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Original Article

A study on related risk factors and prognosis for lymph node metastasis in patients with early gastric cancer

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Abstract: The aim of this study was to analyze the risk factors and prognosis for lymph node metastasis (LNM) in patients with early gastric cancer (EGC) in order to provide theoretical evidence for establishing a reasonable therapeutic schedule. This study retrospectively reviewed 112 patients who underwent surgery (open or laparoscopic). Clinical characteristics and pathological features were analyzed by using Chi-square and binary logistic regression. Survival data for the operated patients were analyzed using the Kaplan-Meier method. Logistic regression analysis revealed that age, depth of infiltration, neoplasms by histological type and lymphatic embolus were independent risk factors for LNM. Furthermore, no LNM was observed in patients who had mucousal cancer, were over 60 years old, and had a highly differentiated tumor without lymphatic embolus. However, LNM occurred when neoplasms infiltrated within the submucousal layer. Five-year survival for patients without LNM was 93.9%, which was significantly higher than in patients with LNM. LNM in EGC is related to age, depth of infiltration, tumor histological type and lymphatic embolus. The survival rate with negative lymph nodes was higher than in patients with LNM. Therefore, we believe that endoscopic *en bloc* dissection may be considered as a surgical treatment for patients who are ≥60 years old and have a highly differentiated tumor invaded the mucous layer without lymphatic embolus. With respect to patients with high risk factors, we recommend an appropriate lymphadenectomy according to the specific situation.

Keywords: Early gastric cancer, survival analysis, lymphatic metastasis, risk factors, therapeutic schedule

Introduction

With the improvement of people's awareness on health and the advancement of endoscopic techniques and equipment, the detection of early gastric cancer (EGC) in the overall incidence of gastric cancer has increased in recent years [1, 2]. The rate of radical resection and long-term survival are both significantly higher than in advanced gastric cancer [3]. Over the past two decades, most scholars have believed that D2 lymphadenectomy remains as the standard and optimal surgical method for treating patients with EGC. The overall lymph node metastasis (LNM) incidence of EGC is reported to be 10-15% [3]. In addition, the incidence of LNM in EGC ranges from 2.6% to 4.8% in mucosal cancer and from 16.5% to 25% [4, 5] in submucosal cancer. Although the rate of lymphatic metastasis has significantly increased in submucosal EGC, 70-80% of patients continue to undergo unnecessary surgery with D2 lymphadenectomy; thus, increasing surgical trauma and reducing the postoperative life-quality of patients [6]. Meanwhile, the prognosis of submucosal carcinoma was worse than that of mucosal cancer. In recent years, due to minimal trauma and rapid recovery, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been generally accepted as an alternative surgical procedure to improve the quality of life for EGC patients [7]. However, EMR or ESD cannot effectively clear away lymph nodes surrounding the stomach, resulting in an incomplete treatment. Thus, a dispute on the feasibility of endoscopic treatment for EGC continues to exist. The purpose of this study was to analyze related risk factors and the prognosis for lymphatic metastasis in patients with EGC, in order to provide theoretical evidence for establishing a reasonable therapeutic schedule.

Table 1. Baseline characteristics of 112 patients and univariate analysis of potential risk factors for lymph node metastasis

Variables	Number of patients	Lymph node metastasis [n (%)]	X^2	*P*-value
Age (year)			5.549	0.018
<60	62	19 (30.6%)		
≥60	50	6 (12.0%)		
Gender			1.871	0.171
Male	67	12 (17.9%)		
Female	45	13 (28.9%)		
Tumor location			3.840	0.147
Upper	13	1 (7.7%)		
Middle	32	5 (15.6%)		
Lower	67	19 (28.4%)		
Tumor size			1.896	0.169
<2 cm	35	5 (14.3%)		
≥2 cm	77	20 (26.0%)		
Macroscopic type			3.672	0.159
Elevated	12	2 (16.7%)		
Flat	38	5 (13.2%)		
Depressed	62	18 (29.0%)		
Operative type			2.432	0.296
Distal gastrectomy	12	1 (8.3%)		
Proximal gastrectomy	88	23 (26.1%)		
Total gastrectomy	8	1 (12.5%)		
Depth of invasion			6.438	0.011
Mucosa	37	3 (8.1%)		
Submucosa	75	22 (29.3%)		
Histologic type			11.950	0.001
Differentiated	42	2 (4.8%)		
Undifferentiated	70	23 (32.9%)		
Number of lesions			1.346	0.246
Single lesion	103	25 (24.3%)		
Multiple lesions	9	0 (0%)		
Lymphatic invasion			8.492	0.004
Negative	103	19 (18.4%)		
Positive	9	6 (66.7%)		
Carcinoma nodes			-	0.370
Negative	110	24 (20%)		
Positive	2	1 (50%)		
Distant metastasis			-	-
No	112	25 (22.3%)		
Yes	0	0 (0%)		

Materials and methods

General information

This study retrospectively reviewed 112 patients who underwent radical surgery (open or laparoscopic) for EGC in the Beijing Friendship Hospital from January 2008 to January 2015. Complete clinical data was available for all patients. Among the 112 EGC patients, 67 (59.8%) patients were male and 45 (40.2%) patients were female, with a male-to-female ratio of 1.5:1. The age of patients ranged from 30 to 80 years old, with a median age of 57.98 years old. Furthermore, among these patients, 62 (55.4%) patients were <60 years old, while 50 (44.6%) patients were ≥60 years old. Gastroscopy, abdominal and pelvic enhanced CT, electronic ultrasonic gastroscopy and biopsies were performed on all EGC patients before the surgery for a preliminary tumor stage assessment. All patients who underwent R0 resection cleared away ≥15 lymph nodes. Due to bias that may have occurred in our preoperative staging, all patients enrolled in this study underwent D2 lymphadenectomy. The study was approved by the Ethics Review Board of Beijing Friendship Hospital, and written informed consent was obtained from each participant.

Analysis of clinical outcomes

The following postoperative clinicopathological parameters were evaluated: gender, age, tumor location in the stomach (lower one-third, middle one-third and upper one-third), tumor size (<2 cm, or ≥2 cm), macroscopic type (elevated, flat and depressed type), histological classification (differentiated and undifferentiated), depth of infiltration (intramucosal and submucosal), operation type (distal gastrectomy, proximal gastrectomy and total gastrectomy), number of lesions (single and multiple), lymphatic invasion, carcinoma nodes, distant metastasis, and 1-, 3- and 5-year survival. Following the criteria of the World Health

Table 2. Number of patients with lymph node metastasis (n/N)

Lymph node station	Tumor Location			No. of patients
	Lower third	Middle third	Upper third	
First station	19 (19/19)	5 (5/5)	1 (1/1)	25
Second station	2 (2/19)	1 (1/5)	0 (0/1)	3

Table 3. The condition and number of lymph nodes involved (N)

Group of lymph nodes	Tumor Location			No. of patients
	Lower third	Middle third	Upper third	
No. 1	0	1	0	1
No. 3	6	2	1	9
No. 4	5	1	0	6
No. 5	3	1	0	4
No. 6	5	0	0	5
No. 7	0	1	0	1
No. 8	2	0	0	2

Organization (WHO) classification for age, patients were divided into two groups: patients <60 years old and ≥60 years old. The macroscopic appearance of EGC was analyzed in accordance with the Japan Classification of Gastric Cancer (2014.ver 4). Tumor histology was classified into two groups: (a) differentiated, which included well or moderately differentiated adenocarcinomas and tubular adenocarcinomas; (b) undifferentiated, which included poorly differentiated, signet ring cell carcinomas and mucinous adenocarcinomas.

Statistical analysis

All data were analyzed by IBM SPSS 21.0. Univariate and multivariate analysis of risk factors associated with LNM were conducted using the X^2 test and logistic regression models, respectively. Survival data of operated patients were analyzed using the Kaplan-Meier method, and Log-rank test was used to assess differences between prognostic factors. $P<0.05$ was considered statistically significant.

Results

Clinical features of patients

Table 1 summarizes the clinicopathological characteristics of patients in relation to the presence of LNM. Among the 112 EGC patients, tumor was found in the upper third of the stomach in 13 (11.6%) patients, in the middle third of the stomach in 32 (28.6%) patients, and in the lower third of the stomach in 67 (59.8%) patients. Furthermore, 35 patients (31.3%) were found to have a tumor <2.0 cm in size, while 77 (68.7%) patients had a tumor ≥2.0 cm in size. Elevated-type tumors were macroscopically observed in 12 (10.7%) patients, flat-type tumors were observed in 38 (33.9%) patients, and depressed-type tumors were observed in 62 (55.4%) patients. All patients enrolled in this study underwent D2 lymphadenectomy. Among them, distal gastrectomy, proximal gastrectomy and total gastrectomy were performed in 12 (10.7%), 88 (78.6%) and eight (7.1%) patients, respectively; and four (3.6%) patients underwent ESD combined with D2 lymphadenectomy. Based on the degree of anaplasia, 23 (20.5%) patients had well-differentiated adenocarcinomas, four (3.6%) patients had well-moderately differentiated adenocarcinomas, 15 (13.4%) patients had moderately differentiated adenocarcinomas, seven (6.25%) patients had moderate-poorly differentiated adenocarcinomas, 37 (33.0%) patients had poorly differentiated adenocarcinomas, 25 (22.3%) patients had signet ring cell carcinomas, and one (0.9%) patient had mucinous adenocarcinoma. In total, 42 (37.5%) patients were differentiated, while 70 (62.5%) patients were undifferentiated. EGC was limited to the mucosa in 37 (33.1%) patients, while it infiltrated the submucosa in 75 (66.9%) patients. Single and multiple lesions were found in 103 and nine patients, respectively. Nine patients (8.1%) had lymphatic invasion and two patients (1.8%) had carcinoma nodes. All patients had no distant metastasis.

Lymph node metastasis condition

According to NCCN clinical practice guidelines (2015.V3), LNM was found in the first station alone in 22 patients, while LNM was found in both the first and second station in three patients (**Table 2**). Among patients with first station LNM, lymph node No. 3 and No. 4 had a higher metastasis rate than others (nine cases and six cases respectively). Among the three patients at second tier metastasis, two cases were limited to the No. 8 lymph node (**Table 3**). All patients enrolled in this study did not undergo D3 lymphadenectomy.

Table 4. Multivariate analysis of risk factors for lymph node metastasis

Variables	B	S.E	Walds	*P*	Exp (B)	Exp (B) 95% CI
Age	-1.618	0.619	6.820	0.009	0.198	0.059-0.668
Depth of invasion	1.759	0.711	6.117	0.013	5.805	1.441-23.392
Histologic type	2.608	0.834	9.767	0.002	13.568	2.644-69.630
Lymphatic invasion	1.938	0.888	4.766	0.029	6.945	1.219-39.567
Constant	-8.900	2.324	14.666	0.000	0.000	-

Table 5. Rate of lymph node metastasis of 37 EGC patients with mucosal cancer (%)

Variables	Differentiated		Undifferentiated	
	Lymphatic invasion (-)	Lymphatic invasion (+)	Lymphatic invasion (-)	Lymphatic invasion (+)
<60 years old	0% (0/7)	0% (0/1)	14.3% (2/14)	100% (1/1)
≥60 years old	0% (0/6)	0% (0/1)	0% (0/6)	0% (0/1)

Table 6. Rate of lymph node metastasis in 75 EGC patients with submucosal cancer (%)

Variables	Differentiated		Undifferentiated	
	Lymphatic invasion (-)	Lymphatic invasion (+)	Lymphatic invasion (-)	Lymphatic invasion (+)
<60 years old	7.7% (1/13)	100% (1/1)	30.4% (7/23)	100% (2/2)
≥60 years old	8.3% (1/12)	100% (1/1)	36.4% (8/22)	100% (1/1)

Univariate analysis results

Among the 112 EGC patients included in the analysis, LNM was observed in 25 of 112 patients; and the metastasis rate was 22.3%. The metastasis rate of patients aged <60 years old was 30.6% (19/62), while the rate for patients aged ≥60 years old was 12% (6/50) (*P*=0.018). Therefore, patients aged <60 years old were more likely to develop LNM. The observed rate of LNM was 8.1% (3/37) and 29.3% (22/75) in mucosal cancer (T1a) and submucosal cancer (T1b) (*P*=0.011), respectively. The metastasis rate of highly differentiated EGCs was (4.8%, 2/42) lower compared with poorly differentiated tumors (32.9%, 23/70) (*P*=0.001). Nine patients were found with lymphatic invasion, in which six of them were found to be combined with LNM (*P*=0.004). All differences were statistically significant (*P*<0.05). On the contrary, there were no correlations between LNM and other factors including gender, tumor location, tumor size, macroscopic type, operation type, number of lesion, carcinoma nodes and distant metastasis (*P*> 0.05) (**Table 1**).

Multivariate analysis results

Multivariate analysis revealed that age, depth of infiltration, neoplasms by histological type and lymphatic embolus were independent risk factors for LNM in EGC (*P*<0.05) (**Table 4**). Patients who are ≥60 years old with LNM were lower than patients <60 years old (95% CI: 0.059-0.668). LNM of submucosal carcinomas was 5.805 times higher than mucosal carcinomas (95% CI: 1.441-23.392). LNM of poorly differentiated carcinomas was 13.568 times higher than well-differentiated carcinomas (95% CI: 2.644-69.630). The positive lymphatic embolus was 6.945 times higher than the negative lymphatic embolus (95% CI: 1.219-39.567).

Stratification analysis

According to depth of invasion, further analysis was performed on independent risk factors including age, neoplasms by histological type and lymphatic embolus. Furthermore, we have found that no LNM was observed in patients with mucous cancer, regardless of age and lymphatic embolus, with a highly differentiated tumor; while in three patients <60 years old, LNM was observed with a poorly differentiated tumor (**Table 5**). However, LNM occurred when neoplasms infiltrated within the submucosal layer (**Table 6**).

Survival analysis

In the 112 EGC patients included in this study, median follow-up time was 50 months, which ranged from eight to 89 months. Death was due to postoperative tumor recurrence in 12

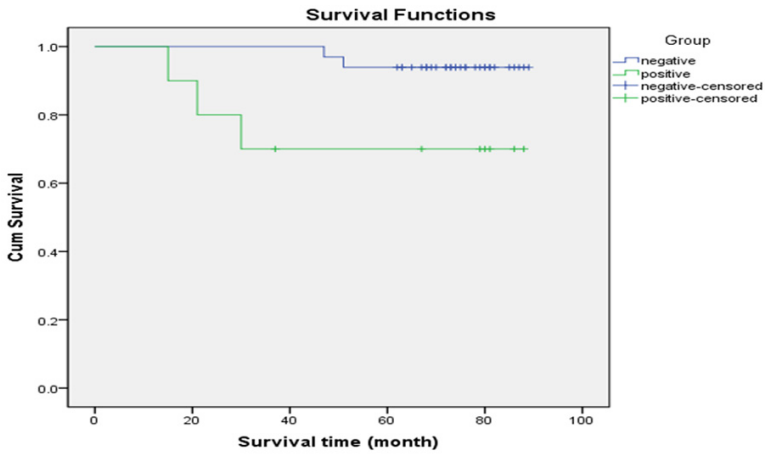

Figure 1. Survival analysis of a 5-year survival rate.

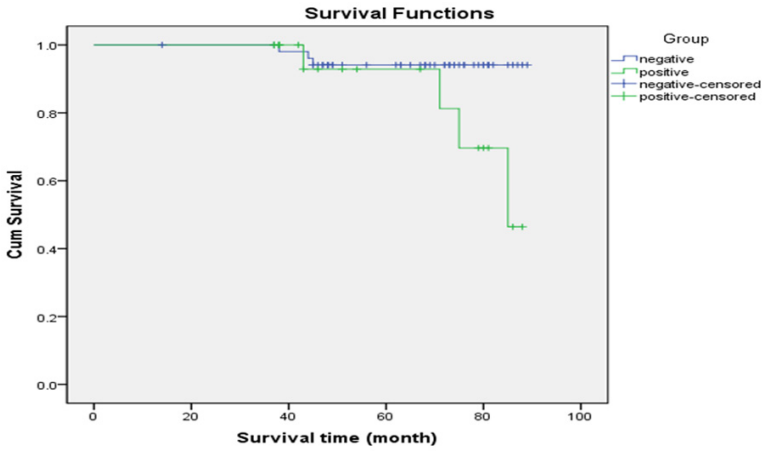

Figure 2. Survival analysis of a 3-year survival rate.

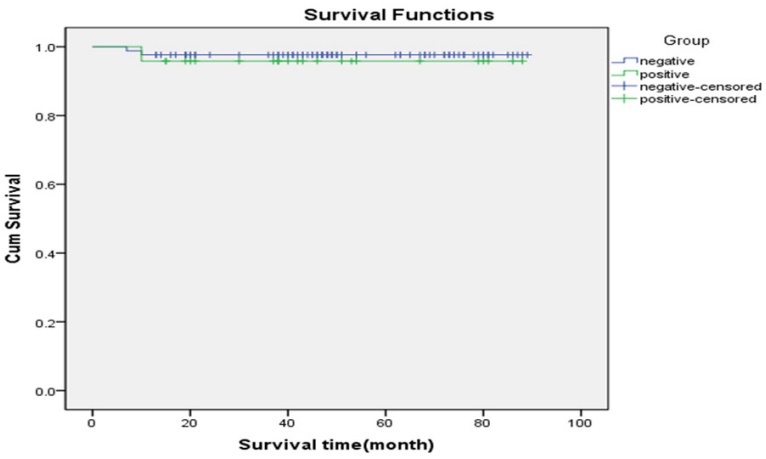

Figure 3. Survival analysis of a one-year survival rate.

patients. A total of 43 EGC patients were followed-up over five years postoperative. Five-year survival rates were 93.9% for patients without LNM and 70% for patients with LNM, and the difference between these two groups was statistically significant (*P*=0.019, **Figure 1**). A total of 73 EGC patients were followed-up for over three years postoperative. The difference in 3-year survival was 94.3% in patients without LNM and 80% in patients with LNM (*P*=0.057, **Figure 2**). Furthermore, 109 EGC patients were followed-up over one year postoperative. Among them, three EGC patients were followed-up for <1 year. One-year survival rates were 97.6% for patients without LNM and 95.8% for patients with LNM, and the difference was not statistically significant (*P*= 0.640, **Figure 3**).

Discussion

It has been reported that the 5-year survival rate for EGC patients who underwent radical surgery is more than 90% [3, 8]. Among them, 5-year survival rate has been reported to be 84.3%-88.7% in patients with regional LNM and 94.2%-98.8% [5, 9] in patients without lymph node involvement. Thus, it is important to find a precise model of LNM evaluation in order to choose the optimal extent of dissection and establish a reasonable therapeutic schedule.

In order to determine the risk factors of LNM in EGC, we retrospectively reviewed the clinical data of 112 patients. Several prognostic factors including age, depth of infiltration, neoplasms by histologic type and lymphatic embolus have been demonstrated to be

related to LNM in EGC. Meanwhile, our results were similar to the results of Lim [10] and Choi [11]. Although some research teams reported [12] that gender, tumor size, macroscopic type and hematogenous metastasis were also independent risk factors for LNM in EGC, many controversial issues continue to exist on the correlation between the above mentioned indices and the presence of LNM. Nomura *et al.* [13] revealed that the rate of LNM in mucosal carcinomas was lower than in submucosal carcinomas (1%-6% *vs.* 14%-25%), and LNM of submucosal carcinomas was 5.805 times higher than mucosal carcinomas. In our study, the observed rate of LNM was 8.1% (3/37) and 29.3% (22/75) in mucosal cancers (T1a) and submucosal cancers (T1b), respectively. Although it was similar to the results of Nomura *et al.*, the incidence of LNM in mucosal tumors was slightly higher than in previous studies. Due to the lack of standardization in pathological biopsy procedures in our center during the early period, the occurrence of bias in tumor stage is possible. Yasuda *et al.* [14] reported that none of the 118 patients had LNM when the depth of infiltration was ≤0.3 mm. Furthermore, the rate of LNM in submucosal invasion of approximately 0.3 mm-1 mm was 19%, while the rate of LNM in submucosal invasion of more than 1 mm was 40%. The reason behind this observation may be due to the presence of substantial lymphatic capillaries in the gastric submucosa and in the large gap between adjacent endothelial cells. If the tumor infiltrated into the submucosa, cancer cells would invade the lymphatic capillaries through the endothelial cell space, resulting in LNM.

In terms of histological type and lymphatic invasion, tumor differentiation determines its biological characteristics. Lower degrees of differentiation have higher incidences of LNM. The root cause of LNM is that poorly differentiated tumors have higher heterogeneity, resulting in stronger and more aggressive biological characteristics compared to other histological types. In addition, nine cases were found with lymphatic embolus, in which six of them were found to be combined with LNM. The reason may be that endothelial cells consist of a capillary lymphatic wall without a basement-membrane and pericyte, and an imbricated arrangement. Consequently, lymphatic capillaries have higher permeability than blood capillaries, making them more prone to LNM. Ti YX *et al.* [15] found lymphatic invasion in 54 patients, in which 51 patients were combined with LNM; making the rate of LNM 94.4%. However, it is difficult to determine the presence of LNM prior to surgery. Thus, age, histologic type and depth of invasion provide a relatively valuable reference.

In addition, some related studies have also reported tumor diameter as a risk factor [16]. Gotoda *et al.* [17] reported that LNM with a tumor diameter of <1 cm is seldom detected with a rate of 2.8%, while the LNM rate for tumor sizes that range from 1.1 cm to 2 cm or more, compared to 2 cm, increased to 7.0% and 19.4%. On the contrary, tumor size was not an independent risk factor for LNM in our analysis, and Mitsumori [18] also reported the same results. The reason for this conclusion may be that the number of patients included in this study was too small to further analyze. Therefore, more high quality studies with a larger sample size are needed in order to arrive at some final conclusions.

LNM has been conformed to be one of the most important prognostic factors for gastric cancer. Shimada held the opinion [19] that the number of metastatic nodes that occur in patients with EGC is associated with the survival rate. Patients with LNM had shorter survival time compared to patients without node involvement. It was remarkable that three or more LNMs could predict a poorer prognosis. Seto *et al.* [20] revealed that the 5-year survival of EGC patients with more than four metastatic nodes is definitively worst with a rate of 74%. Folli *et al.* [21] revealed that a lower than 5-year survival, especially for patients with more than three LNMs. Similar to the data in this study, 5-year survival rates of patients without LNM were significantly higher than in patients with LNM; and the rates were 93% and 70%, respectively. Although the 3-year survival rates of patients without LNM and with LNM were not statistically significant, postoperative survival of patients without metastatic nodes revealed a longer mean survival time compared to patients with metastatic nodes. It has been reported that the 93% 5-year survival rate for EGC for tumors with one to two positive lymph nodes declined to 68.4% for gastric carcinoma with three to six positive metastatic nodes. Miwas *et al.* [22] also drew a similar conclusion.

Based on the study of risk factors for LNM in EGC, the Japanese gastric cancer treatment guideline (2014.v4) made clear that early endoscopic treatment indications include: (a) the size of mucosal carcinoma ≤2 cm, and (b) the pathological types for differentiation without ulceration. Expanded indications include: (a) size of the differentiated tumor >2 cm without ulcer lesions, (b) size of the differentiated tumor <3 cm with ulcer lesions, and (c) size of the undifferentiated tumor <2 cm with no ulceration. The NCCN (2015.V3) is almost similar to the Japanese gastric cancer treatment guideline for treating EGC, with a difference in the depth of tumor invasion expanding from the mucosal layer to the submucosal layer, and without blood or lymphatic vessel invasion. In this study, the depth of infiltration, neoplasms by histologic type and lymphatic embolus have been demonstrated to be related to LNM in EGC, in which results were similar to the above written guidelines. Age as a risk factor for LNM is a new finding. It has reported that young patients always have poor differentiation compared with elder patients [23]. Takatsu *et al.* reported that the incidence of having seven or more LNMs in young patients was higher (25%) than in elder patients (16%) [24].

For patients with EGC, the choice of an appropriate surgical approach relies on the accurate assessment of the depth of invasion, histological type and condition of LNMs prior to surgery. The identification of LNM can be achieved via CT or endoscopic ultrasonography. If necessary, we can perform a biopsy to determine the depth of infiltration in order to choose a reasonable surgical method. With respect to patients with high risk factors, we recommend ESD combined with lymphadenectomy under laparoscope (LLND). In a group of 21 patients with high risk factors, Abe *et al.* [25] found the presence of LNM in two of 21 patients. Two patients who had LNM were followed without any additional surgery. During the median follow-up of 61 months, all patients were alive without any recurrence. Therefore, ESD combined with LLND may be an effective and minimally invasive approach for EGC patients with potential risk of LNM, maintaining the patient's long-term quality of life.

In conclusion, our study suggests that age, depth of infiltration, tumor histological type, and lymphatic embolus are independent risk factors for LNM in EGC patients. The survival rate with negative lymph nodes is better than in patients with LNM. Therefore, we hold the opinion that ESD might be considered as a surgical treatment for patients who are ≥60 years of age with highly differentiated tumors that invaded the mucous layer without lymphatic embolus. All patients should be regularly followed-up after the operation in order to avoid tumor recurrence. With respect to patients with high risk factors, we recommend an appropriate lymphadenectomy according to the specific situation of the patient. Due to the fact that the sample of patients included in this study was relatively small, more high quality studies or RCTs are expected in order to further investigate the risk factors and prognosis of EGC.

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Disclosure of conflict of interest

None.

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