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Retrospective Study

Feasibility of endoscopic treatment and predictors of lymph node metastasis in early gastric cancer

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Abstract

BACKGROUND

Endoscopic submucosal dissection (ESD) has been routinely performed in applicable early gastric cancer (EGC) patients as an alternative to conventional surgical operations that involve lymph node dissection. The indications for ESD have been recently expanded to include larger, ulcerated, and undifferentiated mucosal lesions, and differentiated lesions with slight submucosal invasion. The risk of lymph node metastasis (LNM) is the most important consideration when deciding on a treatment strategy for EGC. Despite the advantages over surgical procedures, lymph nodes cannot be removed by ESD. In addition, whether patients who meet the expanded indications for ESD can be managed safely remains controversial.

AIM

To determine whether the ESD indications are applicable to Chinese patients and to investigate the predictors of LNM in EGC.

METHODS

We retrospectively analyzed 12552 patients who underwent surgery for gastric cancer between June 2007 and December 2018 at the Affiliated Hospital of Qingdao University. A total of 1262 (10.1%) EGC patients were eligible for

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inclusion in this study. Data on the patients' clinical, endoscopic, and histopathological characteristics were collected. The absolute and expanded indications for ESD were validated by regrouping the enrolled patients and determining the positive LNM results in each subgroup. Predictors of LNM in patients were evaluated by univariate and multivariate analyses.

RESULTS

LNM was observed in 182 (14.4%) patients. No LNM was detected in the patients who met the absolute indications (0/90). LNM occurred in 4/311 (1.3%) patients who met the expanded indications. According to univariate analysis, LNM was significantly associated with positive tumor marker status, medium (20-30 mm) and large (>30 mm) lesion sizes, excavated macroscopic-type tumors, ulcer presence, submucosal invasion (SM1 and SM2), poor differentiation, lymphovascular invasion (LVI), perineural invasion, and diffuse and mixed Lauren's types. Multivariate analysis demonstrated SM1 invasion (odds ratio [OR] = 2.285, $P = 0.03$), SM2 invasion (OR = 3.230, $P < 0.001$), LVI (OR = 15.702, $P < 0.001$), mucinous adenocarcinoma (OR = 2.823, $P = 0.015$), and large lesion size (OR = 1.900, $P = 0.006$) to be independent risk factors.

CONCLUSION

The absolute indications for ESD are reasonable, and the feasibility of expanding the indications for ESD requires further investigation. The predictors of LNM include invasion depth, LVI, mucinous adenocarcinoma, and lesion size.

Key words: Early gastric cancer; Lymph node metastasis; Predictors; Endoscopic submucosal dissection; Expanded indications

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Core tip: We aimed to re-evaluate and verify the current indications and guidelines for endoscopic treatment and to analyze the clinicopathological predictors of lymph node metastasis in early gastric cancer (EGC), which have been inconsistently identified across studies. To the best of our knowledge, this study involves the largest number of EGC patients in China, and is the first study to perform statistical analyses on certain clinical features, such as drinking, smoking, obesity, family history of tumors, and tumor markers.

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INTRODUCTION

Gastric cancer is currently the fifth most common cancer and the third leading cause of cancer-related death worldwide^[1]. Early gastric cancer (EGC) is defined as a tumor that is confined to the mucosa and submucosa of the stomach, irrespective of regional lymph node metastasis (LNM)^[2]. Several studies have reported a frequency of LNM ranging from 5%-10% among EGC patients undergoing radical surgery^[3], suggesting that over 90% of surgeries could potentially be avoided if curative endoscopic resection (ER) is accurately predicted based on the histopathology of an endoscopic-resected specimen.

Endoscopic submucosal dissection (ESD) has notable advantages over conventional surgical resection, as it causes less trauma, minor bleeding, and fewer postoperative complications^[4]. The absolute indications for ESD for curative resection in EGC that were proposed by the Japanese Gastric Cancer Association (JGCA) initially include nonulcerated, well-differentiated mucosal lesions ≤ 2 cm in diameter^[5]. The absolute indications for ESD, however, are so strict that unnecessary surgeries may be performed. Subsequently, the expanded indications for ESD, which include larger, ulcerated, and undifferentiated mucosal lesions as well as differentiated lesions with

slight submucosal invasion, were proposed. A recent meta-analysis involving 12 studies revealed that the incidence of LNM was only 0.2% among patients who met the absolute indications, compared with an LNM incidence of 0.7% among patients who met the expanded indications^[6]. Furthermore, several studies have shown that LNM is closely related to an unsatisfactory prognosis in EGC^[7-10].

To date, universal preoperative examination methods, such as gastroscopy, endoscopic ultrasonography, computed tomography, and X rays, fail to provide adequate data on the lesion and regional lymph node status before surgery or ER^[11]. However, evaluating the risk of LNM is critical for determining the best course of management for EGC patients^[12]. Unfortunately, the risk factors that have been identified in different studies are diverse, and controversy still exists regarding the expanded indications for ESD. Therefore, in this study, which involved a relatively large number of EGC patients, we aimed to reevaluate and verify the current guidelines for endoscopic treatment of EGC in a Chinese population and to investigate the predictors of EGC with LNM.

MATERIALS AND METHODS

Patients

We retrospectively reviewed all patients who were diagnosed with gastric cancer and underwent gastrectomy with lymphadenectomy between June 2007 and December 2018 at the Affiliated Hospital of Qingdao University. This study was performed in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Our study was also approved by the Institutional Review Board of the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFY WZLL 2019-04-04). In all, 12552 patients were reviewed. Patients were excluded if they had: (1) Advanced-stage gastric cancer ($n = 11099$); (2) Intestinal metaplasia or intraepithelial neoplasia ($n = 72$); (3) Metastatic gastric cancer or multiple carcinomas ($n = 38$); (4) Lymphoma ($n = 28$); (5) Gastric stump carcinoma ($n = 36$); and (6) Other life-threatening diseases ($n = 17$). Ultimately, 1262 EGC patients were enrolled in this study.

Data collection

The included patients underwent gastrectomy with lymph node dissection. All operations were performed according to the 4th edition of the JGCA treatment guidelines^[5]. The specimens were serially sectioned into 3-mm-thick slices, and two experienced pathologists individually examined the histological slides immediately after resection. The diagnostic criterion for LNM is the presence of cancerous tissue inside the lymph node capsule, as shown in Figures 1 and 2. We collected the clinical data, endoscopic features, and pathological characteristics of all enrolled patients. These data included age, sex, incidence of hypertension, heart disease and diabetes mellitus, drinking and smoking history, body mass index (BMI), family history, carcinoembryonic antigen (CEA) level, tumor location, lesion size, macroscopic type, depth of invasion, number of tumors, presence of ulcers, tumor differentiation, Lauren type, presence of lymphovascular invasion (LVI), perineural invasion, and LNM.

Based on the distribution of gastric glands, we classified the tumor locations as cardia, fundus/corpus, or antrum. According to the Paris endoscopic classification, the macroscopic features of EGC were divided into the following five subtypes: Type 0-I (protruded), type 0-IIa (superficial elevated), type 0-IIb (flat), type 0-IIc (superficial depressed), and type 0-III (excavated)^[13]. Tumors were also graded as small (≤ 20 mm), medium (20-30 mm), and large (≥ 30 mm) to further analyze the indications for ESD. For invasion depth, submucosal lesions were classified into two groups: SM1 (≤ 500 μ m depth of invasion) and SM2 (> 500 μ m depth of invasion). In accordance with the JGCA, when multiple lesions were present, the tumor with the most advanced T category (or the largest lesion when the T stages were identical) was classified^[2].

Statistical analysis

Statistical analyses were conducted with SPSS software (SPSS, version 23.0, Chicago, IL, United States). Continuous variables, such as age and BMI, were translated into categorical variables. For age, we calculated the mean value (59.25 years) of the patients and set 60 years as the cut-off value. According to the criteria for obesity, the enrolled patients were divided into a nonobesity group (BMI < 28) and an obesity group (BMI ≥ 28). Differences among categorical variables associated with predictors and LNM were assessed using a chi-square test or Fisher's exact test, and variables

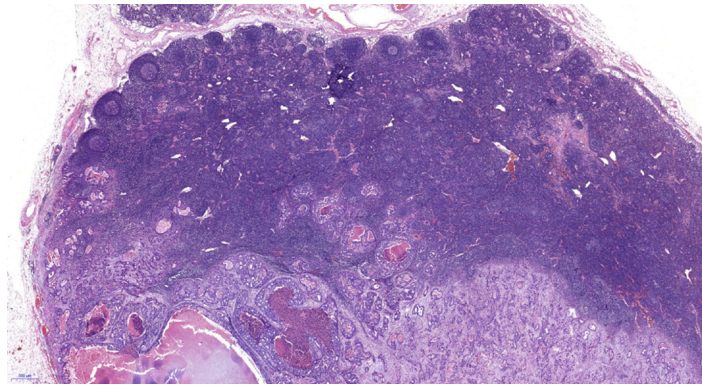


Figure 1 Pathological image of lymph node metastasis (20×).

that were significant in the univariate analysis were subsequently entered into a multivariate logistic regression model for analysis of independent risk factors for LNM in EGC. The association between variables and LNM was described by an odds ratio (OR) and a 95% confidence interval (CI). $P < 0.05$ (two-sided) was considered statistically significant.

The statistical methods and analyses of this study were reviewed by professor Xiaobin Zhou from the Department of Health Statistics, Qingdao University.

RESULTS

Clinical characteristics

We assessed 12552 patients who underwent radical gastrectomy with lymph node dissection. A total of 1262 (10.1%) eligible EGC patients with LNM ($n = 182$) and without LNM ($n = 1080$) were included in this study. The sex distribution was 899 (71.2%) males and 363 (28.8%) females (ratio: 2.48:1), with an average age of 59.25 years (range, 24-90 years). Data on the clinical characteristics are shown in [Table 1](#). Patients with a CEA value that exceeded the normal level were more likely to have LNM, and this association was statistically significant ($P = 0.007$). However, other clinical parameters, such as age, sex, underlying diseases, lifestyle habits, family history, and *Helicobacter pylori* (*H. pylori*) infection, failed to reach statistical significance.

Positive LNM results in EGC according to indications for ESD

According to further analysis, no LNM metastasis was observed in patients who met the absolute indications for ESD (0/90). However, LNM occurred in a few patients (4/311) who met the following expanded indications for ESD: (1) Differentiated mucosal tumors, ≤ 30 mm in size, without LVI, and with ulceration (3/86 cases, 3.5%); (2) Differentiated mucosal tumors, without ulcer and LVI, and of any size (1/32 cases, 3.1%); (3) Undifferentiated mucosal tumors without ulcer and LVI, and ≤ 20 mm in size (0/110 cases, 0%); and (4) Differentiated tumors with SM1 invasion, no LVI, and ≤ 30 mm in size (0/83 cases, 0%). As shown in [Table 2](#), patients who met the surgical indications had a higher risk of LNM ($P < 0.001$). [Table 3](#) contains more details on the frequency of LNM among EGC patients who met the indications for ESD.

Comparison of endoscopic features

The endoscopic features are shown in [Table 4](#). More EGCs were in the angle/antrum of the stomach ($n = 928$, 73.5%) than in the cardia ($n = 46$, 3.6%) and in the fundus/corpora ($n = 288$, 22.8%). Forty-two (3.3%) patients had multifocal lesions. The univariate analysis revealed that the location and number of tumors were not significantly associated with LNM. Regarding tumor size, LNM occurred significantly more frequently in patients with medium ($P = 0.016$) or large ($P = 0.000$) tumors than in patients with small tumors. With regard to macroscopic features, type IIc ($n = 486$, 38.5%) occurred most frequently among the five subtypes, but type III ($n = 481$, 38.1%) occurred more frequently in patients with LNM ($P = 0.001$). Ulcerative lesions also occurred more frequently in patients with LNM ($P = 0.013$).

Analysis of histopathological characteristics

Among the 1262 EGC patients, 182 (14.4%) had LNM according to the pathological diagnostic criteria, including 123 (67.6%) with stage N1, 39 (21.4%) with stage N2, and

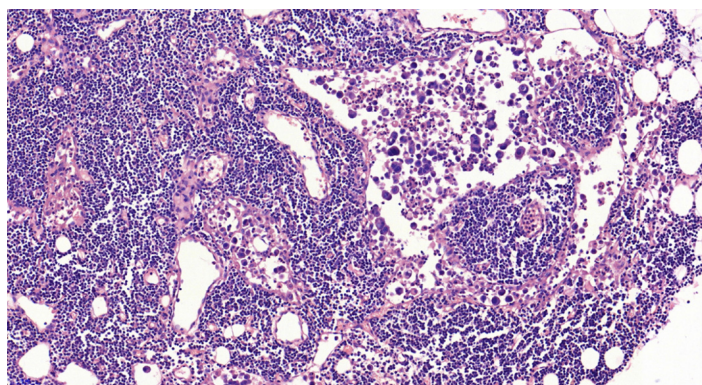


Figure 2 Pathological image of lymph node metastasis (200×).

20 (11.0%) with stage N3 LNM according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual. The mean number of metastatic lymph nodes was 2.8 (range, 1-17). Regarding lesion depth, 596 (47.2%) patients had tumors limited to the mucosal (M) layer, whereas 245 had SM1 (superficial submucosal) tumors (19.4%), and 421 had SM2 (deep submucosal) tumors (33.4%). The percentages of lymph node positivity were 5.2%, 19.6%, and 24.5% for M, SM1, and SM2, respectively. In terms of tumor differentiation, the undifferentiated type ($n = 807$, 63.9%) was the major histologic type of EGC based on the JGCA criteria and was significantly more likely to occur in patients with LNM than the differentiated type ($n = 455$, 36.1%) ($P = 0.001$). Regarding cell histology, the patients with mucinous adenocarcinoma had a higher risk of LNM than patients with other histologic lesion types ($P = 0.019$). Based on the Lauren classification, LNM was observed more frequently in diffuse-type (DT) and mixed-type (MT) tumors ($P = 0.003$) than in intestinal-type (IT) tumors. Moreover, LNM was found significantly more frequently in patients with LVI ($P = 0.001$) and perineural invasion ($P = 0.001$) than in the patient subgroup without invasion. Additional detailed histopathologic features of the enrolled patients are summarized in [Table 5](#).

Univariate analysis

The univariate analysis results showed that 10 out of the 20 factors were significantly associated with a higher risk of LNM. The risk factors included high CEA levels, medium and large lesion sizes, excavated macroscopic type, presence of ulcers, deep submucosal invasion (SM1 and SM2), poor differentiation, LVI, mucinous adenocarcinoma, perineural invasion, and diffuse and mixed Lauren classifications.

Multivariate logistic regression analysis of lymph node metastasis

Based on stepwise multivariate analysis, the significant independent risk factors for LNM in EGC were SM1 invasion (OR = 2.285, $P = 0.030$), SM2 invasion (OR = 3.230, $P < 0.001$), LVI (OR = 15.702, $P < 0.001$), pathological pattern of mucinous adenocarcinoma (OR = 2.823, $P = 0.015$), and lesion size over 30 mm (OR = 1.900, $P = 0.006$). The independent risk factors are listed in [Table 6](#).

DISCUSSION

Following the introduction of the expanded indications for ESD, many studies have reevaluated the risk of LNM in EGC. A meta-analysis involving 9798 EGC patients showed that among the expanded indications for ESD, the inclusion of mucosal differentiated lesions of any size that were not ulcerated and of differentiated mucosal lesions < 30 mm that were ulcerated can be justified with a minimally increased risk. Nonetheless, the reasonableness of expanding the indications for ESD to include undifferentiated lesions smaller than 20 mm and differentiated lesions with slight submucosal invasion still requires careful investigation^[6]. Our study demonstrated that the rate of LNM for patients who met the expanded indications for ESD was 4/311 (1.3%). No LNM occurred in patients who met the absolute indications. Similarly, reassessment of the expanded indications in Korea also showed an LNM rate of 2.4% among patients who met the expanded indications^[14], which is inconsistent with the results of a large dataset from Japan that revealed no LNM in patients who met the expanded indications^[15]. It is difficult to identify the reasons for this difference. A probable interpretation is that the existing indications are still not

Table 1 Lymph node metastasis risk according to clinical parameters

	Total (n = 1262), n (%)	LNM negative (n = 1080), n (%)	LNM positive (n = 182), n (%)	Univariate OR (95%CI)	P-value
Age (yr)					0.090
≤ 60	628 (49.8)	548 (50.7)	80 (44.0)	1	
> 60	634 (50.2)	532 (49.3)	102 (56.0)	1.313 (0.960, 1.800)	
Sex					0.239
Male	899 (71.2)	776 (71.9)	123 (67.6)	1	
Female	363 (28.8)	304 (28.1)	59 (32.4)	0.817 (0.580, 1.150)	
Hypertension					0.554
Absence	958 (75.9)	823 (76.2)	135 (74.2)	1	
Presence	304 (24.1)	257 (23.8)	47 (25.8)	1.115 (0.78, 1.60)	
Heart disease					0.449
Absence	1146 (90.8)	978 (90.4)	168 (92.3)	1	
Presence	116 (9.2)	102 (9.6)	14 (7.7)	0.799 (0.446, 1.430)	
Diabetes mellitus					0.933
Absence	1142 (90.5)	977 (90.5)	165 (90.7)	1	
Presence	120 (9.5)	103 (9.5)	17 (9.3)	0.977 (0.570, 1.675)	
BMI					0.086
≤ 28	1134 (89.9)	964 (89.3)	170 (93.4)	1	
> 28	128 (10.1)	116 (10.7)	12 (6.6)	0.587 (0.317, 1.086)	
Drinking					0.104
Absence	827 (65.6)	698 (64.7)	129 (70.9)	1	
Presence	434 (34.4)	381 (35.3)	53 (29.1)	0.753 (0.534, 1.061)	
Smoking					0.138
Absence	692 (54.8)	583 (54.0)	109 (59.9)	1	
Presence	570 (45.2)	497 (46.0)	73 (40.1)	0.786 (0.571, 1.082)	
Family history					0.872
Absence	1011 (80.1)	866 (80.2)	145 (79.7)	1	
Presence	251 (19.9)	214 (19.8)	37 (20.3)	1.033 (0.699, 1.526)	
<i>H. pylori</i> infection					0.225
Negative	634 (50.2)	535 (49.5)	99 (54.4)	1	
Positive	628 (49.8)	545 (50.5)	83(45.6)	0.823 (0.601, 1.128)	
CEA					0.007
Negative	960 (76.1)	836 (77.4)	124 (68.1)	1	
Positive	302 (23.9)	244 (22.6)	58 (31.9)	1.603 (1.137, 2.258)	

LNM: Lymph node metastasis; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; CEA: Carcinoembryonic antigen.

sufficiently comprehensive. The JGCA added invasion depth, ulceration, tumor size, differentiation, and LVI to its criteria for ESD. Based on our results, it is necessary to take the cellular histology of tumors into consideration when deciding upon the ESD indications. If ESD is performed in a more selective subgroup, the risk of LNM will likely be reduced. Therefore, predictive factors may be used to optimize the ESD criteria.

In line with other relevant studies, our study also concluded that deeper invasion significantly increased LNM risk. Additionally, the measurement of the width of the infiltration could be a useful additional parameter in the indications for supplemental gastrectomy after ESD. Therefore, a detailed measurement of invasion depth is truly necessary during the pathological evaluation of endoscopic-resected specimens^[16]. Regarding lesion size, we found that larger tumor size was a significant predictor of regional LNM in our patients with EGC, which is similar to the conclusions of many other investigators^[7,9,17-19]. However, the cut-off values varied among these studies, which increased the difficulty in determining a uniform standard. Two possible explanations can be identified: First, this parameter is a continuous variable, and the cut-off values are inconsistent in different studies; alternatively, the study subjects are diverse and included individuals with signet ring cell EGC, undifferentiated-type

Table 2 Lymph node metastasis in early gastric cancer according to therapeutic indications

	LNM (%)	95%CI	P-value
Absolute indications for ESD	0/90 (0.0)	0%-4.1%	< 0.001
Expanded indications for ESD	4/311 (1.3)	0.35%-3.29%	
Surgical indications	178/861 (20.7)	17.75%-23.94%	

LNM: Lymph node metastasis; CI: Confidence interval; ESD: Endoscopic submucosal dissection.

EGC, and mixed type EGC among others, which may also account for the difference.

In the latest gastric cancer treatment guidelines (2014 ver. 4), the JGCA noted that endoscopic dissection should be defined as noncurative if mucinous adenocarcinoma is found in the submucosal layer, regardless of whether the mucinous cells are believed to be derived from a differentiated or undifferentiated-type tumor. We conclude that the histological pattern of mucinous adenocarcinoma is an independent risk factor for LNM based on multivariate analysis, which provided powerful evidence to support this statement. With regard to signet ring cell carcinoma in EGC, it has been reported that the LNM rate of signet ring cell-type tumors is lower than that of other undifferentiated-type carcinomas and is equivalent to that of differentiated-type carcinomas^[20], which is in line with our results. This suggests that ESD is more feasible for signet ring cell carcinoma compared with other early undifferentiated-type gastric carcinomas. However, the cellular histology of signet ring cell carcinoma is an important factor for LNM in EGC^[21]. Huh *et al*^[22] also stated that EGC with a mixed signet ring cell histology exhibited more aggressive behavior than pure tubular adenocarcinoma or pure signet ring cell carcinoma. Hence, a more accurate application of the classification of signet ring cell carcinoma could improve the ESD criteria.

In a previous study that focused on the prognosis of different types of gastric cancer as classified by the Lauren classification, patients with MT carcinomas were found to be significantly more likely to have LNM than patients with IT and DT carcinomas, which was also confirmed in our study. A possible explanation of this difference is that patients with MT tumors always exhibit severe characteristics, including larger lesion sizes and a higher frequency of spread into local lymphatic and venous vessels or regional lymph nodes^[23]. In various clinical and pathological studies, LVI has been reported to be the strongest risk factor for nodal metastasis in EGC^[24], and we confirmed this finding by showing that LVI predicted a high risk of LNM in EGC. However, unlike other risk factors that can be observed by endoscopic investigation and other auxiliary examinations, LVI is difficult to detect before the ER specimen is obtained. However, based on the criteria for local treatment, the presence of LVI commonly requires additional extended surgery, which is clinically significant. As shown in Table 3, every histopathological factor included in this study was significantly associated with LNM, which indicates that all of these factors are vitally important for performing an accurate pathological analysis after gastroscopic examination.

Researchers have previously concluded that the overall 3-year survival rate was higher in patients without LNM and that patients with LNM had a higher rate of tumor recurrence^[25]. Several factors are associated with an increased rate of LNM. The risk factors varied in some relevant studies, but LVI, submucosal invasion, histological type, and tumor size were found to be significantly related to LNM in almost every study. Consistent with other studies^[7,18,26], our study demonstrated that age, sex, tumor location, macroscopic type, presence of ulcers, tumor differentiation, Lauren type, and *H. pylori* infection were not independent risk factors for LNM, although some of these factors were statistically significant in the univariate analysis. Specifically, we analyzed other clinical features, such as drinking and smoking history, obesity, family history of tumors, and the levels of the tumor marker CEA, which is an innovative aspect of this study. In recent years, biomarkers have begun to play an increasingly important role in the detection and management of patients with gastrointestinal malignancies^[27]. Serum CEA is considered a complementary test, although it is insufficient to diagnose EGC and LNM. In this study, a higher than normal CEA value was found to be statistically significant in univariate analysis, which attaches great importance to its preoperative detection. However, inconsistencies were found among the test items of the included patients, which made it difficult to perform an analysis of other less common tumor markers. Buckland *et al*^[28] reported that nicotine and alcohol played an important role in the development of gastric cancer, and therefore, we further analyzed the relationships between drinking

Table 3 Lymph node metastasis in early gastric cancer according to the endoscopic submucosal dissection indications

	LNM negative	LNM positive	LNM rate (%)	95%CI	P-value
Ab (<i>n</i> = 90)	90	0	0.0	0%-4.1%	0.021
Ex1 (<i>n</i> = 86)	83	3	3.5	0.75%-10.56%	
Ex2 (<i>n</i> = 32)	31	1	3.1	0.08%-17.91%	
Ex3 (<i>n</i> = 110)	110	0	0	0%-3.35%	
Ex4 (<i>n</i> = 83)	83	0	0	0%-4.44%	

Ex1: Differentiated mucosal tumors, ≤ 30 mm in size, without lymphovascular invasion (LVI), and with ulceration. Ex2: Differentiated mucosal tumors, without ulcer and LVI, and of any size. Ex3: Undifferentiated mucosal tumors without ulcer and LVI, and ≤ 20 mm in size. Ex4: Differentiated tumors with SM1 invasion, no LVI, and ≤ 30 mm in size. LNM: Lymph node metastasis; CI: Confidence interval; Ab: Absolute indications for endoscopic submucosal dissection; Ex: Expanded indications for endoscopic submucosal dissection.

and smoking with LNM. Despite the lack of significant association between the occurrence of LNM and these lifestyle habits in this study, we cannot ignore these factors because the clinical data collected in retrospective studies may be incomplete. Although this research, to the best of our knowledge, involved the largest number of EGC patients in China, the limitation that it was a retrospective study at a single institution should still be noted. Therefore, a well-designed multicentric prospective study is needed.

In conclusion, the absolute indications for ESD can be applied to Chinese patients, while the feasibility of expanding these indications requires further investigation. The predictive factors for LNM included submucosal invasion depth, LVI, mucinous adenocarcinoma, and large lesion size. Taking the histology of tumors into consideration when deciding upon the ESD indications is therefore of great necessity.

Table 4 Lymph node metastasis risk according to endoscopic features

	Total (n = 1262), n (%)	LNM negative (n = 1080), n (%)	LNM positive (n = 182), n (%)	Univariate OR (95%CI)	P-value
Location					0.462
Cardia	46 (3.6)	40 (3.7)	6 (3.3)	1	
Fundus/corpora	288 (22.8)	240 (22.2)	48 (26.4)	1.333 (0.535, 3.320)	0.537
Angle/antrum	928 (73.5)	800 (74.1)	128 (70.3)	1.067 (0.443, 2.567)	0.885
Lesion size					< 0.001
Small (≤ 20 mm)	761 (60.3)	680 (63.0)	81 (44.5)	1	
Middle (20-30 mm)	285 (22.6)	239 (22.1)	46 (25.3)	1.616 (1.093, 2.388)	0.016
Large (> 30 mm)	216 (17.1)	161 (14.9)	55 (30.2)	2.868 (1.955, 4.207)	< 0.001
Macroscopic type					0.001
0-I(Protruded)	86 (6.8)	71 (6.6)	15 (8.2)	1.712 (0.823, 3.564)	0.147
0-IIa (Elevated)	36 (2.9)	35 (3.2)	1 (0.5)	0.232 (0.030, 1.788)	0.128
0-IIb (Flat)	173 (13.7)	154 (14.3)	19 (10.4)	1	
0-IIc (Depressed)	486 (38.5)	432 (40)	54 (29.7)	1.013 (0.582, 1.763)	0.963
0-III (Excavated)	481 (38.1)	388 (35.9)	93 (51.1)	1.943 (1.146, 3.293)	0.012
Number of tumors					0.191
Single	1220 (96.7)	1044 (96.7)	176 (96.7)	1	
Multitude	42 (3.3)	36 (3.3)	6 (3.3)	1.724 (0.641, 4.635)	
Ulcer					0.013
Absence	558 (44.2)	493 (45.6)	65 (35.7)	1	
Presence	704 (55.8)	587 (54.4)	117 (64.3)	1.512 (1.091, 2.094)	

LNM: Lymph node metastasis; OR: Odds ratio; CI: Confidence interval.

Table 5 Lymph node metastasis risk according to histopathological characteristics

	Total (n = 1262), n (%)	LNM negative (n = 1080), n (%)	LNM positive (n = 182), n (%)	Univariate OR (95%CI)	P-value
Invasion depth					< 0.001
M	596 (47.2)	565 (52.3)	31 (17.0)	1	
SM1	245 (19.4)	197 (18.2)	48 (26.4)	4.441 (2.748, 7.176)	< 0.001
SM2	421 (33.4)	318 (29.4)	103 (56.6)	5.903 (3.862, 9.024)	< 0.001
Differentiation					< 0.001
Differentiated	455 (36.1)	412 (38.1)	43 (23.6)	1	
Undifferentiated	807 (63.9)	668 (61.9)	139 (76.4)	1.994 (1.386, 2.867)	
Histology					0.019
Pap/Tub/Por	1004 (79.6)	866 (80.2)	138 (75.8)	1	
Sig	223 (17.7)	190 (17.6)	33 (18.1)	1.090 (0.723, 1.644)	0.681
Muc	35 (2.8)	24 (2.2)	11 (6.1)	2.876 (1.378, 6.004)	0.005
LVI					< 0.001
Absence	1104 (87.5)	1021 (94.5)	83 (45.6)	1	
Presence	158 (12.5)	59 (5.5)	99 (54.4)	20.641 (13.942, 30.559)	
Perineural invasion					< 0.001
Absence	1181 (93.6)	1026 (95)	155 (85.2)	1	
Presence	81 (6.4)	54 (5.0)	27 (14.8)	3.310 (2.024, 5.413)	
Lauren's type					0.003
Intestinal type	500 (39.6)	448 (41.5)	52 (28.6)	1	
Diffuse type	399 (31.6)	335 (31.0)	64 (35.2)	1.646 (1.112, 2.437)	0.013
Mixed type	363 (28.8)	297 (27.5)	66 (36.3)	1.915 (1.294, 2.833)	0.001

SM1: Tumor invading the superficial (< 0.5 mm in depth) submucosa. SM2: Tumor invading the deep (> 0.5 mm in depth) submucosa. LNM: Lymph node metastasis; OR: Odds ratio; CI: Confidence interval; M: Tumor confined within the mucosal layer; Pap: Papillary adenocarcinoma; Tub: Tubular adenocarcinoma; Por: Poorly differentiated adenocarcinoma; Sig: Signet ring cell carcinoma; Muc: Mucinous adenocarcinoma; LVI: Lymph-vascular

invasion.

Table 6 Multivariate logistic regression analysis of lymph node metastasis in early gastric cancer

Factor	OR (95%CI)	P-value
Lesion size		0.025
Middle lesion size (20-30 mm)	1.230 (0.774, 1.955)	0.380
Large lesion size (>30 mm)	1.900 (1.197, 3.015)	0.006
Histology		0.049
Sig	1.146 (0.698, 1.881)	0.590
Muc	2.823 (1.225, 6.505)	0.015
LVI	15.702 (10.405, 23.695)	< 0.001
Invasion depth		< 0.001
SM1	2.285 (1.317, 3.965)	0.003
SM2	3.230 (2.006, 5.201)	< 0.001

SM1: Invading the superficial (<0.5 mm in depth) submucosa. SM2: Invading the deep (> 0.5 mm in depth) submucosa. LNM: Lymph node metastasis; OR: Odds ratio; CI: Confidence interval; LVI: Lymph-vascular invasion; Sig: Signet ring cell carcinoma; Muc: Mucinous adenocarcinoma.

ARTICLE HIGHLIGHTS

Research background

The indications for endoscopic submucosal dissection (ESD) have been recently expanded to include larger, ulcerated, and undifferentiated mucosal lesions, and differentiated lesions with slight submucosal invasion. Despite the advantages over surgical procedures, lymph nodes cannot be removed by ESD. However, the risk of lymph node metastasis (LNM) is the most important consideration when deciding on a treatment strategy for early gastric cancer (EGC).

Research motivation

Evaluating the risk of LNM is critical for determining the best course of management for EGC patients. Unfortunately, the risk factors that have been identified in different studies are diverse, and whether patients who met the expanded indications for ESD can be managed safely remains controversial.

Research objectives

We aimed to determine whether the ESD indications are applicable to Chinese patients and to investigate the predictors of LNM in EGC. After working hard on this topic, we have re-evaluated and verified the current indications and guidelines for endoscopic treatment and analyzed the clinicopathological predictors of LNM, which provides strong evidence and reference to future research.

Research methods

We retrospectively analyzed 12552 patients who underwent surgery for gastric cancer between June 2007 and December 2018 at the Affiliated Hospital of Qingdao University. A total of 1262 (10.1%) EGC patients were eligible for inclusion in this study. Data on the patients' clinical, endoscopic, and histopathological characteristics were collected. The absolute and expanded indications for ESD were validated by regrouping the enrolled patients and determining the positive LNM results in each subgroup. Predictors of LNM in patients were evaluated by univariate and multivariate analyses. Specifically, we analyzed other clinical features, such as drinking and smoking history, obesity, family history of tumors, and the levels of the tumor marker carcinoembryonic antigen (CEA), which is an innovative aspect of this study.

Research results

LNM was observed in 182 (14.4%) patients. No LNM was detected in the patients who met the absolute indications (0/90). LNM occurred in 4/311 (1.3%) patients who met the expanded indications. According to univariate analysis, LNM was significantly associated with positive tumor marker status, medium (20-30 mm) and large (>30 mm) lesion sizes, excavated macroscopic-type tumors, ulcer presence, submucosal invasion (SM1 and SM2), poor differentiation, lymphovascular invasion (LVI), perineural invasion, and diffuse and mixed Lauren's types. Multivariate analysis demonstrated SM1 invasion (OR = 2.285, $P = 0.03$), SM2 invasion (OR = 3.230, $P < 0.001$), LVI (OR = 15.702, $P < 0.001$), mucinous adenocarcinoma (OR = 2.823, $P = 0.015$), and large lesion size (OR = 1.900, $P = 0.006$) to be independent risk factors. Also, the results of this research affirmed the feasibility of the absolute indications for ESD. However, whether it is reasonable to expand the indications remains to be further discussed.

Research conclusions

The absolute indications for ESD can be applied to Chinese patients, while the feasibility of expanding these indications requires further investigation. The predictive factors for LNM included submucosal invasion depth, LVI, mucinous adenocarcinoma, and large lesion size. This study provides clinicians with important reference when evaluating the risk of LNM and determining the best course of management for EGC patients.

Research perspectives

Besides invasion depth, LVI, and lesion size, taking the histology of tumors into consideration when deciding upon the ESD indications is vitally important. In addition, preoperative detection of tumor markers is of great necessity. The direction of the future research is to further optimize the ESD indications by analyzing the predictive factors for LNM in EGC. A well-designed multicentric prospective study is the best method for the future research.

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