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BRIEF ARTICLE

Prediction of risk factors for lymph node metastasis in early gastric cancer

Gang Ren, Rong Cai, Wen-Jie Zhang, Jin-Ming Ou, Ye-Ning Jin, Wen-Hua Li

Gang Ren, Wen-Hua Li, Department of Radiology, Xinhua Hospital, Shanghai Jiaotong University Medical School, Shanghai 200092, China
Rong Cai, Ye-Ning Jin, Department of Radiochemotherapy, Ruijin Hospital, Shanghai Jiaotong University Medical School, Shanghai 200025, China
Wen-Jie Zhang, Jin-Ming Ou, Department of Surgery, Xinhua Hospital, Shanghai Jiaotong University Medical School, Shanghai 200092, China
Author contributions: Ren G and Cai R contributed equally to this paper; Ren G and Cai R performed the data acquisition, statistical analysis and interpretation; Zhang WJ, Ou JM and Jin YN performed data acquisition; Li WH designed the study and wrote the manuscript.
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Correspondence to: Dr. Wen-Hua Li, Department of Radiology, Xinhua Hospital, Shanghai Jiaotong University Medical School, 1665 Kongjiang Road, Shanghai 200092, China. liwhxh120819@hotmail.com
Telephone: +86-21-25078999 Fax: +86-21-65153984
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Abstract

AIM: To explore risk factors for lymph node metastases in early gastric cancer (EGC) and to confirm the appropriate range of lymph node dissection.

METHODS: A total of 202 patients with EGC who underwent curative gastrectomy with lymphadenectomy in the Department of Surgery, Xinhua Hospital and Ruijin Hospital of Shanghai Jiaotong University Medical School between November 2003 and July 2009, were retrospectively reviewed. Both the surgical procedure and the extent of lymph node dissection were based on the recommendations of the Japanese gastric cancer treatment guidelines. The macroscopic type was classified as elevated (type Ⅰ or Ⅱa), flat (Ⅱb), or depressed (Ⅱc or Ⅲ). Histopathologically, papillary and tubular adenocarcinomas were grouped together as differentiated adenocarcinomas, and poorly differentiated and signet-ring cell adenocarcinomas were regarded as undifferentiated adenocarcinomas. Univariate and multivariate analyses of lymph node metastases and patient and tumor characteristics were undertaken.

RESULTS: The lymph node metastases rate in patients with EGC was 14.4%. Among these, the rate for mucosal cancer was 5.4%, and 8.9% for submucosal cancer. Univariate analysis showed an obvious correlation between lymph node metastases and tumor location, depth of invasion, morphological classification and venous invasion (χ^2 = 122.901, P = 0.001; χ^2 = 7.14, P = 0.008; χ^2 = 79.523, P = 0.001; χ^2 = 8.687, P = 0.003, respectively). In patients with submucosal cancers, the lymph node metastases rate in patients with venous invasion (60%, 3/5) was higher than in those without invasion (20%, 15/75) (χ^2 = 4.301, P = 0.038). Multivariate logistic regression analysis revealed that the depth of invasion was the only independent risk factor for lymph node metastases in EGC [P = 0.018, Exp (B) = 2.744]. Among the patients with lymph node metastases, 29 cases (14.4%) were at N1, seven cases were at N2 (3.5%), and two cases were at N3 (1.0%). Univariate analysis of variance revealed a close relationship between the depth of invasion and lymph node metastases at pN_1 (P = 0.008).

CONCLUSION: The depth of invasion was the only independent risk factor for lymph node metastases. Risk factors for metastases should be considered when choosing surgery for EGC.

Key words: Gastric neoplasm; Lymph node metastasis; Risk factors; Gastrectomy; Lymphadenectomy

Core tip: Early gastric cancer (EGC) is defined as a lesion confined to the mucosa or the submucosa, irrespective of the presence of regional lymph node metastases. In this study, we retrospectively evaluated the distribution of metastatic nodes in a two-center cohort of 202 patients with EGC. To assess nodal status in EGC, we applied an index calculated by the multiplication of the incidence of metastases in the respective node stations. Univariate and multivariate analyses were applied to confirm the clinicopathological factors associated with lymph node metastases, and to provide a basis for choosing the optimal surgical treatment and for determining the appropriate range of lymph node dissection.

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INTRODUCTION

Early gastric cancer (EGC) is defined as a lesion confined to the mucosa or the submucosa, irrespective of the presence of regional lymph node metastases[1]. Five-year survival rates in EGC tend to be greater than 90%, with lymph node status being the most important prognostic factor[2,3]. In patients with EGC and lymph node metastases, a 5-year survival rate of 87.3% has been reported, compared to 94.2% in those without nodal involvement[4]. Considering the low rate of lymph node metastasis in EGC[5,6], the Japanese guidelines recommend endoscopic mucosal resection, reduction surgery D1 plus No. 7 and 8a and D1 plus No. 7, and 8a and 9 lymph node resection, for the treatment of patients with phase T1 disease. However, this approach is controversial outside Japan. At present, the general consensus is that endoscopic mucosal resection (EMR) or distal gastrectomy plus limited lymph node resection can be undertaken in most patients with mucosal cancer, and a distal gastrectomy plus D2 lymph node resection should be performed in most patients with submucosal cancer[2,3].

Recently, in order to reduce operative and post-operative complications, and to improve quality of life, less invasive surgical alternatives, such as EMR, endoscopic submucosal dissection, laparoscopy-assisted gastrectomy and limited surgery, are used for the treatment of EGC. Although there has been substantial research on the prediction of risk factors for lymph node metastases in EGC, no definitive criteria are available. In addition, controversy surrounds the indications for local treatment in EGC, and limited surgery and the appropriate extent of lymphadenectomy.

In this study, we retrospectively evaluated the distribution of metastatic nodes in a two-center cohort of 202 patients with EGC. To assess nodal status in EGC, we applied an index calculated by the multiplication of the incidence of metastases in the respective node stations. Univariate and multivariate analyses were performed to confirm the clinicopathological factors associated with lymph node metastases, and to provide a basis for choosing the optimal surgical treatment and for determining the appropriate range of lymph node dissection.

MATERIALS AND METHODS

Ethics

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by the Institutional Review Board of Shanghai Jiaotong University. All patients provided written informed consent.

Patients

A total of 202 patients with EGC, as defined by the Japanese Classification of Gastric Carcinoma[7], who underwent curative gastrectomy with lymphadenectomy in the Department of Surgery, Xinhua Hospital and Ruijin Hospital of Shanghai Jiaotong University Medical School between November 2003 and July 2009, were retrospectively reviewed. Of these, there were 132 men and 70 women, ranging in age from 25 to 87 years (mean 58.1 ± 12.9 years). Mucosal tumors were found in 122 patients (60.4%) and submucosal tumors in 80 (39.6%). Lymph node involvement was detected in 29 patients (Table 1).

Surgery

All operations were performed with curative intent. Curative surgery was defined as the removal of all gross tumors and the demonstration of tumor-negative surgical margins by microscopic examination of the entire circumference. Surgical procedures comprised 171 distal gastrectomies, 24 proximal gastrectomies and seven total gastrectomies. Proximal gastrectomy involved resection of the proximal half of the stomach via an abdominal approach, with an intraabdominal esophagogastric anastomosis. Following a total gastrectomy with D2 lymph node dissection, an esophagojejunostomy was used routinely for Roux-en-Y reconstruction. Proximal and distal resection margins were evaluated intraoperatively to confirm freedom from disease. Both the surgical procedure and the extent of lymph node dissection were based on the recommendations of the Japanese gastric cancer treatment guidelines[7]. A total of 2926 lymph nodes (LNs), with a median of 14.5 LNs per patient, were removed. No patient received neoadjuvant therapy before surgery.

Pathological examination

In both hospitals, the surgical team immediately examined the lymph nodes macroscopically, which were then divided and classified into lymph node stations, as defined by the Japanese Classification of Gastric Carcinoma. No

Table 1 Demographics of 202 patients with early gastric cancer

	Patients (n = 202)
Age	
< 60 yr	109
⩾ 60 yr	93
Sex	
Male	132
Female	70
Tumor site	
Upper	25
Middle	98
Lower	79
Size of tumor	
⩽ 2 cm	97
> 2 cm	105
No. of resected nodes	
< 15	114
⩾ 15	88
Tumor depth	
Mucosal	122
Submucosal	80
Macroscopic type	
Elevated	25
Flat	21
Depressed	156
Histologic type	
Differentiated	121
Undifferentiated	81
Lyphovessel ambolus	
+	2
-	200
Vessel ambolus	
+	5
-	197
Nerve invasion	
+	0
-	202
CEA	
+	1
-	201

CEA: Carcinoembryonic antigen.

size limitation was imposed for lymph node harvesting. Specimens were fixed in formalin, stained with hematoxylin and eosin, and sent for histopathological evaluation, following which the number of histologically confirmed lymph nodes was recorded for each lymph node station. Each lymph node was embedded in paraffin and at least two sections were performed. Immunhistochemistry for micrometastasis was not performed.

Tumor size was recorded as the maximum diameter. The depth of infiltration was measured at the deepest point of penetration of the cancer cells. The macroscopic type was classified as elevated (type Ⅰ or Ⅱa), flat (Ⅱb), or depressed (Ⅱc or Ⅲ), according to the Japanese Classification of Gastric Carcinoma[7]. Of the 202 patients, 26 (12.9%), 21 (10.4%) and 155 (76.7%) were elevated, flat or depressed, respectively. Histopathologically, papillary and tubular adenocarcinomas were grouped together as differentiated adenocarcinomas, and poorly differentiated and signet-ring cell adenocarcinomas were regarded as undifferentiated adenocarcinomas. Overall, tumors were differentiated in 121 patients and undifferentiated in 81.

The relationship between various clinicopathological factors and the presence or absence of lymph node metastases was then examined. Clinicopathological parameters included patient age (< 60 years or ⩾ 60 years), sex, tumor location (U = upper third, M = middle third, or L = lower third of the stomach), tumor size (maximum dimension ⩽ 20 mm or > 20 mm), macroscopic type (elevated, flat, or depressed), depth of invasion (mucosal or submucosal), histological type (differentiated or undifferentiated), carcinoembryonic antigen levels (CEA, < 5 ng/mL or ⩾ 5 ng/mL), lymphatic invasion (present or absent) and venous invasion (present or absent). Evaluation of these factors was undertaken according to the Japanese Classification of Gastric Carcinoma established by the Japanese Research Society for Gastric Cancer.

Statistical analysis

Descriptive data are presented as the mean ± SD. For between group comparisons, continuous variables were analyzed using the Student's t test, and categorical variables with the χ^2 test. Factors found to be significant ($P < 0.05$) in univariate analysis were included in subsequent multivariate logistic regression analysis, in order to identify independent variables associated with lymph node metastases. All statistical analyses were undertaken using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 17.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Univariate analysis of lymph node metastases in EGC and clinicopathological factors

Univariate analysis was performed on the relationship between lymph node metastases and clinicopathological factors. The findings revealed a close relationship between tumor location, depth of invasion, morphological classification, venous invasion and lymph node metastases ($\chi^2 = 122.901$, $P = 0.001$; $\chi^2 = 7.14$, $P = 0.008$; $\chi^2 = 79.523$, $P = 0.001$; $\chi^2 = 8.687$, $P = 0.003$, respectively). There was no correlation between lymph node metastases and sex, age, tumor size, number of retrieved lymph nodes, histological type, lymphatic invasion, nervous invasion, and serum levels of carcinoembryonic antigen (CEA) (Table 2).

In patients with mucosal cancers, no significant differences in the occurrence of lymph node metastases were found in relation to sex, age, tumor location, tumor size, number of retrieved lymph nodes, morphological classification, histological type, lymphatic invasion, venous invasion, nervous invasion and CEA levels (Table 2).

In patients with submucosal cancers, there was no significant difference in the occurrence of lymph node metastases in relation to sex, age, tumor location, tumor size, number of retrieved lymph nodes, morphological classification, histological type, lymphatic invasion, nervous invasion and CEA levels. However, the lymph node

Table 2 Univariate analysis of lymph node metastases in early gastric cancer and clinicopathological factors *n* (%)

Clinicopathological factors	LN (+)	LN (-)	*P*[1]
The entire study population			
Age			0.887
< 60 yr	16 (14.7)	93 (85.3)	
⩾ 60 yr	13 (14.0)	80 (86.0)	
Sex			0.213
Male	16 (12.1)	116 (87.9)	
Female	13 (18.6)	57 (81.4)	
Tumor site			0.001
Upper	2 (8.0)	23 (92.0)	
Middle	15 (15.3)	83 (84.7)	
Lower	12 (15.2)	67 (84.8)	
Size of tumor			0.240
⩽ 2 cm	11 (11.3)	86 (88.7)	
> 2 cm	18 (17.1)	87 (82.9)	
No. of resected nodes			0.580
< 15	15 (13.2)	99 (86.9)	
⩾ 15	14 (15.9)	74 (84.1)	
Tumor depth			0.008[a]
Mucosal	11 (9.0)	111 (91.0)	
Submucosal	18 (22.5)	62 (77.5)	
Macroscopic type			0.001[a]
Elevated	4 (16)	21 (84)	
Flat	3 (14.3)	18 (85.7)	
Depressed	22 (14.1)	134 (85.9)	
Histologic type			0.332
Differentiated	15 (12.4)	106 (87.6)	
Undifferentiated	14 (17.3)	67 (82.7)	
Lyphovessel ambolus			0.149
+	1 (50.0)	1 (50.0)	
-	28 (14.0)	172 (86.0)	
Vessel ambolus			0.003[a]
+	3 (60.0)	2 (40.0)	
-	26 (13.2)	171 (86.8)	
Nerve invasion			N
+	0 (0)	0 (0)	
-	29 (14.4)	173 (85.6)	
CEA			0.681
+	0 (0)	1 (100)	
-	29 (14.4)	173 (85.6)	
Mucosa cancer			
Age			0.234
< 60 yr	8 (11.8)	60 (88.2)	
⩾ 60 yr	3 (5.6)	51 (94.4)	
Sex			0.578
Male	6 (7.9)	70 (92.1)	
Female	5 (10.9)	41 (89.1)	
Tumor site			0.976
Upper	1 (10.0)	9 (90.0)	
Middle	6 (9.4)	58 (90.6)	
Lower	4 (8.3)	44 (91.7)	
Size of tumor			0.142
⩽ 2 cm	3 (5.1)	56 (94.9)	
> 2 cm	8 (12.7)	55 (87.3)	
No. of resected nodes			0.580
< 15	7 (10.3)	61 (89.7)	
⩾ 15	4 (7.4)	50 (92.6)	
Macroscopic type			0.539
Elevated	2 (11.1)	16 (88.9)	
Flat	0 (0)	11 (100)	
Depressed	9 (9.7)	84 (90.3)	
Histologic type			0.073
Differentiated	4 (5.3)	71 (94.7)	
Undifferentiated	7 (14.9)	40 (85.1)	
Lyphovessel ambolus			N
+	0 (0)	0 (0)	
-	11 (9.0)	111 (91.0)	
Vessel ambolus			N
+	0 (0)	0 (0)	
-	11 (9.0)	111 (91.0)	
Nerve invasion			N
+	0 (0)	0 (0)	
-	11 (9.0)	110 (91.0)	
CEA			0.752
+	0 (0)	1 (100)	
-	11 (9.1)	110 (90.9)	
Submucosal cancer			
Age			0.512
< 60 yr	8 (19.5)	33 (80.5)	
⩾ 60 yr	10 (25.6)	29 (74.4)	
Sex			0.129
Male	10 (17.9)	46 (82.1)	
Female	8 (33.3)	16 (66.7)	
Tumor site			0.265
Upper	1 (6.7)	14 (93.3)	
Middle	9 (26.5)	25 (73.5)	
Lower	8 (25.8)	23 (74.2)	
Tumor size			0.768
⩽ 2 cm	8 (21.1)	30 (78.9)	
> 2 cm	10 (23.8)	32 (76.2)	
No. of resected nodes			0.203
< 15	8 (17.4)	38 (82.6)	
⩾ 15	10 (29.4)	24 (70.6)	
Macroscopic type			0.742
Elevated	2 (28.6)	5 (71.4)	
Flat	3 (30.0)	7 (70.0)	
Depressed	13 (20.6)	50 (79.4)	
Histologic type			0.725
Differentiated	11 (23.9)	35 (76.1)	
Undifferentiated	7 (20.6)	27 (79.4)	
Lyphovessel ambolus			0.346
+	1 (50.0)	1 (50.0)	
-	17 (21.8)	61 (78.2)	
Vessel ambolus			0.038[a]
+	3 (60.0)	2 (40.0)	
-	15 (20.0)	60 (80.0)	
Nerve invasion			N
+	0 (0)	0 (0)	
-	18 (22.5)	62 (77.5)	
CEA			N
+	0 (0)	0 (0)	
-	18 (22.5)	62 (77.5)	

[1]Statistically significant. Tumor site: middle and lower *vs* upper; Tumor depth: submucosa *vs* mucosa; Macroscopic type: flat and depressed *vs* elevated; Vessel ambolus: + (present) *vs* - (absent), [a]$P < 0.05$. In patients with mucosal cancers, no significant differences in the occurrence of lymph node metastases were found in relation to the clinicopathological factors. CEA: Carcinoembryonic antigen.

metastases rate in patients with venous invasion (60%, 3/5) was higher than in those without invasion (20%, 15/75), and the difference was significant ($\chi^2 = 4.301$, $P = 0.038$) (Table 2). Venous invasion, as a source variable, was therefore used in the logistic regression model. This revealed that it was not an independent risk factor for lymph node metastases in submucosal cancer [B = 1.792, SE = 0.957, Wals = 3.502, $P = 0.061$, Exp (B) = 6.000] (Table 2).

Multivariate analysis of lymph node metastases in EGC

Multivariate analysis revealed that the depth of invasion was an independent risk factor for lymph node metastases [$P = 0.018$, Exp (B) = 2.744]. Venous invasion was

also an important influencing factor [P = 0.116, Exp (B) = 4.147, Table 3]. Tumor location, depth of invasion, morphological classification, and venous invasion had no significant impact on nodal involvement rates.

Relationship between depth of invasion and number of metastatic lymph nodes

There was no significant difference between mucosal and submucosal tumors in terms of number of retrieved lymph nodes, using the independent sample t test (t = 0.350, df = 200, P = 0.727, mean difference = 0.534). The number of metastatic lymph nodes in those with mucosal tumors was slightly higher than in those with submucosal tumors. The results of dissected nodes were as follows: mucosa (n = 122), 14.70 ± 9.894; submucosa (n = 80), 14.16 ± 11.656, P = 0.727; for the metastasis nodes, mucosa (n = 122), 3.91 ± 5.576; submucosa (n = 80), 3.72 ± 3.102, P = 0.908. The difference was not significant.

Number of retrieved lymph nodes and lymph node metastasis ratios for involved lymph nodes at each nodal station in EGC

The metastatic ratio is the ratio of metastatic nodes to the total number of dissected nodes and was recorded for each nodal station for all regional lymph nodes. There were 110 metastatic lymph nodes, an incidence of 3.8%. Among them, more lymph nodes were retrieved in stations No. 3, 4, 6, 7, 1, 9, 8 and 12. The number of retrieved lymph nodes in above stations was between 108 and 861, and the metastatic ratio was between 0% and 5.9%. Fewer lymph nodes were retrieved in stations No. 5, 13, 2, 11, 14, 10 and 15. The retrieved number was between 13 and 78, and the metastatic ratio was between 0% and 34.8%. Only one patient received station No. 16 lymph node dissection, and no metastasis was found. According to the Japanese Classification of Gastric Carcinoma[7], 29 cases (14.4%) were at N1, seven cases were at N2 (3.5%), and two cases were at N3 (1.0%). A direct skip to N2, without moving through N1, occurred in two cases (1.0%). There were no skips to N3 without going through N2. The incidence of lymph node metastases in each station, from high to low, was as follows: station No. 14 (34.8%), No. 2 (11.1%), No. 6 (5.9%), No. 3 (4.8%), No. 11 (3.7%), No. 4 (3.4%), No. 5 (2.6%), No. 8 (2.5%), No. 9 (2.2%), No. 7 (1.5%), and No. 1 (0.6%). There were no station No. 10 and No. 11 lymph node metastases in two patients who had undergone a total gastrectomy combined with a splenectomy (Table 4).

Lymph node metastasis ratios and incidence at each station in upper third, middle third and lower third gastric cancers

The extent of metastases in 25 cases with upper third gastric cancer was as follows: four cases were at N1 (2.0%), an incidence of 3.4%, and a metastatic rate of 16.0%; one case was at N2 (0.5%), an incidence of 4.5%, and a metastatic rate of 4.0%; and no metastases was found at N3. At N1, lymph node metastases occurred in stations No. 2, 3, and 4, but not in station No. 1. The incidence of metastases was 5.3%, 5.5%, and 1.6% in stations No. 2, 3, and 4, respectively, and the metastatic rate was 4.0%, 8.0%, and 4.0%, respectively. At N2, lymph node metastases occurred only in station No. 8, and the incidence of metastases was 16.7%, and the metastatic rate was 4.0% (Table 5).

The extent of metastases in middle third gastric cancers was as follows: 18 cases (8.9%) occurred at N1, an incidence of 3.5% and a rate of 18.4%; five cases occurred at N2 (2.5%), an incidence of 1.4%, and a rate of 5.1%; and two cases occurred at N3 (1.0%), an incidence of 14.3%, and a rate of 2.0%. At N1, station No. 1, 3, 4, 5, and 6 had lymph node metastases, a rate of 1.0%, 9.2%, 5.1%, 1.0% and 2.0%, respectively. At N2, station No. 8, 9 and 11 had lymph node metastases, a rate of 1.0%, 3.1%, and 1.0%, respectively. At N3, only station No. 2 and 14 had lymph node metastases, a rate of 1.0%. No distal lymph node metastasis was identified (Table 5).

The extent of metastases in lower third gastric cancers was: 20 cases (9.9%) had metastases at N1: an incidence of 5.7%, and a rate of 25.3%; two cases (1.0%) had metastases at N2: an incidence of 1.8%, and a rate of 2.5%; there were no cases of metastases at N3 or at

Table 3 Multivariate analysis of lymph node metastases in early gastric cancer for the entire study population

	RR	95%CI	P[1]
Tumor site	1.159	0.84-1.478	0.644
Invasion depth	2.744	2.316-3.172	0.018[a]
Macroscopic type	0.864	0.57-1.158	0.620
Vessel amblous	4.147	3.242-5.052	0.116
Constant term	0.037	-2.568	0.010

[1]Statistically significant, invasion depth: submucosa *vs* mucosa, [a]P < 0.05.

Table 4 Number of retrieved lymph nodes and lymph node metastasis ratios for involved lymph nodes at each nodal station in early gastric cancer

Node group	No. of dissected nodes	No. of metastasis nodes	Incidence of lymphnode metastasis (%)
No. 1	165	1	0.6
No. 2	27	3	11.1
No. 3	861	41	4.8
No. 4	670	23	3.4
No. 5	78	2	2.6
No. 6	358	21	5.9
No. 7	263	4	1.5
No. 8	120	3	2.5
No. 9	134	3	2.2
No. 10	16	0	0.0
No. 11	27	1	3.7
No. 12	108	0	0.0
No. 13	58	0	0.0
No. 14	23	8	34.8
No. 15	13	0	0.0
No. 16	5	0	0.0
Total	2926	110	3.8

Table 5 Lymph node metastasis ratios and incidence at each station in upper third, middle third and lower third gastric cancers

Node group	Upper			Middle			Lower		
	pN category	Incidence	Ratio	pN category	Incidence	Ratio	pN category	Incidence	Ratio
No. 1	pN1	0.0 (0/52)	0.0 (0/25)	pN1	7.4 (1/73)	1.0 (1/98)	pN2	0.0 (0/40)	0.0 (0/79)
No. 2	pN1	5.3 (1/19)	4.0 (1/25)	pN3	28.6 (2/7)	1.0 (1/98)	M	0.0 (0/1)	0.0 (0/79)
No. 3	pN1	5.5 (7/128)	8.0 (2/25)	pN1	3.8 (17/445)	9.2 (9/98)	pN1	5.9 (17/288)	8.9 (7/79)
No. 4	pN1	1.6 (1/62)	4.0 (1/25)	pN1	4.3 (15/347)	5.1 (5/98)	pN1	2.7 (7/261)	6.3 (5/79)
No. 5	pN3	0.0 (0/6)	0.0 (0/25)	pN1	2.6 (1/38)	1.0 (1/98)	pN1	2.9 (1/34)	1.3 (1/79)
No. 6	pN3	0.0 (0/21)	0.0 (0/25)	pN1	2.2 (4/182)	2.0 (2/98)	pN1	11.0 (17/155)	8.9 (7/79)
No. 7	pN2	0.0 (0/21)	0.0 (0/25)	pN2	0.0 (0/141)	0.0 (0/98)	pN2	4.0 (4/101)	1.3 (1/79)
No. 8	pN2	16.7 (2/12)	4.0 (1/25)	pN2	1.6 (1/63)	1.0 (1/98)	pN2	0.0 (4/45)	0.0 (0/79)
No. 9	pN2	0.0 (0/5)	0.0 (0/25)	pN2	3.5 (3/85)	3.1 (3/98)	pN2	0.0 (4/44)	0.0 (0/79)
No. 10	pN2	0.0 (0/2)	0.0 (0/25)	pN3	0.0 (0/3)	0.0 (0/98)	M	0.0 (0/11)	0.0 (0/79)
No. 11	pN2	0.0 (0/4)	0.0 (0/25)	pN2	7.1 (1/14)	1.0 (1/98)	pN2	0.0 (0/9)	0.0 (0/79)
No. 12	pN3	0.0 (0/6)	0.0 (0/25)	pN2	0.0 (0/61)	0.0 (0/98)	pN2	0.0 (0/41)	0.0 (0/79)
No. 13	M	0.0 (0/10)	0.0 (0/25)	pN3	0.0 (0/31)	0.0 (0/98)	pN3	0.0 (0/17)	0.0 (0/79)
No. 14	M	0.0 (0/2)	0.0 (0/25)	pN3	41.2 (7/17)	1.0 (1/98)	pN2	25.0 (1/4)	1.3 (1/79)
No. 15	M	0.0 (0/1)	0.0 (0/25)	M	0.0 (0/9)	0.0 (0/98)	M	0.0 (0/3)	0.0 (0/79)
No. 16	M	0.0 (0/0)	0.0 (0/25)	pN3	0.0 (0/5)	0.0 (0/98)	pN3	0.0 (0/0)	0.0 (0/79)

Table 6 Correlation between lymph node metastases at pN1 and pN2 and clinicopathological factors

	pN1			pN2		
	-	+	*P*	-	+	*P*
Tumor size (cm)			0.24			0.295
≤ 2.0	86 (88.7)	11 (11.3)		95 (97.9)	2 (2.1)	
> 2.0	87 (82.9)	18 (17.1)		100 (95.2)	5 (4.8)	
Macroscopic type			0.969			0.259
Elevated	21 (84.0)	4 (16.0)		24 (96.0)	1 (4.0)	
Flat	18 (85.7)	3 (14.3)		19 (90.5)	2 (9.5)	
Depressed	134 (85.9)	22 (14.1)		152 (97.4)	4 (2.6)	
Invasion depth			0.008			0.334
Mucosal	111 (91.0)	11 (9.0)		119 (97.5)	3 (2.5)	
Submucosal	62 (77.5)	18 (22.5)		76 (95.0)	4 (5.0)	
Differentiate			0.332			0.349
Differentiated	106 (87.6)	15 (12.4)		118 (97.5)	3 (2.5)	
	67 (82.7)	14 (17.3)		77 (95.1)	4 (4.9)	
Undifferentiated						
Lymphovascular invasion			0.126			0.804
No	174 (87.0)	26 (13.0)		194 (97.0)	6 (3.0)	
Yes	1 (50.0)	1 (50.0)		2 (100.0)	0 (0.0)	

distal lymph nodes. In N1, the metastatic rate, from high to low, was 8.9%, 8.9%, 6.3% and 1.3% respectively, and incidence was 5.9%, 11.0% 2.7%, and 2.9%, respectively in stations No. 3, 6, 4, and 5. In N2, lymph nodes in stations No. 7 and 14 were most frequently involved, while no metastases occurred in stations No. 1, 8, 9, 11, and 12. At N2, lymph node metastases occurred in station No. 7, in a depressed type and differentiated submucosal tumor with a diameter 3.0 cm. Lymph node metastases occurred in a mucosal tumor in station No. 14 with a diameter 6.0 cm. It was a type 0-Ⅲ differentiated cancer (Table 5).

Correlation between lymph node metastases at pN1 and pN2 and clinicopathological factors

Univariate analysis of variance revealed a close relationship between the depth of invasion and lymph node metastases at pN1 ($P = 0.008$). There was no obvious relationship between the depth of invasion and lymph node metastases at pN2 ($P = 0.334$). There was no significant correlation between tumor size, morphological classification, differentiation, lymphatic invasion and the presence of lymph node metastases at pN1 and pN2 (Table 6).

DISCUSSION

Five-year survival rates in EGC tend to be greater than 90%, with lymph node status the most important prognostic factor. In those with lymph node metastases, a 10-year survival rate of 72% has been reported, compared to 92% for those without nodal involvement[2]. Although research has explored the issue of predicting risk factors for lymph node metastases in EGC, as yet there are no definitive criteria. In addition, controversy surrounds indications for local treatment and a limited surgical approach, and the range of lymph node dissection. Hence, in this study, we aimed to explore the risk factors for the development of lymph node metastases in EGC, to confirm the optimal range of lymph node dissection, and to provide a basis for a rational approach to surgical management.

Reported rates of lymph node metastases in EGC range from 5.7% to 20%[8-16]. However, Hayes *et al*[17] reported a rate over 40% during surgery. Depending on the depth of invasion, EGC can be classified as mucosal or submucosal, with a rate of lymph node involvement of 0%-21%[11,18,19] for mucosal tumors, and 16.5%-30%[2,3,19-22] for submucosal tumors. Based on anatomical and histological characteristics, there is a close relationship between the depth of tumor invasion and lymph node metastases in EGC. Once the tumor has invaded the submucosal layer, the rate of lymph node metastases increases significantly. In our group of 202 patients with EGC, lymph node metastases occurred in 29. Among these, there were 11 cases of mucosal and 18 cases of submucosal cancer. The rate of involved lymph nodes was higher in those with submucosal cancer than

in mucosal cancer (22.5% *vs* 9.0%, $\chi^2 = 7.14$, $P = 0.008$).

In our group, male patients predominated, accounting for 65.3%, while was similar to other reports[18,23-26]. Studies to date suggest that EGC frequently occurs in the lower third of the stomach[18,22,26]. In our study, 48.5% of cases originated in the middle third, which was similar to the report from Fujimoto *et al*[14]. Also in our group, 52.0% of patients had tumors greater than 2 cm. Larger tumors have higher rates of lymph node metastases. Of the 29 cases with lymph node metastases, the tumor size in 18 was greater than 2 cm, accounting for 62.1% of all metastases. Morphological classification was mainly of the depressed type (77.2%). Among these, type 0-Ⅱc and type 0-Ⅲ accounted for approximately 50%. Histologically, most tumors were differentiated, accounting for 59.9%, which was similar to that reported by Abe *et al*[27].

Although the lymph node metastatic rate in EGC is relatively low, it has been shown that the presence of lymph node metastases predicts a poor prognosis[28-32]. Thus, many researchers have attempted to investigate the relationship between nodal involvement and clinicopathological factors. The size of the primary tumor, undifferentiated histopathological characteristics, lymphatic or venous invasion, and a cancerous ulcer are associated with nodal metastases in EGC[8,9,12,14,32-42]. Univariate analysis confirmed a correlation between tumor location, depth of invasion, morphological classification, venous invasion and lymph node metastases in EGC in our study ($\chi^2 = 122.901$, $P = 0.001$; $\chi^2 = 7.14$, $P = 0.008$; $\chi^2 = 79.523$, $P = 0.001$; $\chi^2 = 8.687$, $P = 0.003$, respectively), while nodal metastases were not associated with sex, age, tumor size, number of retrieved lymph nodes, histological type, lymphatic invasion, nervous invasion, and CEA levels. Boku *et al*[12] reported an association between lymph node metastases and the tumors arising from the distal third of the stomach, indicating that cancers arising from this section have a worse prognosis. In our study, tumors originating in the upper third of the stomach had a nodal metastatic rate of 8%, compared to 15.3% for the middle third and 15.2% for the lower third, which was similar to that reported by Boku *et al*[12]. Reports have suggested both a lack of association between the occurrence of lymph node metastases and mucosal tumors of the upper and middle third of the stomach[19], and a marked increase in nodal involvement with distal gastric cancers[43]. Data from our study revealed a lymph node metastases rate in mucosal and submucosal tumors of 9.0% and 22.5%, respectively, which was similar to other reports[19,44]. At present, endoscopic submucosal resection is often used for patients with mucosal cancer, while data from Hölscher contradicts this approach[19]. Our data indicates that, prior to surgery, determination of the depth of invasion is important for predicting lymph node metastases. Preoperative staging technology, particularly endoscopic ultrasonography, can determine the depth of invasion, but there can be errors of judgment[11,16,45,46]. In Japan, the morphological classification of EGC is summarized as elevated, flat and depressed type. The rate of lymph node metastases in the elevated subtype was relatively high, being 16% in our study. The rate of lymph node metastases tends to be markedly higher in patients with venous or lymphatic invasion[46]. However, our results did not concur with this, which might be explained by the fact that the number of specimens varied, and the quantity of venous or lymphatic invasion that we included was low.

It is generally acknowledged that tumor size is closely related to lymph node metastases. Hölscher[19] found no evidence of lymph node metastases in mucosal cancers less than 1 cm, and in submucosal cancers. Moreover, lymph node metastases have not been identified in patients with mucosal cancers less than 2 cm[19]. Tumors greater than 2 cm appear to be independent risk factors for lymph node metastases[19,22,47,48]. In our group, although the rate of lymph node metastases in patients with tumors greater than 2 cm (17.1%) was clearly greater than that observed with smaller tumors (11.3%), the difference was not significant, which is similar to the results from Lee *et al*[18].

Histological type is also closely related to nodal status[9,18,35,41,42]. In our group, the rate of lymph node metastases in non-differentiated tumors was higher than in differentiated cancer, 17.3% and 12.4%, respectively. However, a non-differentiated tumor was not an independent risk factor for lymph node metastases. Abe *et al*[49] suggest that, apart from tumor size, submucosal invasion and lymphatic invasion, a correlation also exists between females and the occurrence of lymph node metastases. In females, the biological behavior of gastric cancer tends to be more invasive. Moreover, it has also been shown that the extent of the invasiveness of gastric cancer cannot be fully explained by tumor size, depth of invasion or lymphatic invasion[49]. A possible explanation for the fact that gastric cancer tends to be more invasive in females could be related to endogenous estrogen levels, which might promote tumor growth.

In recent years, endoscopic surgery has become one of the standard procedures, and is indicated for patients with mucosal tumors, tumors less than 2 cm in size, and those without lymph node metastases. Our results suggest that the rate of lymph node metastases is markedly higher in those with cancers of the middle and lower third of the stomach, and those with submucosal tumors, who are therefore not suitable for endoscopic surgery.

Multivariate analysis found that only depth of invasion was an independent risk factor for lymph node metastases in EGC [$P = 0.018$, Exp (B) = 2.744], which is consistent with previous studies[18,26,31,32,35,37,50-55]. Multivariate analysis by Kim *et al*[3] on 748 cases of EGC, indicated that tumor size, poorly differentiated tumors and submucosal cancers were all independent risk factors for lymph node metastases. Hyung *et al*[56] suggest that poorly differentiated tumors, submucosal cancer, tumor size, and venous or lymphatic invasion are independent risk factors for nodal metastases. Many other studies have reached similar conclusions, namely that tumor

size, depth of invasion, histological type, morphological classification, venous or lymphatic invasion, are all independent risk factors for lymph node metastases in EGC[3,14,22,26,27,47,48,50,56-62].

A consideration of the number of lymph node is related to the extent of surgical intervention, which is also related to the depth of tumor invasion. Thus the depth of tumor invasion is also associated with the number of lymph nodes: as the depth increases, the number of lymph nodes also increases. In our group, all 202 cases of EGC had a radical gastrectomy. Post-operatively, 2892 regional lymph nodes were located. In 122 cases, where tumor invasion was limited to the mucosal layer, 1790 lymph nodes were found, with an average of 14.67 per case. In 80 cases with tumor invading the submucosa, 1102 lymph nodes were detected, with an average of 13.77 per case. The difference between the number of lymph nodes in mucosal and in submucosal cancer was not significantly different ($P = 0.727$). Five hundred and sixty lymph nodes were found in 29 cases with lymph node metastases, an average of 19.31 per case. In our study, there was a relationship between the number of lymph nodes and the presence of lymph node metastases. In 29 patients with metastases, the number of involved nodes with tumor depth limited to the mucosa was similar to that observed for submucosal tumors, with no significant difference between the two groups.

Our results showed that there was no obvious correlation between lymph node metastases in mucosal cancer, and sex, age, tumor location, tumor size, the number of retrieved lymph nodes, morphological classification, histological type, lymphatic invasion, nervous invasion and CEA levels. Currently, there is much interest in the optimal management approach for patients with submucosal tumors and involved lymph nodes[36-40]. In a univariate analysis, An *et al*[22] demonstrated that tumor size, histological type, the Lauren classification, the depth of tumor invasion, lymphatic invasion and nervous invasion, were all relevant in terms of the risk of lymph node metastases in submucosal cancer. Of these factors, tumor size and lymphatic invasion are independent risk factors for nodal involvement[22,36-39]. In our study, there was no obvious correlation between the presence of lymph node metastases in patients with submucosal cancer, and sex, age, tumor location, tumor size, the number of retrieved lymph nodes, morphological classification, histological type, lymphatic invasion, nervous invasion, and CEA levels. Nonetheless, the lymph node metastases rate (60%, 3/5) in those with venous invasion was higher than that observed in patients without invasion (20%, 15/75), and the difference was significant. However, an analysis of venous invasion, as a source variable, in the logistic regression model, did not confirm it as an independent risk factor for lymph node metastases. An *et al*[22] considered that, for 19.4% of patients with submucosal cancer and lymph node metastases, laparoscopic subtotal distal gastrectomy plus lymph node dissection improved both the resection rate and quality of life. Controversy continues as to which surgical approach is the optimal for the management of patients with submucosal cancer[40].

Most lymph node metastases in EGC are limited to N1 and/or N2. In line with previous reports[34,63], and our own experience, approximately 80%-90% of nodal metastases in EGC are limited to the N1. The proportion of involved N2 and N3 lymph nodes is lower at 10%-19% and 0%-1%, respectively[22,34,63,64]. This appears to support R2 resection[65]. In our group, of 29 patients with lymph node metastases, all were N1, seven were N2 (24.1%), and two were N3 (6.9%). These results are all higher than those reported by An *et al*[22]. Among them, the two N3 patients had the following clinicopathological features: both were mucosal cancers; the tumor size was relatively large, at 6 cm and 2.5 cm, respectively; and both tumors were depressed subtypes. Both patients underwent a radical gastrectomy plus a D2 lymph node dissection. Even in EGC, extensive lymph node metastases can occur. Surgeons should avoid conventional limited surgery, and assess the range of possible surgical resections[22]. Kunisaki *et al*[55] believe that, for most cases of mucosal cancer, the routine D2 lymph node dissection might also be too invasive. Therefore, the method and range of lymph node dissection should be based on clinicopathological features before and after surgery. However, Yoshikawa *et al*[44] suggest that, during surgical treatment of mucosal cancers, apart from perigastric lymph node dissection, it is necessary to perform lymph node dissection at the coeliac trunk and beside the common hepatic artery. Our results support this recommendation. In our group, there was one case of mucosal cancer with a station No. 8 lymph node metastasis.

Since the mid 1900s, D2 lymph node dissection has been the standard procedure worldwide for the management of EGC, particularly for submucosal tumors. Studies have shown that the rate of lymph node metastases for N1 is 9%-16%, 4%-6% for N2, and 0.3%-1% for N3[49,56,59,66]. Accordingly, if D2 surgery is performed in all patients with EGC, 70%-80% would undergo unnecessary lymph node evacuation, and analysis suggests that these patients do not necessarily benefit as a result[40]. Consequently, indications for standard D2 lymph node dissection should be reconsidered. Our study revealed that, for cancers originating in the middle third of the stomach, the lymph node metastasis rate at N2 was 5.1%, mainly station No. 9, whereas there were no metastases in stations No. 7 and No. 12. Similarly, the metastasis rate in lower third tumors was 2.5%, mainly station No. 7 and No. 14. There was one case of metastasis (1.3%) in each of these. In upper third cancers, the rate was 4.0%, predominately station No. 8, with one case of metastasis (4.0%). Thus, when performing D2 surgery, patients with station No. 7 and No. 12 lymph nodes in tumors from the middle third of the stomach, stations No. 1, 8, 9, 11, and 12 lymph nodes in those from the lower third, and stations No. 7, 9-11 lymph nodes in the upper third should not be referred for routine dissection. In tumors of the middle third of the stomach, there was only one

case of N3 lymph node metastasis in both stations No. 2 and No. 14, and the metastasis rate was 1.0%. There were no N3 and distal lymph node metastases in tumors from both the upper and the lower third of the stomach. The benefit of performing D3 dissection in EGC is extremely low, with a long operative time and relatively more complications, which adversely affect quality of life. Therefore, D3 dissection should be avoided in EGC. There were no distal lymph node metastases in our study, and thus expanded lymph node dissection was not required.

Investigating the correlation between pN1 and pN2 lymph node metastases and clinicopathological factors, we found no significant associations between nodal status at pN1 and pN2 and tumor diameter, morphological classification, tumor differentiation and lymphatic invasion. The lymph node metastasis rate (22.5%, 18/80) at N1 in patients with submucosal cancers was higher than in those with mucosal cancers (9.0%, 11/122), and the difference was significant ($\chi^2 = 7.144$, $P = 0.008$). A histological study performed by Asao *et al*[67] on 417 patients with gastric cancer who had routine gastrectomy plus D2 lymph node dissection, reported a rate of lymph node metastases in submucosal cancer of 1.3% (2/154), and in mucosal cancer distal to the perigastric part of 18% (17/96). These nodal metastases were mainly concentrated around the common hepatic artery and the coeliac trunk. In submucosal cancer, there was no nodal metastases elsewhere[67]. However, our study highlighted that tumors with N2 lymph node metastases were usually submucosal, with a diameter greater than 2.0 cm and were of the depressed subtype. Thus, we suggest that submucosal cancers, with a diameter greater than 2.0 cm, and of the depressed subtype are risk factors lymph node metastases. Patients with these factors should be identified during surgery.

There are limitations to this study. Firstly, it was retrospective, based on the examination of morphological samples after surgery. Prospective studies are needed to confirm whether our approach could be applied to endoscopic surgery based on biopsies. It is essential to define the acute T stage before surgery, in order to safely implement limited lymph node dissection. Although the accuracy of endoscopic ultrasonography is relatively high, overestimation or underestimation occurs[46]. Secondly, according to a previous Japanese study based on different depths of tumor invasion, mucosal cancer can be further subdivided into m1, m2, and m3 cancer, and submucosal cancer into sm1, sm2 and sm3 cancer. Moreover, there were obvious differences between the subgroups, with m1 and m2 cancers not usually associated with lymph node metastases, and the rate of nodal metastases in m3 cancers varies from 0% to 12.8%. At present, most endoscopic specialists agreed that all patients with mucosal cancers are suitable for EMR, while Hölscher *et al*[19] oppose this view. Unfortunately, our two hospitals do not routinely perform sub-classifications for mucosal and submucosal cancers, which we plan to redress in future studies. Thirdly, the number of patients in our study was lower than in the Japanese study. In a seminal study by Gotoda[46], 5000 patients with EGC were enrolled. Results from our study need to be confirmed in larger studies.

In summary, our research revealed a lymph node metastasis rate of 14.4% in patients with EGC, with a rate of 5.4% for mucosal tumors and 8.9% for submucosal tumors. The occurrence of lymph node metastasis in EGC is related to tumor location, depth of invasion, morphological classification and venous invasion, with depth of invasion identified as the only independent risk factor for nodal involvement. Lymph node metastases should be considered when deciding on the surgical management of EGC.

COMMENTS

Background

Five-year survival rates in early gastric cancer (EGC) tend to be greater than 90%, with lymph node status the most important prognostic factor. Recently, in order to reduce operative and post-operative complications, and to improve quality of life, less invasive surgical alternatives, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), laparoscopy-assisted gastrectomy and limited surgery, are used for the treatment of EGC. Although there has been substantial research on the prediction of risk factors for lymph node metastases in EGC, no definitive criteria exist.

Research frontiers

The presence of lymph node metastases in EGC predicts a poor prognosis. In the area of the appropriate extent of lymphadenectomy in EGC, the research hotspot is to investigate the relationship between nodal involvement and clinicopathological factors, predict risk factors for lymph node metastases in EGC and determine the indications for local treatment in EGC, and limited surgery and the appropriate extent of lymphadenectomy.

Innovations and breakthroughs

The presence of lymph node metastases predicts a poor prognosis, univariate analysis confirmed a correlation between tumor location, depth of invasion, morphological classification, venous invasion and lymph node metastases in EGC in this study. The results suggest that the rate of lymph node metastases is markedly higher in those with cancers of the middle and lower third of the stomach, and those with submucosal tumors, who are therefore not suitable for endoscopic surgery. When performing D2 surgery, patients with station No. 7 and No. 12 lymph nodes in tumors from the middle third of the stomach, stations No. 1, 8, 9, 11, and 12 lymph nodes in those from the lower third, and stations No. 7, 9, 10, and 11 lymph nodes in the upper third should not be referred for routine dissection. D3 dissection should be avoided in EGC. There were no distal lymph node metastases in this study, and thus expanded lymph node dissection was not required. The authors suggest that submucosal cancers, with a diameter greater than 2.0 cm, and of the depressed subtype, are risk factors for lymph node metastases. Patients with these factors should be identified during surgery.

Applications

The depth of invasion is the only independent risk factor for lymph node metastases. Risk factors for metastases should be considered when choosing surgery for EGC.

Terminology

EGC: A lesion confined to the mucosa or the submucosa, irrespective of the presence of regional lymph node metastases; EMR: A technique used for providing accurate histological staging of superficial gastrointestinal neoplasms and providing a minimally invasive technique for removal of superficial malignancies; ESD: A technique for the resection of early gastrointestinal neoplasia, whose main advantage is that lesions can be resected without almost any size limit.

Peer review

The paper is good and complex. The authors thoroughly explained the problem of prediction of risk factors for lymph node metastasis in early gastric cancer.

They have described, in detail, the research results, as well as, the discussion. The conclusion was a logical consequence of the research results.

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