis of the diameters of the main and minor lesions

The mean diameter sizes of the main and minor lesions were 20.7 ± 8.3 mm and 13.1 ± 6.4 mm, respectively, and

Table 2 Comparison of the main and minor lesion characteristics of SMGN

Main lesions	Number (%) of cases of minor lesions				χ^2	<i>P</i>	ϕ^2/r_s
Vertical location	Upper	Middle	Lower				
Upper	9 (60.0)	13 (41.9)	12 (24.5)		11.62	0.02	0.25
Middle	3 (20.0)	10 (32.3)	10 (20.4)				
Lower	3 (20.0)	8 (25.8)	27 (55.1)				
Horizontal location*	Anterior	Posterior	Lesser curvature	Great curvature			
Anterior	6 (46.2)	8 (29.6)	4 (10.5)	4 (23.5)	27.47	<0.001	0.32
Posterior	4 (30.8)	16 (59.3)	9 (23.7)	4 (23.5)			
Lesser curvature	2 (15.4)	3 (11.1)	16 (42.1)	8 (47.1)			
Great curvature	1 (7.7)	0 (0)	9 (23.7)	1 (5.9)			
Macroscopic type*	Elevated	Flat	Depressed				
Elevated	15 (62.5)	2 (11.8)	5 (9.3)		53.8	<0.001	0.60
Flat	1 (4.2)	11 (64.7)	2 (3.7)				
Depressed	8 (33.3)	4 (23.5)	47 (87.0)				
Histology*	Dysplasia	Differentiated	Undifferentiated				
Dysplasia	46 (67.6)	7 (26.9)	0 (0)		22.04	<0.001	0.37
Differentiated	20 (29.4)	19 (73.1)	0 (0)				
Undifferentiated	2 (2.9)	0 (0)	1 (100.0)				
Depth of invasion	Mucosa	Muscularis mucosa					
Mucosa	62 (78.5)	0 (0)			39.35	<0.001	0.58
Muscularis mucosa	13 (16.5)	15 (93.8)					
Submucosa	4 (5.1)	1 (6.3)					

SMGN synchronous multiple gastric neoplasms

*Fisher exact test

these values showed statistically significant differences ($P < 0.001$). To further analyze the relationship between the size of the main and minor lesions, Pearson's correlation analysis and linear regression analysis were performed to construct regression models (Fig. 4). The results revealed a moderate linear correlation in tumor size between main and minor SMGN lesions, with an r -value of 0.38 [95% confidence interval (CI) 0.19–0.54]. The linear regression model yielded a slope (b) of 0.29 (95% CI 0.14–0.44) and a t -value of 3.94 ($P < 0.001$).

Discussion

This study contributes to understanding the association between SMGN lesions in patients with ESD. Including a larger sample size and focusing on ESD cases provides valuable information on the correlation between the clinical and pathological characteristics of SMGN. Findings on

the association between main and minor lesion size, spatial distribution, endoscopic macrotypes, and microscopic factors, such as pathological features and depth of infiltration, contribute to the knowledge of SMGN. Given the rarity of SMGN and the limited number of studies focused on ESD lesions, this research fills a crucial gap in the literature. By expanding the understanding of the association between SMGN lesions, this study provides essential information for clinical practice.

From a gastroscopic diagnostic point of view, we have identified correlations between lesion size, gross gastroscopic morphology, and spatial distribution. Figure 5 shows a typical case. These findings are consistent with a study conducted by Kim et al., who analyzed 37 patients with SMEGC after surgical and ESD procedures and observed similarities between lesions [10]. However, our study addressed some limitations in their analysis by examining the association between these factors in more detail. We also conducted a detailed correlation analysis,

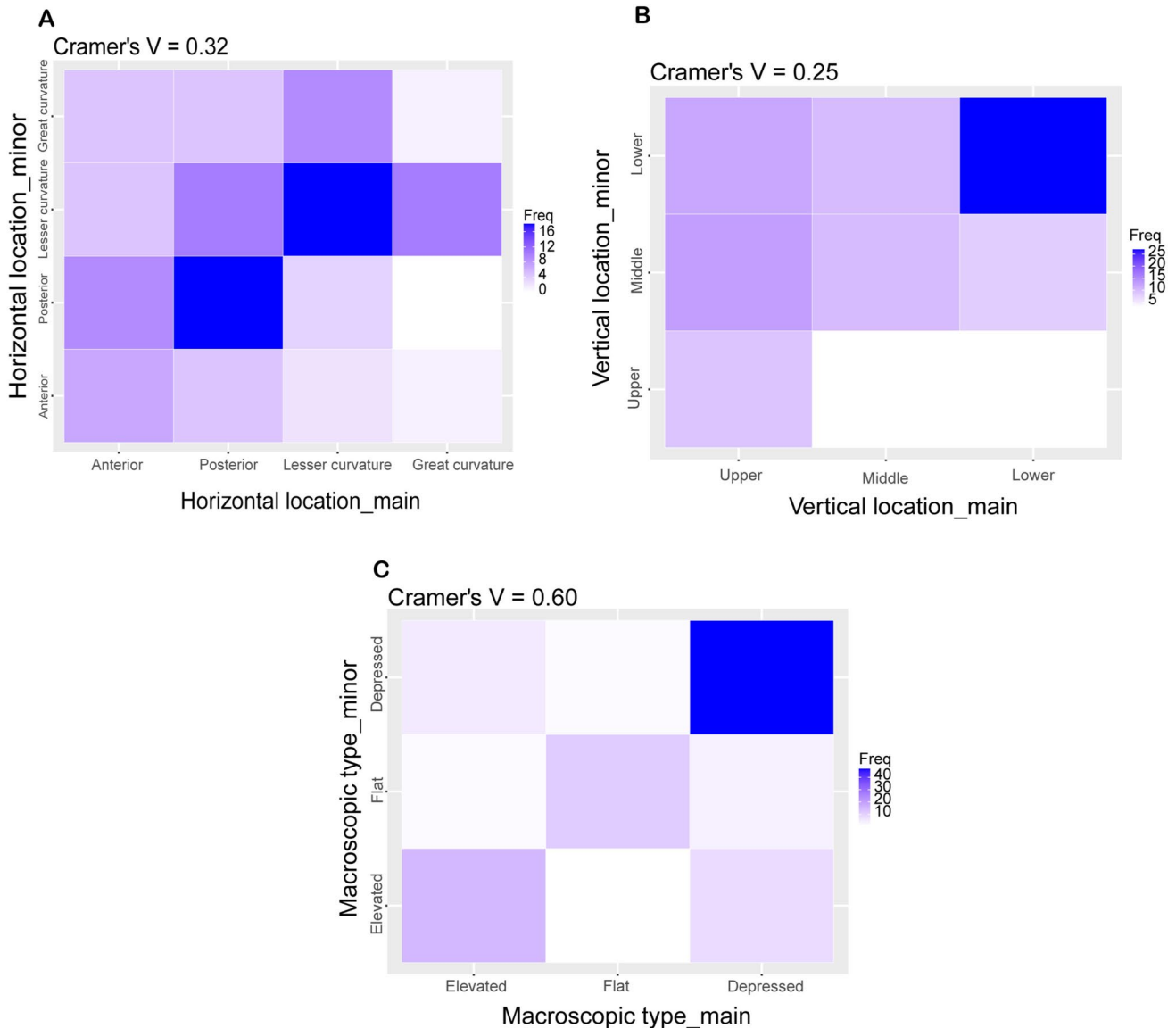


Fig. 2 Cramer's V correlation heat map. Data types are unordered multi-categorical variables, using Cramer's V test. Vertical distribution. $\phi_c=0.25$, $P=0.02$ (A). Horizontal distribution. $\phi_c=0.32$,

$P<0.001$ (B). Gross endoscopic morphology. $\phi_c=0.60$, $P<0.001$ (C). There is a correlation between the spatial distribution of the main and minor lesions or the gross endoscopic morphology

calculating correlation coefficients that had not been previously analyzed. We speculate that progressive gastric cancer can develop by merging adjacent SMGN with the main and minor lesions. Currently, two theories are proposed to explain this phenomenon. The first theory is the “tumor collision” hypothesis, which suggests that a single progressive gastric cancer arises from the horizontal or vertical fusion of several adjacent lesions. The second theory is the “regional carcinogenesis” theory, which proposes that the gastric mucosa is exposed to a pathogenic environment, simultaneously developing carcinoma in multiple neighboring or distant sites [17]. The pattern observed in SMGN lesions, and SMEGC is strikingly

similar, highlighting the importance of closely examining the surrounding mucosa for similar morphological characteristics when detecting EGC lesions during gastroscopy. This approach could reduce the likelihood of missed diagnoses. Numerous studies have investigated factors contributing to missed diagnoses of SMEGC, revealing that small flat lesions and lesions in the upper part of the stomach are particularly prone to be overlooked [4, 18]. Our study identified a significant difference in size between main and minor lesions, indicating a higher probability of missing minor lesions within the SMGN, especially smaller lesions located in the upper part of the stomach. A multicenter retrospective cohort study emphasized that

Fig. 3 Heat map of the correlations of main and minor lesions. There was similarity in pathological type between the main and minor lesions ($r_s=0.37$); a positive correlation between infiltration depth or lesion diameter ($r_s=0.58$, $r_s=0.49$); a positive correlation between lesion size and pathological type or degree of intestinal metaplasia of mucosal background atrophy ($r_s=0.30$, $r_s=0.33$). No association was found between gender, age, gastric mucosal background, lesion characteristics, or pathological features. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

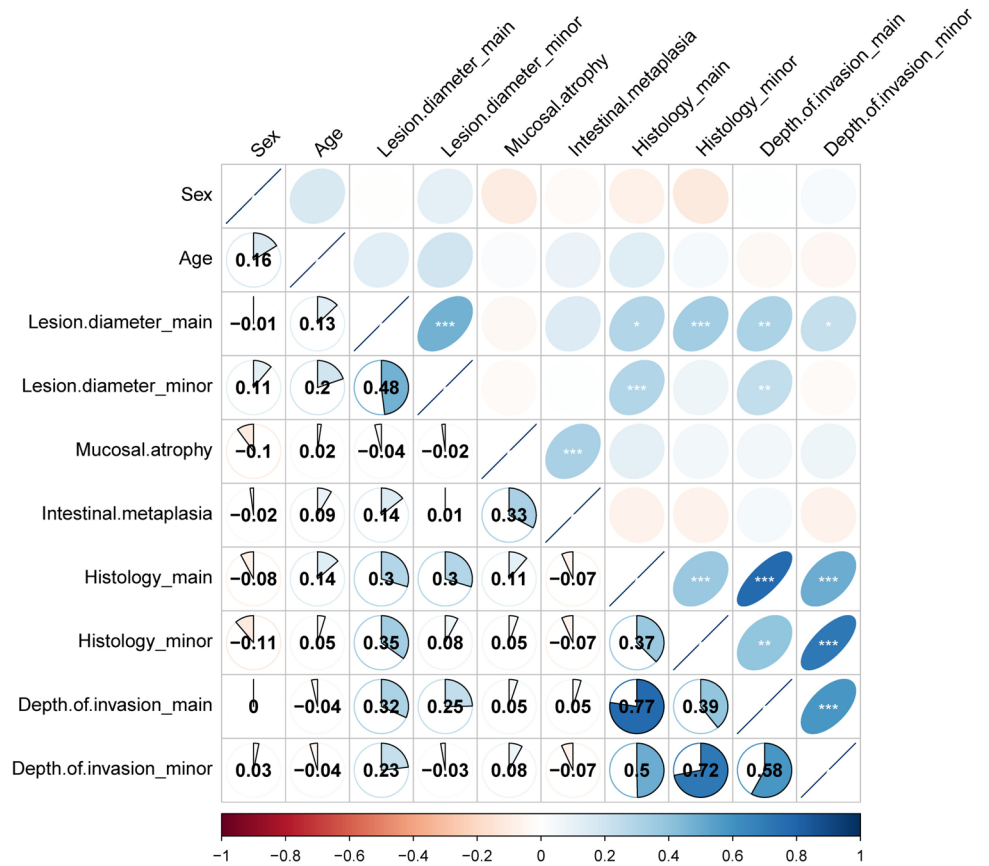
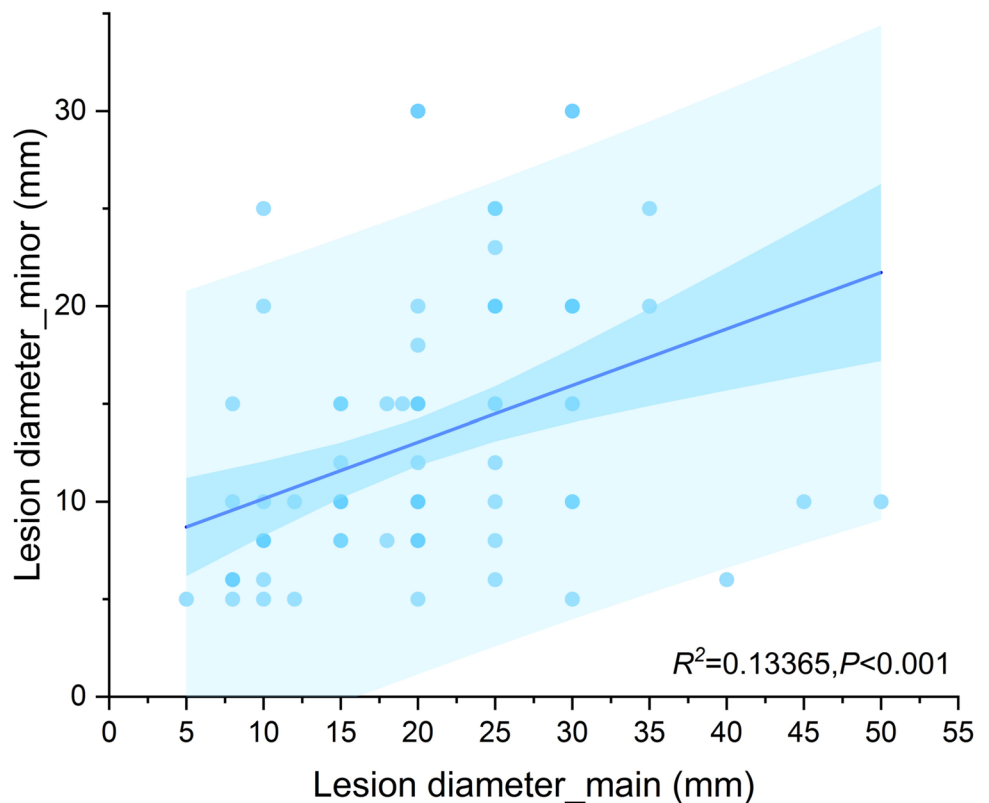


Fig. 4 Linear regression of main and minor lesion diameters for SMGN. The straight line shows a linear correlation in tumor size between major and minor lesions. $b=0.29$ (95% CI 0.14–0.44), $t=3.94$, $P < 0.001$. Person’s $r=0.38$ (95% CI 0.19–0.54). *SMGN* synchronous multiple gastric neoplasms



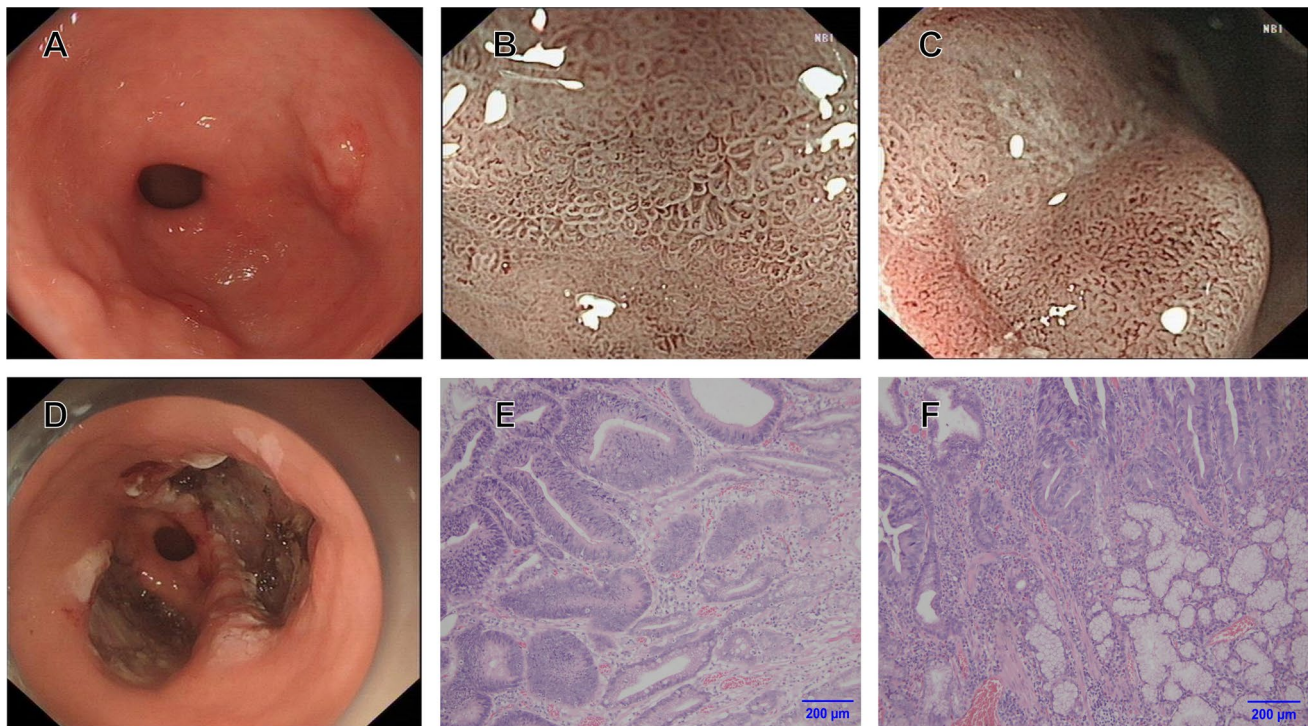


Fig. 5 Endoscopic presentation of main and minor SMGN lesions. In this older woman, a gently elevated lesion with a central depression is observed in the posterior and anterior walls of the gastric sinus. Regional disorganization of the glandular ducts is seen under ME-NBI, with a tortuous extension of the microvasculature and demarcation from the background mucosa (A–C). The lesion was marked

by gastroscopy and resected by ESD (D). Postoperative pathology (H&E×200) of the posterior and anterior walls suggested severe atypical hyperplasia (E, F). SMGN synchronous multiple gastric neoplasms, ME-NBI magnifying endoscopy-narrow band imaging, ESD endoscopic submucosal dissection

lack of endoscopic experience also contributed to missed diagnoses of multiple carcinomas [19].

From a pathological diagnostic perspective, we observed a stronger correlation in microscopic characteristics between the main and minor lesions. There is a significant positive correlation between the main and minor lesions in terms of pathological stage and depth of infiltration, respectively (Fig. 5). This could be attributed to the gastric mucosa being exposed to a shared physical and chemical environment. The theory of ‘regional carcinogenesis’ can also elucidate this phenomenon. Microscopy serves as the ‘gold standard’ for diagnosing this disease, and the data we obtained were more reliable and comprehensive, with reduced bias, which could lead to stronger correlation coefficients among the lesions [17]. However, it should be noted that our cohort had only three cases of undifferentiated carcinoma and five instances of infiltrating submucosa, which limits our ability to draw definitive conclusions about these cases. Future studies should aim to collect more samples to further explore these specific scenarios.

Substantial evidence suggests that SMGN have earlier staging and better differentiation than single cancers. Furthermore, Takeuchi et al. demonstrated that multiple

gastric cancers in surgically treated patients tended to exhibit good differentiation but were prone to co-occurring with other systemic tumors [20]. Wittekind et al. conducted a study involving 1664 patients with gastric cancer and reported that multiple cancers exhibited earlier staging and better pathological differentiation compared to single cancers [21]. Our finding supports that SMGNs tend to have more favorable disease progression and differentiation characteristics. Zhao et al. reported that SMGC was observed more frequently in patients with EGC than in those with advanced gastric cancer [6]. These suggest that SMGC may be more common in the early stages of gastric cancer and further highlight the importance of thorough examination and detection of multiple lesions, particularly in patients with EGC. The hypothesis that multiple cancer lesions may fuse in advanced tumor stages, resulting in a higher prevalence of SMGN in the early stages of the tumor, is an interesting one. The timing of detection and intervention may play a role in the formation and development of SMGN. The study by Seo et al. supports the idea that multifocal carcinomas, particularly undifferentiated adenocarcinomas, are more likely to develop into SMGN [22]. If the disease is not detected early, various lesions

can develop and merge, making it difficult to diagnose the disease in time, contributing to its rarity. By closely monitoring these patients, healthcare providers can intervene quickly and provide appropriate treatment strategies to improve patient outcomes.

Our study observed a positive correlation between the degree of background mucosal atrophy and intestinal metaplasia in patients with SMGN. However, we did not find significant associations between intestinalization of mucosal atrophy and factors such as age and sex in this population. Although gastric mucosal atrophic and intestinal metaplasia is typically associated with age and *H. pylori* infection, it is possible that patients with SMGN have similar degrees of gastric atrophic and intestinal metaplasia, with no differences found between sex and age. The prevalence of *H. pylori* infection in SMGN in this study was 52.4%. However, some studies suggest that *H. pylori* infection is not an independent risk factor for SMGN and does not show a statistically significant difference in the *H. pylori* infection rate compared to the solitary cancer cohort [5]. Independent risk factors for SMEGC include advanced age, male, atrophic gastritis, and moderate to severe intestinal epithelial metaplasia of the gastric mucosa [6]. Nakajima et al. conducted a study that demonstrated the influence of physicochemical factors on methylation in gastric mucosa [23]. They found that the methylation level in the gastric mucosa was higher in multiple gastric cancers than in single cancers. These results suggest differences in the degree of mucosal atrophy and intestinal metaplasia between patients with SMGN and those with single carcinomas. Takaoka et al. identified that methylation of the *mutL homolog 1* promoter plays a significant role in the development of the disease. Inactivation of the mismatch repair system leads to the accumulation of somatic mutations, contributing to the progression of SMEGC [7]. Therefore, the presence and severity of these mucosal changes should be carefully evaluated during the diagnosis and treatment of SMGN to assess the risk of developing gastric cancer [20].

This study has several limitations. First, although efforts were made to expand the sample size, there were still relatively few cases of undifferentiated carcinoma and submucosal infiltration in SMGN, limiting the comprehensive exploration of these cases. Further expanded samples are warranted in future studies to provide more information on these specific SMGN subtypes. Second, some patients were referred during the review process, leading to the loss of post-ESD gastroscopy review data for these individuals. This may have resulted in an underestimation of the incidence of SMGNs, as some cases may have been missed or not included in the analysis. These limitations highlight the need for larger sample sizes and careful data collection to enhance the robustness and generalizability of the findings in future studies investigating SMGN.

Conclusions

Through the study of patients with SMGN who underwent ESD, we found that the correlation coefficients for microscopic features were higher than those for gastroscopy. Our study findings suggest a significant positive correlation between the main and minor lesions in terms of pathological stage and depth of infiltration, with a similar spatial distribution of the lesions and the gastroscopic morphology. There was a statistically significant difference between the size of the main and minor lesions and a positive correlation.

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Declarations

Disclosures Yudai Chen, Chaoying Fang, Jianmin Huang, Hui Pan, Liping He, Chenlin Zhuang, and Xiaoling Zheng have no conflicts of interest or financial ties to disclose.

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