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Investigation of Endoscopic and Pathologic Features for Safe Endoscopic Treatment of Superficial Spreading Early Gastric Cancer

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Abstract: Superficial spreading early gastric cancer (EGC) is a rare disease that is treated mainly by surgery. There are few studies on the safety of endoscopic treatment for patients with superficial spreading EGC. The aims of this study were to (1) investigate the risk of lymph node metastasis of superficial spreading EGC and (2) investigate the potential criteria for endoscopic treatment of superficial spreading EGC using surgical specimens.

Between 2000 and 2010, patients who received curative surgery of R0 resection at Severance Hospital (Seoul, Korea) for early gastric cancer were enrolled. The superficial spreading EGC was defined as cancer in which the longest tumor length was $\geq$6 cm. The medical records of the patients were reviewed retrospectively.

Of the 3813 patients with EGC, 140 (3.7%) had lesions $\geq$ 6 cm, whereas 3673 (96.3%) had lesions $<$ 6 cm. Patients with superficial spreading EGC had higher rates of submucosal cancer (59.3% vs 45.7%, $P = 0.002$), lymphovascular invasion (18.6% vs 9.8%, $P < 0.001$), and lymph node metastasis (15.7% vs 10.1%, $P = 0.033$) compared with patients with common EGC ($<$ 6 cm). Multivariate analysis revealed that a tumor $\geq$ 6 cm was not strongly associated with lymph node metastasis in EGC, as compared with a tumor $<$ 6 cm, but submucosal invasion and lymphovascular invasion were strongly associated with lymph node metastasis in EGC. In mucosal cancer without ulcers, tumors $\geq$ 6 cm had a higher rate of lymph node metastasis than tumors $\leq$ 2 cm; however, this trend was not significant (7.7% vs 5.3%, $P = 0.455$).

Superficial spreading EGC was not associated with an increased risk of lymph node metastasis compared with common EGC. We suggest that differentiated intramucosal superficial spreading EGC without ulceration can be treated by endoscopic submucosal dissection.

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Abbreviations: EGC = early gastric cancer, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, QOL = quality of life.

INTRODUCTION

Gastric cancer is the third leading cause of cancer death in Korea.[1,2] The detection of early gastric cancer (EGC) has been aided by increased upper endoscopy screening and the development of endoscopic technology. The mortality from gastric cancer has therefore decreased due to early detection, that is, increased diagnosis in the early stages.[3,4]

Gastrectomy with lymph node dissection is a standard treatment for EGC, and the presence of lymph node metastasis is an important prognostic factor for patient outcomes. Currently, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is performed for endoscopic resection of EGC without evidence of lymph node metastasis.[5–7] The expanded criteria provided by Gotoda et al have been applied to endoscopic treatment of early gastric cancer.[8] If the tumor is confined to the mucosa, lacks ulcers, and has differentiated histology, the success of endoscopic resection is independent of tumor size.[8]

Occasionally, a large but superficially deep gastric cancer is encountered. This type of gastric cancer was first mentioned in 1949 by Golden and Stout, who described it as a ''superficial spreading carcinoma'' characterized by wide and superficial extension with a limited depth of vertical invasion.[9] Since then, this type of gastric cancer has been reported in many studies.[10,11] Recently, superficial spreading EGC has become a focus of endoscopic treatment. Although surgical resection is considered the standard treatment for superficial spreading EGC, endoscopic treatment has been attempted for EGC of any size that meets the criteria outlined by Gotoda et al in limited conditions. However, few studies have investigated the safety of endoscopic treatment of superficial spreading EGC with respect to the risk of lymph node metastasis. In this study, we aimed to investigate the rate of lymph node metastasis of superficial spreading EGC to identify endoscopic and pathologic features of patients without lymph node metastasis in order to help develop criteria for the safe endoscopic resection for this type of cancer using surgical specimens.

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METHODS

Patients

All patients who received radical gastrectomy in Severance Hospital, Yonsei University College of Medicine (Seoul, Korea), were enrolled in this study. The operation method for inclusion was radical subtotal gastrectomy or total gastrectomy with D2 lymph node dissection.[12] The paraffin-embedded surgical specimens from gastrectomy were sliced at 2-mm intervals. Generally, special immunohistochemical staining was not performed to discover submucosal invasion or lymphovascular invasion. The pathology reports of tumor diameter, histology, depth of invasion, lymphovascular invasion, and lymph node metastasis were reviewed. According to the criteria of the Japanese Gastric Cancer Association,[13] patients with 4 types of pathology were included: well-differentiated adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiated carcinoma, and signet ring cell carcinoma. The exclusion criteria were a history of previous gastrectomy or endoscopic treatment and R1 and R2 resections. This study was approved by the Institutional Review Board for Human Research of Yonsei University College of Medicine. The need for informed consent was waived because the data were anonymized before analysis.

Definition

Superficial spreading EGC was defined as EGC with a tumor >60 mm in diameter, in accordance with established Japanese cancer criteria (Figure 1).[14] The diameter was measured from the resected specimen after operation and the longest diameter of the tumor was used. The differentiated and undifferentiated types were defined according to the criteria outlined by the Japanese Gastric Cancer Association.[13] The differentiated type included well differentiated and moderately differentiated adenocarcinomas, whereas the undifferentiated type included poorly differentiated and signet ring cell carcinomas.

Statistical Analysis

Statistical analysis was performed using SPSS software, version 12.0 (SPSS Inc., Chicago, IL). Categorical variables were compared using the chi-square test and continuous variables in 2 groups were compared using Student's *t*-test. Logistic regression analysis was used to evaluate the risk of lymph node metastasis. Results are expressed as odds ratios (OR) and 95% confidence intervals (CI). P values < 0.05 were considered significant for all statistical analyses.

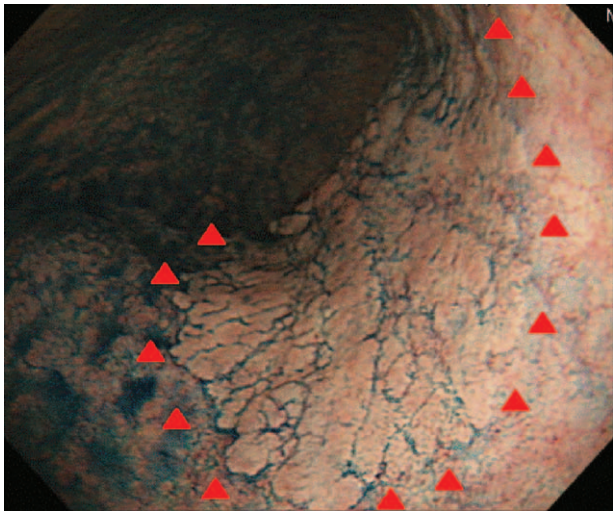

FIGURE 1. Superficial spreading early gastric cancer. On the greater curvature of the mid-body, large spreading nodular lesions were found after indigocarmine dye spray.

RESULTS

A total of 3989 patients with EGC underwent gastrectomy with lymph node dissection between March 2000 and February 2010. Of these, 176 were excluded due to previous treatment (n = 129) and unclassified pathology (n = 47). Of the remaining 3813 patients, 140 (3.67%, 76 men and 64 women) were classified as superficial spreading EGC (Figure 2).

The rate of superficial spreading EGC was significantly higher than that of common EGC (<6 cm) in women (45.7% vs 34.6%, $P = 0.007$) (Table 1). Age, tumor location, and presence of ulcers were not significantly different between these 2 groups. The superficial spreading EGC group had a higher rate of undifferentiated cancer compared with the common EGC group (<6 cm); however, this trend was not significant ($P = 0.178$). Submucosal invasion (59.3% vs 45.7%, $P = 0.002$), lymphovascular invasion (18.6% vs 9.8%, $P < 0.001$), and lymph node metastasis (15.7% vs 10.1%, $P = 0.033$) were all significantly higher in the superficial spreading EGC group compared with the common EGC group (< 6 cm).

The rate of total gastrectomy was higher in the superficial spreading EGC group than in the common EGC group (<6 cm) (21.4% vs 12.7%, $P = 0.012$) (Table 2). Moreover, the total numbers of dissected lymph nodes were higher in the superficial spreading EGC group than in the common EGC group (<6 cm) ($P = 0.019$). However, the total number of metastatic lymph nodes was not different between the superficial spreading EGC and the common EGC group ($P = 0.491$).

Univariate analysis revealed that lymph node metastasis was strongly associated with superficial spreading EGC (OR: 1.65, 95% CI, 1.03–2.64; $P = 0.035$) (Table 3). However, multivariable analysis revealed that lymph node metastasis was not associated with superficial spreading EGC (OR: 1.33, 95% CI: 0.82–2.15; $P = 0.253$). Undifferentiated cancer type, submucosal invasion, and lymphovascular invasion were all strongly associated with an increased risk of lymph node metastasis. For patients with mucosal cancers without ulcers, the rate of lymph node metastasis of superficial spreading EGC (7.7%) was higher than that of common EGC (<6 cm, 5.3%; < 3 cm, 4.9%; and < 2 cm, 5.3%). However, these differences were not significant ($P = 0.458$, 0.358, and 0.455, respectively) (Table 4).

The clinicopathologic features of the 4 cases of superficial spreading EGC with mucosal invasion and no ulcers are listed in Table 5. All cases had undifferentiated cancer.

DISCUSSION

The multivariable analysis performed in this study revealed that superficial spreading EGC was not associated with an increased risk of lymph node metastasis. However, univariate analysis showed that the rate of lymph node metastasis was higher for tumors ≥6 cm than for tumors < 6 cm. These findings suggest that histological characteristics, depth of invasion, and lymphovascular invasion are more strongly associated with lymph node metastasis than tumor size in superficial spreading EGC.

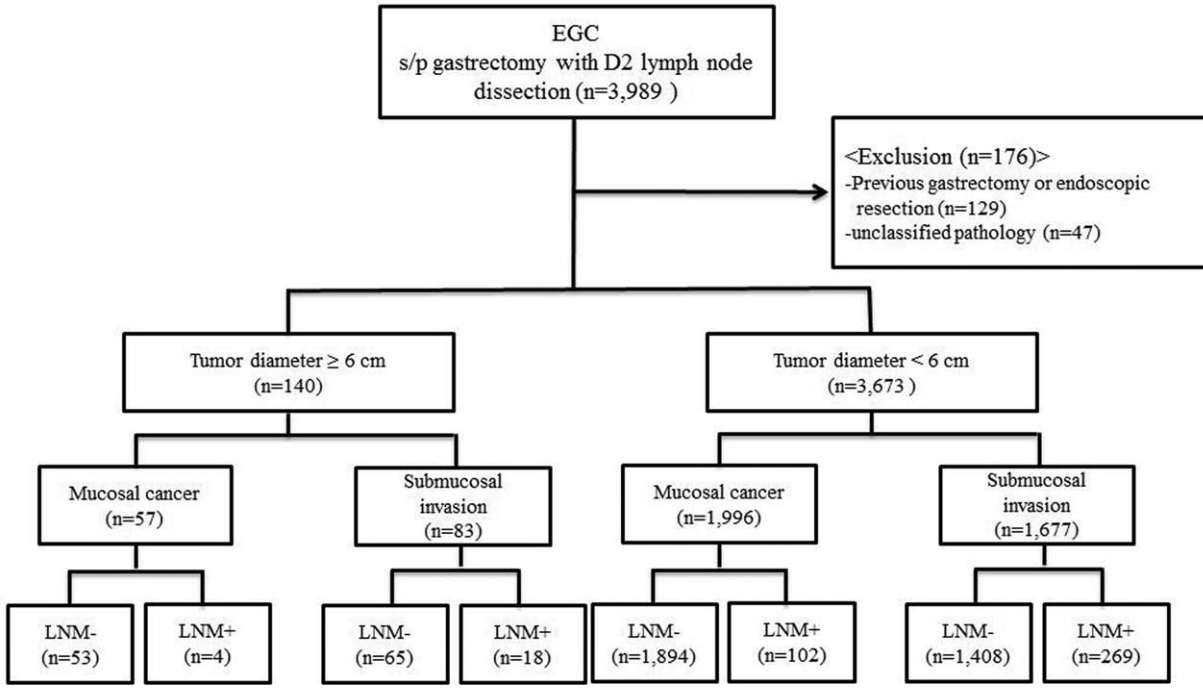

FIGURE 2. Flowchart of patient enrollment.

Although a standard definition of superficial spreading EGC has not yet been established, tumors with a longest diameter >60 mm and with limited invasion depth are generally defined as superficial spreading type in Japan and Korea.[15] Although superficial spreading is typical of this type of EGC, the pathophysiology of this feature has not been elucidated. Similarly, the mechanism by which the invasion depth is limited has not been identified. The rate of superficial spreading EGC is

TABLE 1. Clinicopathological Characteristics of the Superficially Spreading and Common Types of Early Gastric Cancer

	Tumor Size		
Variable	**≥6 cm (n = 140)**	**<6 cm (n = 3673)**	***P* Value**
Sex (men:women)	76 (54.3%):64 (45.7%)	2403 (65.4%):1270 (34.6%)	0.007
Age, years (mean ± SD)	55.2 ± 11.9	56.8 ± 11.5	0.101
Location			0.186
Upper third	11 (7.9%)	353 (9.6%)	
Middle third	50 (35.7%)	1053 (28.7%)	
Lower third	79 (56.4%)	2267 (61.7%)	
Ulcerative lesion			0.975
Presence	19 (13.6%)	492 (13.5%)	
Tumor diameter, mm (mean ± SD)	71.9 ± 16.8	22.4 ± 11.9	<0.001
Histology			0.178
Well differentiated	24 (17.1%)	829 (22.6%)	
Moderately differentiated	36 (25.7%)	1086 (29.6%)	
Poorly differentiated	38 (27.1%)	813 (22.1%)	
Signet ring cell	42 (30%)	945 (25.7%)	
Depth of invasion			0.002
Intramucosal	57 (40.7%)	1996 (54.3%)	
Submucosal	83 (59.3%)	1677 (45.7%)	
Lymphovascular invasion	26 (18.6%)	361 (9.8%)	<0.001
Lymph node metastasis	22 (15.7%)	371 (10.1%)	0.033

Nominal variables were analyzed by the chi-square test; continuous variables were analyzed by Student's *t*-test.
SD = standard deviation.

TABLE 2. Comparison of Operation-Related Findings Between the Superficially Spreading and Common Types of Early Gastric Cancer

Variable	Tumor Size		*P* Value
	≥6 cm (n = 140)	<6 cm (n = 3673)	
Approach			0.104
Open	126 (90%)	3123 (85%)	
Laparoscopy	14 (10%)	550 (15%)	
Gastrectomy type			0.012
Total gastrectomy	30 (21.4%)	469 (12.7%)	
Subtotal gastrectomy	110 (78.6%)	3204 (87.3%)	
Operation time, min (mean ± SD)	153.6 ± 48.9	155.9 ± 50.6	0.619
Dissected lymph nodes (mean ± SD)	38.6 ± 14.6	35.6 ± 13.7	0.019
Metastatic lymph nodes (mean ± SD)	0.36 ± 1.02	0.28 ± 1.26	0.491

Nominal variables were analyzed by the chi-square test; continuous variables were analyzed by Student's *t*-test.
SD = standard deviation.

low, ~6.5% to 11.0% of all EGC cases,[15–18] whereas the incidence of lymph node metastasis in superficial spreading EGC ranges from 18% to 30%.[15,16,18] In our study, superficial spreading EGC accounted for 3.7% of all EGC cases, with a lymph node metastasis rate of 15.7%. The overall prognoses of the superficial spreading and common types of EGC appear to be similar. Kim et al reported that the superficial spreading and common types of EGC did not exhibit significant differences in their overall 5-year and 10-year survival rates.[19]

Although lymph node metastasis was more prevalent in the superficial spreading EGC group compared with the common EGC group, the incidence was within the range reported in previous studies.[20–22] A few studies have reported that superficial spreading EGC (but not common EGC) is significantly associated with lymph node metastasis; however, these studies did not adjust for confounding variables.[16,18]

Although the tumor behavior of superficial spreading EGC is not well established, some studies have indicated that these tumors may display milder biological behavior than common EGC.[23,24] For example, reduced expression levels of epidermal growth factor and transforming growth factor-ß were observed in superficial spreading EGC compared with common EGC; moreover, apoptosis was higher in superficial spreading EGC than in common EGC.[23,24] In addition, lower DNA ploidy patterns were seen in superficial spreading EGC.[25] This evidence might explain the lack of association between superficial spreading EGC and lymph node metastasis. However, further studies of tumor behavior and

TABLE 3. Risk Factors of Lymph Node Metastasis in Early Gastric Cancer With Curative Resection (n = 3813)

Variable	Univariate Analysis Odds Ratio (95% CI)	*P* Value	Multivariate Analysis Odds Ratio (95% CI)	*P* Value
Age (>60)	1.06 (0.86–1.31)	0.548	1.04 (0.83–1.29)	0.741
Sex (male)	1.07 (0.86–1.34)	0.493	0.89 (0.71–1.12)	0.318
Location				
Upper third	1		1	
Middle third	1.89 (1.18–3.03)	0.008	2.07 (1.29–3.35)	0.003
Lower third	1.86 (1.18–2.92)	0.007	2.16 (1.37–3.41)	0.001
Ulcerative lesion	1.6 (1.22–2.1)	0.001	1.32 (0.99–1.75)	0.053
Tumor size				
<6 cm	1		1	
≥6 cm	1.65 (1.03–2.64)	0.035	1.33 (0.82–2.15)	0.253
Histology				
Differentiated	1		1	
Undifferentiated	1.16 (0.94–1.42)	0.164	1.31 (1.04–1.65)	0.021
Depth of invasion				
Mucosal	1		1	
Submucosal	3.55 (2.81–4.48)	<0.001	3.59 (2.83–4.56)	<0.001
Lymphovascular invasion	1.65 (1.23–2.23)	0.001	1.53 (1.12–2.08)	0.007

CI = confidence interval

TABLE 4. Clinicopathologic Findings in Patients According to the Size of Mucosal Cancers Without Ulcerative Lesions (n = 2977)

Variable	≥6 cm	<6 cm	<3 cm	<2 cm	*P* Value*	*P* Value†	*P* Value§
n	52	1787	1376	1138			
Sex (men: women)	23 (44.2%):29 (55.8%)	1125 (63%):662 (37%)	872 (63.4%):504 (36.6%)	711 (62.5%):427 (37.5%)	0.006	0.005	0.008
Age, y (mean ± SD)	54.7 ± 12	55.9 ± 11.4	56.2 ± 11.2	56.1 ± 11	0.477	0.369	0.372
Location					0.199	0.174	0.155
Upper	3 (5.8%)	145 (8.1%)	110 (8%)	93 (8.2%)			
Middle	20 (38.5%)	488 (27.3%)	369 (26.8%)	301 (26.4%)			
Lower	29 (55.8%)	1154 (64.6%)	897 (65.2%)	744 (65.4%)			
Histology					0.023	0.012	0.013
Differentiated	18 (34.6%)	905 (50.6%)	721 (52.4%)	594 (52.2%)			
Undifferentiated	34 (65.4%)	882 (49.4%)	655 (47.6%)	544 (47.8%)			
Lymphovascular invasion	6 (11.5%)	151 (8.4%)	107 (7.8%)	86 (7.6%)	0.432	0.324	0.293
Lymph node metastasis	4 (7.7%)	95 (5.3%)	67 (4.9%)	60 (5.3%)	0.458	0.358	0.455

*≥6 cm versus < 6 cm.
†≥6 cm versus < 3 cm.
§≥6 cm versus < 2 cm.SD = standard deviation.

investigations on the molecular level are needed to fully test this hypothesis.

In this study, we sought to investigate the characteristics of patients with superficial spreading EGC and no lymph node metastasis. In these patients, endoscopic treatment could be applied carefully. As subtotal gastrectomy and total gastrectomy with D2 lymph node dissection are relatively invasive procedures, the risk of adverse postoperative events is a serious concern. Moreover, the quality of life (QOL) is typically affected during the first 3 months after curative surgery, with 20% to 35% of all patients continuing to suffer from functional or symptomatic problems.[26–28] Endoscopic treatments such as EMR and ESD are widely used. The QOL after endoscopic treatment is superior to that after surgery, because recovery is relatively fast and the preserved stomach functions properly. Due to these advantages, the indications of ESD have recently been expanded. However, Kim et al reported that careful consideration is needed before endoscopic resection is applied to superficial spreading EGC, due to the higher risk of submucosal invasion and lymph node metastasis.[19] Our study is consistent with the study by Kim et al in that submucosal invasion and lymph node metastasis were more prevalent in superficial spreading EGC than in common EGC. We sought to identify the circumstances in which lymph node metastasis is absent, as these conditions are ideal for ESD. To this end, we compared the clinicopathological findings of patients with intramucosal superficial spreading EGC, intramucosal EGC <6 cm, and intramucosal EGC <2 cm without ulceration. Although undifferentiated histology was more common in intramucosal superficial spreading EGC without ulceration, lymph node metastasis was not significantly different between intramucosal superficial spreading EGC and intramucosal common EGC without ulceration. Subgroup analysis of intramucosal superficial spreading EGC identified 4 patients with lymph node metastasis and undifferentiated pathology. Therefore, we suggest that ESD is a potential alternative method for treating differentiated intramucosal superficial spreading EGC without ulceration.

The major strength of our study was the large number of patients with superficial spreading EGC, which allowed for robust analysis, in contrast to previous studies. Moreover, this may be the first study to investigate the conditions under which ESD is considered to be a safe treatment modality. However, this study also had some limitations. First, this study was retrospective in nature and only examined surgically resected cases. Second, all subjects were enrolled at a single tertiary institution, which may have introduced a selection bias. For example, our rates of undifferentiated type EGC were high, as compared with Kim et al's study (47.8% vs 38%).[19] This might have been caused by endoscopic treatment in cases of small and differentiated EGC in practice. We attempted to exclude this bias by using a multivariable regression test. In addition, D2 lymph node dissection was considered a standard procedure for lymph node dissection during the enrollment period for patients.[13,18] D1 dissection is recommended in differentiated small tumors with T1a and cT1bN0. This point should be carefully interpreted.[12,29]

In conclusion, superficial spreading EGC was not associated with an increased risk of lymph node metastasis. In cases of mucosal cancer with differentiated pathology and no ulceration, superficial spreading EGC was not accompanied by any lymph node metastasis. These findings suggest that ESD is a suitable option for a limited number of patients with superficial spreading EGC. Further large-scale prospective studies should be

TABLE 5. Characteristics of Patients With Lymph Node Metastasis in Superficial Spreading Mucosal Cancer Without Ulceration (n = 4)

No.	Sex	Age	Location	Tumor size	Ulcerative Lesion	LND	LNM	Histology	LVI
1	Female	40	Antrum	60 mm	(−)	21	1	Signet ring cell	(−)
2	Female	59	Antrum	60 mm	(−)	43	1	Poorly differentiated	(−)
3	Male	43	Antrum	85 mm	(−)	53	1	Poorly differentiated	(−)
4	Female	57	Antrum	74 mm	(−)	61	2	Signet ring cell	(−)

LND = total number of dissected lymph nodes; LNM = total number of lymph node metastases; LVI = lymphovascular invasion.

performed to definitively establish the safety and feasibility of ESD in superficial spreading EGC.

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