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Original Article

Gender differences of risk factors for early gastric cancer with lymph node metastasis

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Abstract: Backgrounds: Lymph node metastasis (LNM) is an independent prognostic risk factor for early gastric cancer (EGC). However, the relationship between gender and LNM remains largely unknown. Methods: We retrospectively analyzed 426 cases of EGC. Their clinicopathological data were subjected to univariate and multivariate analyses to identify the risk factors of LNM, and then a sex-control study was performed. Results: The 426 cases included 292 males and 134 females (sex ratio, 2.18:1). There were 55 (12.91%) cases with LNM. The rate of LNM in the female group (21.64%) was higher than that of the male group (8.90%) (P=0.000). In the female group, the rate of premenopausal females (27.50%) was higher than that of menopausal females (19.15%). Univariate analysis showed gender, age, location, tumor size, pathological type, Lauren classification and depth of invasion had significant differences. Multivariate analysis showed gender (P=0.008, OR=2.359), age (P=0.014, OR=1.923) and depth of invasion (P=0.000, OR=4.208) were the risk factors for LNM in EGC. The LNM rate of females was significantly higher than that of males. Conclusion: The rate of LNM in EGC was 12.91%. Gender, age and depth of invasion were the risk factors for LNM. All the risk factors had significant gender differences, i.e. females had a higher rate of LNM than that of males.

Keywords: Stomach neoplasm, early gastric cancer, lymph node metastasis, gender difference

Introduction

Early gastric cancer (EGC) is defined as tumor localized to the mucosa (M) or submucosa (SM), irrespective of lymph node metastasis (LNM). With increasing incidence rate of EGC, patients require endoscopic submucosal dissection (ESD) or endoscopic mucosal resection. EGC has a better prognosis, for which LNM is an independent prognostic risk factor [1]. The rates of LNM vary from 8% to 25.3% [1-3], and tumor size, depth of invasion and histopathological type are usually the risk factors for LNM. However, the relationship between gender and LNM in EGC has never been reported hitherto. Therefore, we performed a sex-control analysis to clarify the effect of gender factor on LNM.

Materials and methods

We collected the clinicopathological data of EGC patients who underwent standard gastrectomy with D2 lymph node dissection from July 2010 to June 2016 in General Surgery Department of Drum Tower Hospital, Medical School of Nanjing University. Finally, 426 cases were diagnosed as EGC by postoperative pathological examination (**Figure 1**).

Inclusion criteria: Tumor invaded M or SM, no matter whether LNM occurred. Exclusion criteria: Tumor invaded the muscularis propria or serosa.

The resected specimens were then subjected to hematoxylin-eosin staining and immunohistochemical staining (**Figure 2**). All the EGC cases were diagnosed, classified and staged according to the criteria of Japanese Gastric Cancer Treatment Guidelines 2010 (ver. 3) [4]. Japanese Classification of Gastric Carcinoma: 3rd English edition [5] and the World Health Organization classification (well, moderately, and poorly differentiated). Histological classifi-

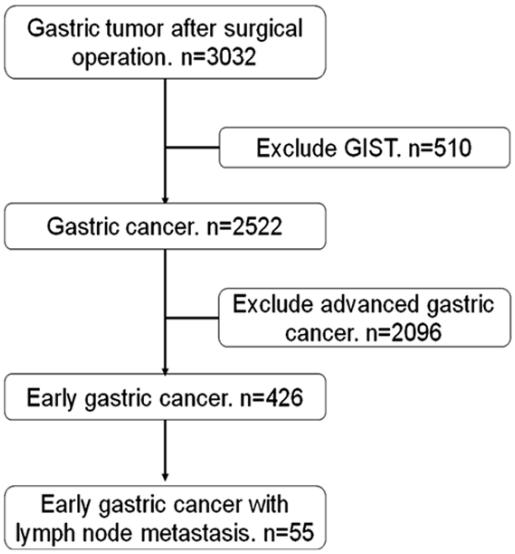

Figure 1. Flow chart of study.

cation: Papillary adenocarcinoma, tubular adenocarcinoma, well differentiated, moderately differentiated, poorly differentiated adenocarcinomas, signet-ring cell carcinoma and mucinous adenocarcinoma. Depth of invasion: T1a: Tumor invaded M; T1b: tumor invaded SM. N0: Without LNM; N1: regional LNM number 1-2. It was determined by predominant part if there were mixed histological types and degrees of differentiation.

Postoperative follow-up contents included CT or/and gastroscopy, and detection of serum tumor markers. Particularly, the 55 patients with LNM were closely followed up for 2~64 months. We found no cancer recurrence or metastasis, except for 17 cases losing contact.

The clinicopathological data (gender, age, tumor location, tumor size, macroscopic type, pathological type, Lauren classification, degree of differentiation, depth of invasion and location of metastasized lymph node) of 426 cases were analyzed by SPSS 18 software. These data were subjected to univariate (age and tumor size: T test; categorical variable: Chi-square test) and multivariate analyses (binary logistic regression), *P* value <0. 05 indicated a statistically significant difference.

Results

The 426 patients enrolled in this study comprised 292 males and 134 females, with the male/female ratio of 2.18:1. There were 55 cases with LNM, accounting for 12.91% of total ones. They were aged 23~85 years old, with the mean age of 60.62±11.84 and the median age of 62. The mean age of males was (62.40±10.43) years, and their median age was 63. The mean age and median age of females were (56.72±13.68) and 59 years respectively. The morbidity rate of patients aged 60-65 years was highest (**Figure 3**). The median ages of males and females with LNM were 62 and 54 years respectively, suggesting that LNM occurred in females 8 years earlier than in males and age had a significant gender difference.

Of the 55 cases with LNM, 35 (63.64%) had one positive lymph node and 20 (36.36%) had more than one. The positive lymph nodes of 34 (61.82%) cases were located at the lesser curvature (No. 1, 3, 5), and those of 17 (30.91%) cases were located at the greater curvature (No. 2, 4, 6). Notably, the positive lymph nodes of 2 (3.63%) cases were located on two sides of the stomach, and 3 (5.45%) cases suffered from metastasis to second-station lymph node (No. 7, 9, 12).

Univariate analysis

The rate of LNM was 8.90% in the male group but 21.64% in the female group (P=0.000). Then, the patients were divided into three groups. The morbidity rates of premenopausal female, menopausal female and male groups were 40 (9.39%), 94 (22.07%) and 292 (68.54%) respectively, and the LNM rates were 11 (27.50%), 18 (19.15%) and 26 (8.90%) respectively, which were significantly different (*P*=0.001) (**Figure 4**).

The LNM rate of the age <65 group (17.23%) was significantly higher than that of the age ≥65 group (5.66%) (*P*=0.001) (**Table 1**). The LNM rate of females was significantly higher than that of males in either the <65 group (*P*=0.014) or the ≥65 group (*P*=0.018) (**Table 2**).

The LNM rates of the groups of invasion to M and SM were 6.47% and 18.67% respectively, with a significant difference (*P*=0.000) (**Table 1**). Females had a significantly higher LNM rate than that of males in both invasion to M (*P*=0.018) and invasion to SM (*P*=0.006) groups (**Table 2**).

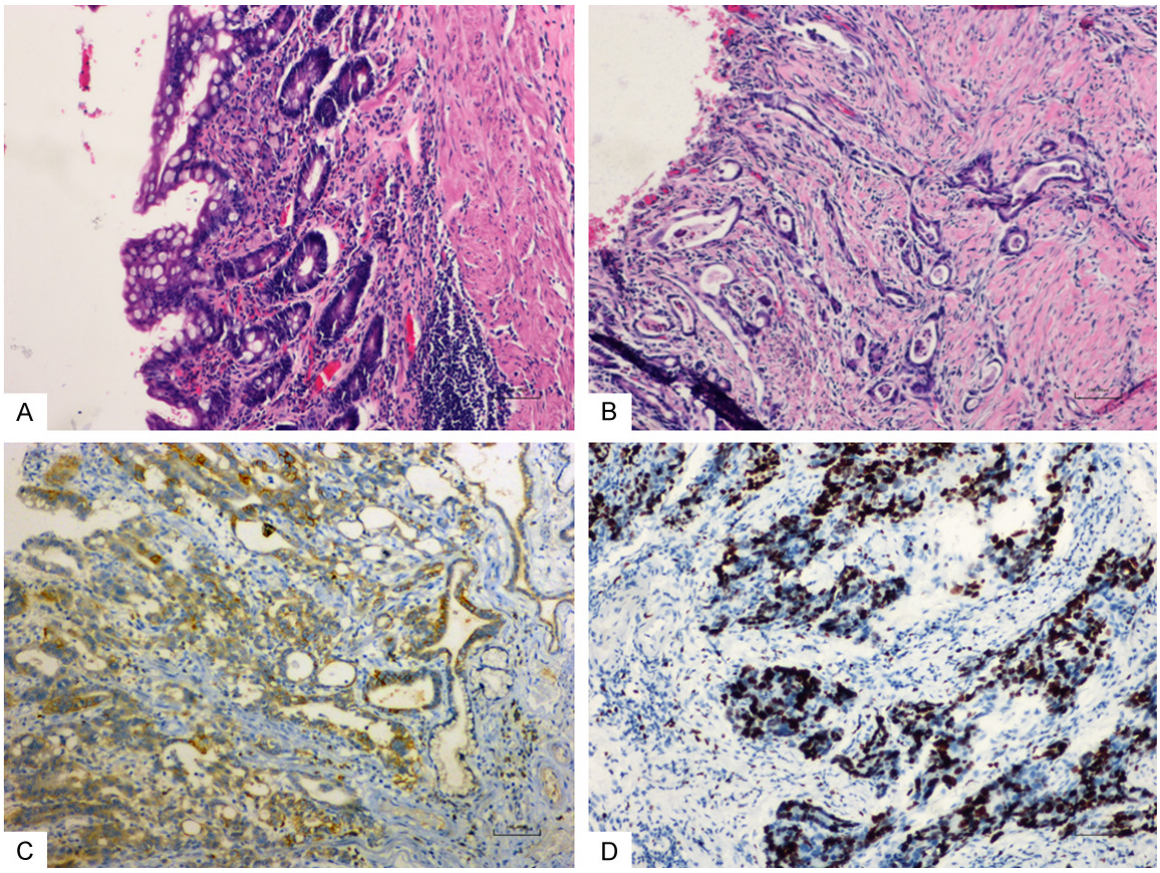

Figure 2. A: Tumor cells are confined to the mucosa, muscularis mucosae is not invaded (HE ×100). B: Tumor cells are invading the submucosa (HE ×100). C: Immunohistochemical staining show tumor express HER2(+), (×100). D: Immunohistochemical staining show tumor express Ki67 (+), (×100).

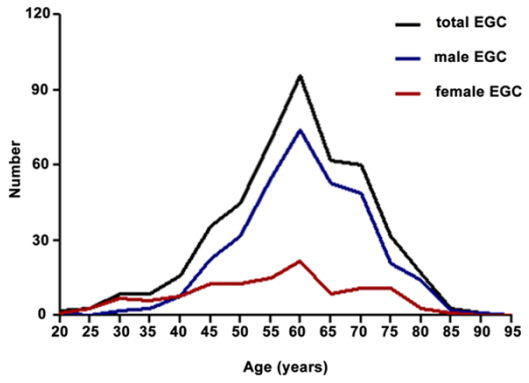

Figure 3. Morbidity of different gender.

Univariate analysis of location (*P*=0.028), tumor size (*P*=0.013), pathological type (*P*=0.000) and Lauren classification (*P*=0.004) also showed significant differences (**Table 1**). Besides, the LNM rate of females was significantly higher than that of males in the subgroups of both tumor size and pathological type (**Table 2**). However, the macroscopic type subgroup did not show a significant difference. The subgroups of location, macroscopic type and Lauren classification had significant gender differences. Although the other subgroups had no significant gender differences, the rate of LNM in females was still higher than that of males (**Tables 1** and **2**).

Multivariate analysis

Multivariate analysis showed gender (*P*=0.008, OR=2.359), age (*P*=0.014, OR=1.923) and depth of invasion (*P*=0.000, OR=4.208) were independent risk factors for LNM (**Table 1**), all of which showed significant gender differences.

Location (*P*=0.100, OR=0.710), tumor size (*P*=0.364, OR=0.732), macroscopic type (*P*=0.973, OR=0.991), pathological type (*P*=0.011, OR=0.393) or Lauren classification (*P*=0.064, OR=1.297, 95% CI 0.985-1.708) was not risk factor

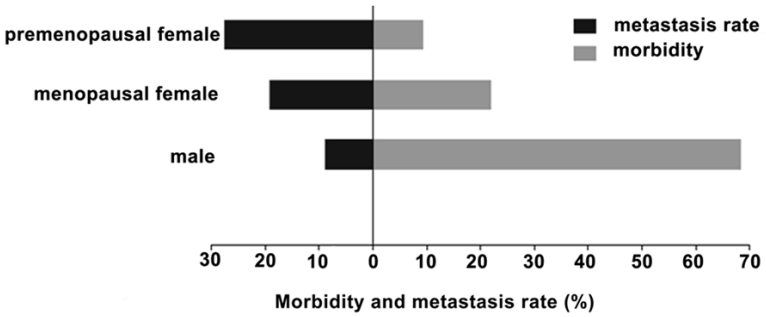

Figure 4. Morbidity and metastasis rate of different gender.

Table 1. Univariate and multivariate analysis of the risk factors of lymph node metastasis

Risk factors	Lymph node		Univariate	Multivariate analysis		
	(+)	(-)	*P* value	*P* value	OR	95% CI
Gender			0.000	0.008	2.359	1.247-4.463
Male	26	266				
Female	29	105				
Age (years)			0.001	0.014	1.923	1.143-3.235
<65	46	221				
≥65	9	150				
Location			0.028	0.100	0.710	0.472-1.067
Upper	7	92				
Middle	10	84				
Lower	38	182				
Multifocal	0	13				
Tumor size (cm)			0.013	0.364	0.732	0.373-1.435
<2	17	155				
≥2	38	216				
Macroscopic type			0.421	0.973	0.991	0.592-1.659
I	4	31				
II	31	174				
III	20	166				
Pathological type			0.000	0.011	0.393	0.191-0.811
Differentiate	15	198				
Undifferentiate	40	173				
Lauren type			0.004	0.064	1.297	0.985-1.708
Intestinal type	18	136				
Mixed type	13	14				
Diffused type	13	49				
Undefined	11	142				
Depth of invasion			0.000	0.000	4.208	2.043-8.668
M	13	188				
SM	42	183				

for LNM in EGC (**Table 1**). Regardless, the LNM rate of females was still higher than that of males (**Table 2**).

Discussion

The Japanese Endoscopic Society put forward the concept of EGC in 1962, defining it as gastric cancer confined to the mucosa or submucosa, regardless the occurrence of LNM. EGC cases account for about 10%-47.4% of all diagnosed ones with gastric cancer. EGC has a better prognosis, with LNM as the independent prognostic risk factor [2], because 8.3%-25.3% [1-3] of EGC cases have LNM and 10%-25% suffer from micrometastasis with negative lymph nodes [3, 6]. LNM seriously affects the postoperative 5-year survival of EGC. Shi et al. found that the postoperative recurrence and liver metastasis rate of EGC patients who underwent ESD was 5.1% after 26 months [7]. According to the guidelines of Japan Gastroenterological En-doscopy Society, endoscopic resection should be carried out when the likelihood of LNM is extremely low, and lesion size and site are amenable to resection en bloc [8]. Nevertheless, there are still no effective methods for determining whether LNM occurs before surgery, so it is of great significance to find the risk factors for LNM. Although depth of invasion and tumor size have been reported to be risk factors, little was known about the relationship between gender and LNM. Therefore, we performed a retrospective analysis to explore the relationship between gender and EGC with LNM.

By analyzing the clinicopathological data of 426 EGC patients, we found that the morbidity rate of males was significantly higher than that of females, and the rates of premenopausal

Table 2. Gender difference of the risk factors

Risk factors	Male (rate)		Female (rate)		*P* value
	LN (+)	LN (-)	LN (+)	LN (-)	
Gender					Sig
	26 (8.90%)	266	29 (21.64%)	105	0.000
Age (years)					Sig
<65	22 (12.94%)	148	24 (24.74%)	73	0.014
≥65	4 (3.28%)	118	5 (10.81%)	32	0.018
Location					
Upper	5 (6.67%)	70	2 (8.33%)	22	0.542
Middle	4 (6.06%)	62	6 (21.43%)	22	0.037
Lower	17 (11.72%)	128	21 (28.00%)	54	0.003
Multifocal	0 (0.00%)	6	0 (0.00%)	7	—
Tumor size (cm)					Sig
<2	5 (4.59%)	104	12 (19.05%)	51	0.002
≥2	21 (11.48%)	162	17 (23.94%)	54	0.012
Macroscopic type					
I	2 (8.70%)	21	2 (16.67%)	10	0.425
II	8 (6.67%)	112	12 (18.18%)	54	0.016
III	16 (10.74%)	133	15 (26.79%)	41	0.005
Pathological type					Sig
Differentiated	7 (4.35%)	154	8 (15.38%)	44	0.012
Undifferentiated	19 (14.50%)	112	21 (25.61%)	61	0.034
Lauren type					
Intestinal type	11 (9.48%)	105	7 (18.42%)	31	0.118
Mixed type	6 (15.79%)	32	7 (36.84%)	12	0.058
Diffused type	5 (13.16%)	33	8 (33.33%)	16	0.075
Undefined	4 (4.00%)	96	7 (13.21%)	46	0.041
Depth of invasion					Sig
M	5 (3.60%)	134	8 (12.90%)	54	0.018
SM	21 (13.73%)	132	21 (29.17%)	51	0.006

female, menopausal female and male groups were 9.39%, 22.07 and 68.54% respectively. In addtion, the morbidity rate of EGC was negatively related to estrogen level. Estrogen may be a protective mechanism against cancer. Zhou et al. found that overexpression of estrogen receptor reduced the motility and invasion of gastric cancer cells probably by inhibiting cell growth and cancer progression [9].

The LNM rates of premenopausal female, menopausal female and male groups were 27.50%, 19.15% and 8.90% respectively. Moreover, the occurrence of LNM was positively related to estrogen level. Similarly, it has previously been reported that ER-α36 expression was highly correlated with LNM of gastric cancer [10].

Age was another crucial risk factor for EGC with LNM, but it also had a gender difference. The mean age of males was (62.40±10.43) years, and the median age was 63. Females had the mean age of 56.72± 13.68 and the median age of 59. The morbidity rate reached maximum at 60-65 years. The median ages of male and female patients with LNM were 62 and 54 years respectively, indicating that LNM occurred in females 8 years earlier than in males, i.e. age had a gender difference.

Depth of invasion is the most important risk factor [1, 3]. The LNM rate of the invasion to SM group significantly exceeded that of the invasion to M group. Meanwhile, this risk factor affected male and female patients differently, even at the same depth of invasion, i.e. the LNM rate of females significantly surpassed that of males.

Univariate analysis showed gender, age, location, tumor size, pathological type, Lauren classification and depth of invasion had significant differences. Multivariate analysis showed only gender, age and depth of invasion were independent risk factors for LNM in EGC. However, all the risk factors (gender, age, tumor size, pathological type and depth of invasion) had significant gender differences. Although the subgroups of risk factors including tumor location, macroscopic type and Lauren classification had no significant gender differences, the LNM rate of females was still higher than that of males.

The different levels of estrogen between males and females (even in premenopausal and menopausal females) may be attributed to the contradictory trends of morbidity and LNM rates. The mechanism remains largely unknown, but Daiva et al. found that females with *Helicobacter pylori* infection were more prone to gastric cancer than males [11]. Additionally, Kim et al. found that obesity (BMI 25 kg/m^2 or

greater but less than 30 kg/m^2) was associated with increased risk of EGC, and its effect on gastric cancer showed a gender difference [12]. Nevertheless, the mechanism for gender differences in EGC with LNM needs further research.

In conclusion, 12.91% of EGC cases had LNM. Gender of female, age and depth of tumor invasion were independent risk factors for LNM, all of which showed significant gender differences, males had a higher incidence rate of EGC than that of females but females had a higher LNM rate. The patients with risk factors mentioned above should receive standard D2 surgery [4, 13, 14] or ESD combined with laparoscopic lymphadenectomy [7].

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Disclosure of conflict of interest

None.

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