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Predictive risk factors associated with synchronous multiple early gastric cancer

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Abstract

The aim of this study was to elucidate the predictive risk factors of synchronous multiple early gastric cancer regardless of the treatment modality.

Patients who underwent early gastric cancer treatment between July 2005 and June 2015 were retrospectively reviewed. In total, 1529 patients who were treated for early gastric cancer were included. We analyzed the patient's data to find predictive factors of synchronous multiple early gastric cancer compared to solitary early gastric cancer. Further analysis was performed to verify the difference between endoscopic and surgical treatment groups.

Among the 1529 patients, synchronous multiple early gastric cancer was diagnosed in 68 (4.4%) patients. Significant differences in sex ($P = .004$), gross appearance ($P = .038$), depth of invasion ($P = .007$), and lymphovascular invasion ($P = .039$) were found between patients with solitary early gastric cancer and synchronous multiple early gastric cancer by univariate analysis. In multivariate analysis, male sex (odds ratio, 2.475; $P = .011$) and submucosal invasion (odds ratio, 1.850; $P = .033$) were independent predictive risk factors of synchronous multiple early gastric cancer. In addition, in multivariate analysis, significant differences in age, tumor size, longitudinal location, depth of invasion, and histology were found between patients groups depending on the mode of treatment.

Male sex and submucosal invasion were predictive risk factors of synchronous multiple early gastric cancer. Patients with these factors should undergo more meticulous endoscopic surveillance.

Abbreviations: AGC = advanced gastric cancer, CI = confidence interval, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, LVI = lymphovascular invasion, OR = odd ratio, SMEGC = synchronous multiple early gastric cancer, SMGC = synchronous multiple gastric cancer, Ver. = version.

Keywords: endoscopy, multiple primary, neoplasms, risk factors, synchronous

1. Introduction

Early gastric cancer (EGC) is defined as gastric adenocarcinoma limited to the mucosa or submucosa, regardless of lymph node metastases. The prognosis of EGC is good with a 5-year survival rate over 90%, whereas the prognosis of advanced gastric cancer (AGC) is poor with a 5-year survival rate of 30% to 60%.[1–4]

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Therefore, detailed and careful endoscopic examination is important for the detection of EGC lesions in the stomach in the early stage.

The quality of life of patients with EGC has recently improved with advances in minimally invasive procedures such as laparoscopic surgery and endoscopic resection.[4–6] However, residual cancer in the remaining stomach after organ-preserving treatment is a major problem in the clinical setting. Two or more malignant cancer lesions in the stomach are defined as synchronous multiple gastric cancer (SMGC). SMGC is more commonly associated with EGC than with AGC. Synchronous multiple early gastric cancer (SMEGC) is defined SMGC associated with EGC. SMEGC has been reported to account for 3% to 15% of all gastric cancer cases.[7–9]

Therefore, when EGC is diagnosed by diagnostic endoscopy, it is very important to detect other possible lesions that may be present. If synchronous cancer lesions are overlooked, these patients may miss the opportunity to be treated in the early stage, and their early cancer may progress to advanced cancer. Some previous studies investigated predicting risk factors of SMEGC.[10–14] However, they only focused on patients who received the same mode of treatment such as surgical or endoscopic treatment. These previous studies are limited by selection bias, and their results are not applicable to the general population.

To date, no studies have evaluated the predictive risk factors of SMEGC among all patients with EGC, regardless of their mode of treatment. Therefore, the present study aimed to elucidate the predictive risk factors of SMEGC compared to solitary EGC, regardless of their initial mode of treatment.

2. Methods

2.1. Study population

The medical records of EGC patients who were treated between July 2005 and June 2015 at Gachon University Gil Medical Center, Incheon, Korea were retrospectively reviewed. We included patients with EGC who were initially treated regardless of the mode of treatment. The exclusion criteria were the following: patients who underwent prior surgical resection that caused a change in the normal anatomy of the stomach and patients who received prior treatment for gastric neoplasms other than the initial treatment.

Of 1617 patients with EGC who were initially treated with endoscopic submucosal dissection (ESD) or surgery, we excluded 88 patients from this study; 75 patients were excluded because of previous ESD. Among the 75 excluded patients, 36 had previous EGC, 33 had previous tubular adenoma with low-grade dysplasia, and 6 had previous tubular adenoma with high-grade dysplasia. Thirteen patients were excluded because of previous surgery, among whom 10 were excluded because of previous subtotal gastrectomy and 3 patients were excluded because of previous antrectomy due to ulcer perforation. Finally, this study analyzed 1529 patients with EGC (68 patients with SMEGC and 1461 patients with solitary EGC) (Fig. 1). This study was approved by the institutional review board of the Gachon University Gil Medical Center (IRB No. GBIRB2016–063).

2.2. Procedure

Each patient with EGC underwent either surgical or endoscopic resection as initial treatment. We used the following indications for ESD until 2010. ESD was performed if the lesions satisfied the following criteria: diagnosis of an adenocarcinoma in a biopsy sample on histopathological examination, diagnosis of mucosal cancer without ulcers, regardless of the tumor size, and diagnosis of mucosal cancer with ulcers in which the tumor size was 3 cm or less. After 2010, we used an expanded indication for ESD according to the 2010 Japanese gastric cancer treatment guidelines (ver. 3).[15] If the lesions did not meet the criteria for endoscopic resection, we performed surgical resection. ESD was performed according to the standard method.[16,17] Abdominal computed tomography was performed in all the patients with/without endoscopic ultrasonography before initial treatment. The attending surgeon decided the type of surgery and the extent of lymphadenectomy depending on the location of the cancer and the conditions of the patient. Whenever the circumstances allowed, R0 resection and D2 lymph node dissection with curative intent were performed.

2.3. Definitions

Solitary EGC was defined as a single malignant gastric cancer lesion. SMEGC was defined as multiple EGC lesions according to Moertel's criteria as follows:[18] each lesion must be pathologically proven to be malignant; each lesion must be distinctly separated from the others by microscopically normal gastric wall; and the lesions do not represent a metastatic tumor or a local extension.

According to the Japanese Gastric Cancer Association criteria, the gastric cancer type were classified based on the location (longitudinal or horizontal), histological findings, and macroscopic type.[15] Anatomically, the longitudinal axis of the stomach is divided into 3 parts: the upper third, middle third, and lower third. Horizontally, the circumference of the stomach is divided into 4 parts: the anterior wall, lesser curvature, posterior wall, and greater curvature. The tumor size during the study was measured by the maximum diameter of the lesion. The macroscopic classification of the tumor was grouped into 3 types as follows: elevated (types 0-I, 0-IIa, 0-I + IIa, 0-IIa + IIb, 0-IIa + IIc); flat (type 0-IIb); and depressed (types 0-IIc, 0-III, 0-IIc + IIa,
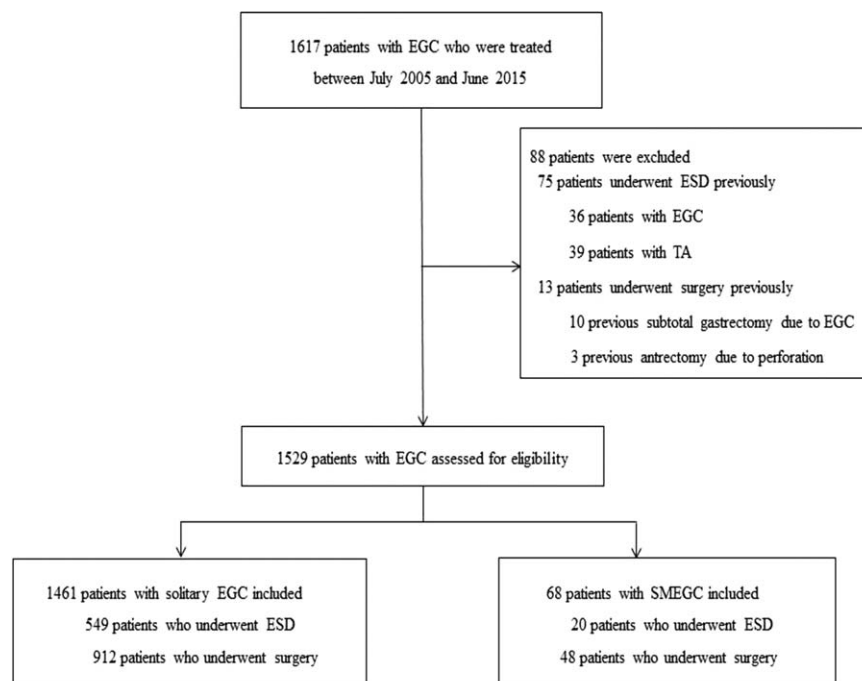

Figure 1. Inclusion criteria for early gastric cancer.

and 0-III + IIa). The histological classification of the tumor was classified into 2 different types as follows: differentiated type, which was divided into papillary adenocarcinoma or well and moderately differentiated tubular adenocarcinoma, and undifferentiated type, which was divided into poorly differentiated tubular adenocarcinoma, signet-ring cell carcinoma, or mucinous adenocarcinoma.

2.4. Statistical analysis

The SPSS 22.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, NY) for MS Windows was used for statistical analysis. Categorical variables are presented as absolute numbers or percentages, and continuous data are presented as means (standard deviations). In univariate analysis, categorical data were analyzed using the Pearson χ^2 or Fisher exact test. Multivariate analysis was performed by logistic regression. P-values <.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the 1529 patients are shown in Table 1. Among the 1529 patients, SMEGC was diagnosed in 68

Table 1

Baseline characteristics of patients with EGC.

	Total (n = 1529)
Age, years, mean ± SD	61.3 ± 11.5
Gender	
Male	1073 (70.2%)
Female	456 (29.8%)
Size of cancer, mm, mean ± SD	24.9 ± 17.4
Longitudinal location	
UT	240 (15.7%)
MT	479 (31.3%)
LT	810 (53.0%)
Horizontal location	
AW	332 (21.7%)
GC	286 (18.7%)
PW	351 (23.0%)
LC	560 (36.6%)
Gross appearance	
Elevate	226 (14.8%)
Flat	461 (30.2%)
Depressed	842 (55.1%)
Depth of invasion	
M	963 (63.0%)
SM	566 (37.0%)
Lymphovascular invasion	
Negative	1338 (87.5%)
Positive	191 (12.5%)
Histology	
Differentiated type	998 (65.3%)
Undifferentiated type	531 (34.7%)
Mode of treatment	
ESD	569 (37.2%)
Surgery	960 (62.8%)
Node metastasis[*]	
No	869 (90.5%)
Yes	91 (9.5%)

[*] Nine hundred sixty patients underwent surgical resection.
AW = anterior wall, EGC = early gastric cancer, ESD = endoscopic submucosal dissection; GC = greater curvature, LC = lesser curvature, LT = lower third, M = mucosa, MT = middle third, PW = posterior wall, SD = standard deviation, SM = submucosa, UT = upper third.

(4.4%) patients. The mean age of all the patients was 61.3 ± 11.5 years. In total, 1073 (70.2%) patients were men and 456 (29.8%) patients were women. The mean size of the tumor was 24.9 ± 17.4 mm. The most common location was the lower third of the stomach (810, 53.0%) and lesser curvature of the stomach (560, 36.6%) in the longitudinal and horizontal axis, respectively. The most common gross appearance was the depressed type (842, 55.1%), and the most common histological type was the differentiated type (998, 65.3%). In total, 566 (37.0%) of the patients had submucosal invasion and 191 (12.5%) had lymphovascular invasion (LVI). Regarding the initial mode of treatment, 569 (37.2%) patients underwent ESD and 960 (62.8%) patients underwent surgery. Among the 960 patients who underwent surgical resection, 91 (9.5%) had lymph node metastasis.

3.2. Predictive risk factors of SMEGC compared to solitary EGC

The proportion of male patients was higher among those with SMEGC than among those with solitary EGC (85.3% [58/68] vs 69.5% [1015/1461], P = .004). Based on the gross appearance, the elevated type was more common among patients with SMEGC than among those with solitary EGC (23.5% [16/68] vs 14.4% [210/1461], P = .038). Submucosal invasion was more common among patients with SMEGC than among those with solitary EGC (52.9% [36/68] vs 36.3% [530/1461], P = .007). LVI was more common among patients with SMEGC than among those with solitary EGC (20.6% [14/68] vs 12.1% [177/1461], P = .039). However, age, size of tumor, longitudinal location, and histology were not significantly different between patients with SMEGC and those with solitary EGC.

In multivariate analysis, male sex (odds ratio [OR], 2.475; 95% confidence interval [CI], 1.234–4.965; P = .011) and submucosal invasion (OR, 1.850; 95% CI, 1.051–3.256; P = .033) were statistically significant independent predictive factors of SMEGC shown in Table 2.

3.3. Differences between patients who underwent ESD or surgery

In univariate analysis, tumor size over 20 mm (69.5% [667/960] vs 27.8% [158/569], P < .001), submucosal invasion (48.5% [466/960] vs 17.6% [100/569], P < .001), undifferentiated type (49.3% [473/960] vs 10.2% [58/569], P < .001), and LVI (17.2% [165/960] vs 4.6% [26/569], P < .001) were more common among the surgery group than among the ESD group (Table 3). Age ≥60 years (63.6% [362/569] vs 47.6% [457/960], P < .001) and longitudinal location in the lower third (63.6% [362/569] vs 46.7% [448/960], P < .001) were reported more frequently in the ESD group than in the surgery group. In multivariate analysis, age (OR, 1.593; 95% CI, 1.222–2.076; P = .001), size of tumor (OR, 3.932; 95% CI, 3.014–5.129; P < .001), longitudinal location (OR, 1.326; 95% CI, 1.021–1.723; P = .035), depth of invasion (OR, 3.008; 95% CI, 2.222–4.072; P < .001), and histology (OR, 6.542; 95% CI, 4.641–9.223; P < .001) differed significantly between patients who underwent ESD and those who underwent surgical resection. However, gender, gross appearance, and LVI were not significant statistically in Table 3.

4. Discussion

Although diagnostic technology using endoscopy has advanced rapidly, inaccuracies in the diagnostic examination of multiple

Table 2

Predictive factors of SMEGC compared with solitary EGC.

	Solitary EGC (n=1461)	SMEGC (n=68)	Univariate P value	Multivariate OR	Multivariate 95% CI	Multivariate P value
Age, years			.387	1.126	0.674–1.880	.650
<60	682 (46.8%)	28 (41.2%)				
≥60	779 (53.3%)	40 (58.8%)				
Gender			.004	2.475	1.234–4.965	.011
Female	446 (30.5%)	10 (14.7%)				
Male	1015 (69.5%)	58 (85.3%)				
Size of cancer, mm			.804	0.854	0.496–1.471	.570
<20	674 (46.1%)	30 (44.1%)				
≥20	787 (53.9%)	38 (55.9%)				
Longitudinal location			.384	1.343	0.809–2.230	.254
UT/MT	691 (47.3%)	28 (41.2%)				
LT	770 (52.7%)	40 (58.8%)				
Gross appearance			.038	0.643	0.348–1.187	.158
Elevate	210 (14.4%)	16 (23.5%)				
Flat/depressed	1251 (85.6%)	52 (76.5%)				
Depth of invasion			.007	1.850	1.051–3.256	.033
M	931 (63.7%)	32 (47.1%)				
SM	530 (36.3%)	36 (52.9%)				
Histology			.244	0.885	0.490–1.599	.686
Differentiated type	949 (65.0%)	49 (72.1%)				
Undifferentiated type	512 (35.0%)	19 (27.9%)				
LVI			.039	1.402	0.703–2.795	.338
Negative	1284 (87.9%)	54 (79.4%)				
Positive	177 (12.1%)	14 (20.6%)				

AW=anterior wall, CI=confidence interval, EGC=early gastric cancer, GC=greater curvature, LC=lesser curvature, LT=lower third, LVI=lymphovascular invasion, M=mucosa, MT=middle third, OR=odds ratio, PW=posterior wall, SM=submucosa, SMEGC=synchronous multiple early gastric cancer, UT=upper third.

Table 3

Differences between ESD and surgery.

	ESD (n=569)	Surgery (n=960)	Univariate P value	Multivariate OR	Multivariate 95% CI	Multivariate P value
Age, years			<.001	1.593	1.222–2.076	.001
<60	207 (36.4%)	503 (52.4%)				
≥60	362 (63.6%)	457 (47.6%)				
Gender			.184	1.288	0.959–1.730	.093
Male	411 (72.2%)	662 (69.0%)				
Female	158 (27.8%)	298 (31.0%)				
Size of cancer, mm			<.001	3.932	3.014–5.129	<.001
<20	411 (72.2%)	293 (30.5%)				
≥20	158 (27.8%)	667 (69.5%)				
Longitudinal location			<.001	1.326	1.021–1.723	.035
UT/MT	207 (36.4%)	512 (53.3%)				
LT	362 (63.6%)	448 (46.7%)				
Gross appearance			.457	0.990	0.687–1.426	.956
Elevate	79 (13.9%)	147 (15.3%)				
Flat/depressed	490 (86.1%)	813 (84.7%)				
Depth of invasion			<.001	3.008	2.222–4.072	<.001
M	469 (82.4%)	494 (51.5%)				
SM	100 (17.6%)	466 (48.5%)				
Histology			<.001	6.542	4.641–9.223	<.001
Differentiated type	511 (89.8%)	487 (50.7%)				
Undifferentiated type	58 (10.2%)	473 (49.3%)				
LVI			<.001	1.467	0.890–2.419	.133
Negative	543 (95.4%)	795 (82.8%)				
Positive	26 (4.6%)	165 (17.2%)				

AW=anterior wall, CI=confidence interval, EGC=early gastric cancer, GC=greater curvature, LC=lesser curvature, LT=lower third, LVI=lymphovascular invasion, M=mucosa, MT=middle third, OR=odds ratio, PW=posterior wall, SM=submucosa, UT=upper thir.

gastric cancer lesions remains a problem. The incidence of synchronous or metachronous EGC after endoscopic resection or after surgical resection was reported to be approximately 4.8% 20.9%.[10,11,19] These additional lesions that are found in a short period after initial treatment are more likely to be lesions that were missed on endoscopy, rather than newly developed lesions. Therefore, meticulous endoscopic examination at the initial diagnosis of EGC is important, as well as identifying the predictive risk factors of additional lesions.

Because of the importance of identifying synchronous lesions, we elucidated predictive risk factors of SMEGC, in order to decrease the number of missed diagnoses of additional gastric cancer lesions. In the present study, male sex and submucosal invasion of EGC were independent predictive risk factors of SMEGC. These findings were relatively inconsistent with those of previous studies.[11–14,20]

The reason for the difference in the findings of the present study and previous studies may be that all patients with EGC, regardless of the mode of treatment, were included in the present study, whereas in previous studies, only patients who underwent ESD or surgical resection were evaluated. In previous studies that evaluated patients who underwent endoscopic resection, the predictive risk factors of SMEGC were reported to be male sex, undifferentiated histological type, and longitudinal location in the lower third.[11,13,14] In previous studies that evaluated patients who underwent surgical resection, the predictive risk factors of SMEGC were reported to be male sex, depth of invasion, elevated type of gross appearance, LVI, and differentiated histological type.[12,20] In some studies, older age was reported to be a predictive risk factor of SMEGC.[11,19]

Some of the predictive risk factors identified in previous studies are consistent and some are inconsistent with those found in the present study. Interestingly, there are some conflicting results depending on the method of treatment. For example, among patients who underwent surgical resection, differentiated histological type was found to be a predictive risk factor of SMEGC,[19] whereas in patients who underwent endoscopic resection, undifferentiated histological type was reported to be a predictive risk factor of SMEGC.[21] In the present study, submucosal invasion was found to be a predictive risk factor of SMEGC, whereas Nitta et al[19] reported less deep invasion as a predictive risk factor of SMEGC.

Because previous studies have reported inconsistent results depending on the method of treatment, we hypothesized that there would be differences in the characteristics of patients according to the mode of treatment. In this regard, we performed an additional analysis in order to confirm the difference between the endoscopic and surgical treatment groups. The results of the multivariate analysis showed that the age, tumor size, longitudinal location, depth of invasion, and histological differentiation differed significantly between patients who underwent endoscopic treatment and those who underwent surgical treatment. Therefore, the results of studies that only evaluated patients who underwent 1 mode of treatment (e.g., endoscopic treatment or surgery) should be interpreted with caution and cannot be generalized to all patients because of selection bias.

Another reason for the differences in the results of the present study and previous studies may be that SMEGC was defined differently in the present study and in previous studies. In some studies, SMEGC was defined as any second lesions that occurred within 6 months or 1 year after the initial diagnosis of EGC.[8,13,19] However, in the present study, SMEGC was defined as multiple EGC lesions that were found during treatment initially, based on the definition of "synchronous"; in other words, a time interval between lesions was not considered. This difference in the definition may have affected the SMEGC prevalence. The prevalence of SMEGC in our study was 4.4% (68/1529), which is relatively lower than that reported in previous studies (5%–15%).[7,8] Differences in the demographic characteristics of patients in the present study and previous studies, such as differences in race and region, may explain the differences in the prevalence of SMEGC. Similar to the present study, other studies performed in South Korea have reported a prevalence of SMEGC of 3% to 8%.[22,23]

In the present study, male sex was found to be a predictive risk factor of SMEGC. Men have a higher risk of gastric cancer.[24] However, the reason for this is not clear. Some hypotheses have been suggested. First, differences in smoking patterns between men and women were suggested to affect the prevalence of upper gastrointestinal adenocarcinoma; however, upper gastrointestinal adenocarcinoma was found to be more predominant among men even in countries where men and women have similar smoking patterns.[25] Second, physiological differences between the sexes may explain why male sex was associated with an increased risk of SMEGC. Estrogens may decrease occurrence of gastric cancer, as suggested by a marked delayed development of upper gastrointestinal adenocarcinoma among women before 50 to 60 years of age.[26]

Consistent with the findings of the present study, in some studies, submucosal invasion was found to be a risk factor for multiple EGC.[11,12] Fujisaki et al[27] reported that progression to AGC was more likely among patients with submucosal invasion. Compared to EGC without submucosal invasion, EGC with submucosal invasion could be more influenced by risk factors for a long time, thereby influencing normal gastric mucosa as well as cancer-related gastric mucosa. Therefore, EGC with submucosal invasion may result in the possibility of SMEGC. These findings support the hypothesis of field carcinogenesis, defined as the entire gastric mucosa with an identical background of carcinogenesis.[7,18]

The present study has some strengths. First, we focused on all patients with EGC irrespective of their mode of treatment. In this regard, our findings of the predictive risk factors of SMEGC may be more useful in the clinical practice. Second, we performed an additional analysis of differences between ESD and surgery groups and identified many different characteristics between the 2 groups. As a result, our findings may be applicable to the general population without selection bias according to mode of treatment. Third, SMEGC was defined to be limited to multiple EGCs that were detected during the initial treatment, which is more consistent with the meaning of "synchronous."

The present study is limited by its retrospective design. Therefore, we were not able to perform a more thorough pathological examination and may have overlooked other small lesions. In addition, we did not investigate lymph node metastasis in all patients because we included patients who were treated by ESD.[28] A total of 91 (9.5%) patients who were treated by surgical resection had lymph node metastasis, and this result was consistent with that of a previous study.[29,30]

In conclusion, the present study showed that male sex and submucosal invasion were predictive risk factors of SMEGC. Therefore, a more meticulous endoscopic surveillance is needed in EGC patients with these risk factors.

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