Differences in the prognosis of early gastric cancer according to sex and age

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Abstract

Background: Few studies have compared early gastric cancer (EGC) outcomes according to sex and age.

Methods: We retrospectively reviewed 2085 patients who underwent curative gastrectomy for EGC between 1989 and 2000. Prognosis and risk factors for nodal involvement were evaluated according to sex and age.

Results: Male sex and age were independent prognostic factors for overall survival (OS) but not relapse-free survival (RFS). In young (⩽55 years) patients, there were no significant differences in RFS and OS between men and women. However, older (>55 years) men had a poorer OS and older women had a poorer RFS. Young female patients had a higher proportion of gastric cancer-related death than young male patients. Female sex was an independent risk factor for nodal involvement in younger patients.

Conclusions: Young women with EGC should be more intensively treated and monitored than other patient groups and should not be treated by endoscopic resection.

Keywords: age, early gastric cancer, prognosis, sex

Introduction

Gastric cancer (GC) is the leading cause of cancer-related death worldwide [Ferlay *et al.* 2010]. The World Health Organization (WHO) classification of tumors and the Japanese Society of Gastroenterological Endoscopy defines early gastric cancer (EGC) by invasion that is confined to either the mucosa or the submucosa, irrespective of lymph node metastasis [Japanese Gastric Cancer Association, 2011a]. In North-Eastern Asia, EGC represents over 50% of all new GC cases [Fujii *et al.* 1999; Kim *et al.* 2006]. The survival of patients with EGC exceeds 90% in Japan and in some western countries [Adachi *et al.* 1997; Oliveira *et al.* 1998; Kubota *et al.* 2000].

Histopathologic type, tumor size, and depth of invasion have been recognized as predictors of lymph node metastasis [Folli *et al.* 2001; Popiela *et al.* 2002; Kim *et al.* 2014] and prognostic factors for GC [Noda *et al.* 1980; Ribeiro *et al.* 1981; Adachi *et al.* 2000]. According to the treatment guidelines of the Japanese Gastric Cancer Association, differentiated EGCs of ⩽2 cm in size with no ulceration and confined to the mucosal layer are indicators for endoscopic treatment [Japanese Gastric Cancer Association, 2011b]. Recently, Kim and colleagues reported that sex was a predictor for lymph node metastasis and that the histologic subtype profile varied according to the male-to-female ratio and mean age [Kim *et al.* 2014]. Because we were unable to find any previous reports on the impact of sex or age on the outcomes of EGC, we evaluated this in our current study.

Methods

We retrospectively evaluated 2085 nonmetastatic patients who underwent curative gastrectomy for EGC between 1989 and 2000 at Asan Medical Center, Seoul, Korea. All patients in our study received intensive lymphadenectomy (above D1 plus) according to the treatment guidelines of the Japanese Gastric Cancer Association [Japanese Gastric Cancer Association, 2011b]. Macroscopic (endoscopic) findings were analyzed in accordance with the Japanese Classification of Gastric Cancer [Japanese Gastric Cancer Association, 2011]. Gastric adenocarcinomas were classified

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into the following histopathologic types according to the WHO classification [Hamilton and Aaltonen, 2000]: papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma (SRC). Tubular adenocarcinoma was further classified as well differentiated (WD-TUB), moderately differentiated (MD-TUB), or poorly differentiated (PD-TUB) using the American Joint Committee on Cancer (AJCC) seventh edition TNM staging [Edge *et al.* 2010]. We reviewed the numeric data, including lymph node metastasis and patient prognosis, and examined the correlation between sex and age. Relapse-free survival (RFS) was defined as time from tumor resection to the earliest of the following outcomes: disease recurrence, last follow up without evidence of disease, or death without evidence of disease. Overall survival (OS) was defined as time from resection until death from any cause or last contact.

Numeric data were expressed as mean with standard deviation and analyzed using Student t tests. Risk factors were analyzed using the chi-squared test (univariate analysis) or a logistic regression model (multivariate analysis). Survival data were analyzed using the Kaplan–Meier method with the log-rank test (univariate analysis) or Cox proportional hazards regression (multivariate analysis). All statistical data were analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL). A p value of 0.05 was considered statistically significant. This study received institutional review board approval (protocol number 2012-0032).

This study received IRB approval (protocol number; 2012-0032). Informed consent was exempted by the IRB.

Results

General clinicopathologic characteristics were summarized in Table 1. All patients underwent curative resection with lymph node dissection. Of the 2085 patients evaluated in this study, 1369 (65.7%) were men and 716 (34.3%) were women. Male patients tended to be older and female patients tended to have a larger tumor size. A larger proportion of female patients had PD-TUB and SRC. In addition, female patients had more lymph node metastases than male patients and cancer stages were higher in the women subjects.

Evaluation of prognostic factors

Male sex, older age, lymph node metastasis, deeper tumor invasion, and histologic subtypes were found to be independent prognostic factors for OS using the Cox proportional hazard model (Table 2) However, lymph node metastasis was the only prognostic factor for RFS in this model (Table 2).

Evaluation of prognostic factors according to sex and age

We further found that prognostic factors differed according to sex and age (Tables 3 and 4). Age, lymph node metastasis, depth of invasion, and histologic subtype were prognostic factors in men (Table 3) but depth of invasion and histologic subtype did not influence prognosis in women. Tumor size and lymph node metastasis were prognostic factors in younger (⩽55 years) patients (Table 4). However, sex, lymph node metastasis, depth of invasion, and histologic type were prognostic factors in older (>55 years) patients. Of these factors, lymph node metastasis had the largest odds ratio (Tables 3 and 4).

Evaluation of survival according to sex and age

Figure 1 shows the relationship between the OS (A) and RFS (B) outcomes and the sex of the GC patient. Men had a poorer OS ($p < 0.05$) but there was no significant difference between the RFS of men and women ($p > 0.05$). Figure 2 indicates the association between the OS (A) and RFS (B) and age in our GC cohort. Older (>55 years) patients had a poorer OS ($p < 0.05$) but there was no significant difference between found in the RFS between younger (⩽55 years) and older (>55 years) patients ($p > 0.05$). The OS was also similar between younger men and younger women (Figure 3A). However, younger women had a poorer RFS (Figure 3B) and older men had poorer OS (Figure 4A, $p < 0.05$). The RFS rate was similar between older men and older women (Figure 4B, $p > 0.05$).

We additionally evaluated the causes of death in our GC series. During the study period, 350 of the male patients in our cohort died: 53 (15.1%) due to GC progression, 249 (71.3%) from a GC-unrelated cause, and 47 (13.4%) of an unknown cause. In the case of the female patients during the study period, 128 died in total: 31

Table 1. Clinicopathologic characteristics of all patients.

Characteristics	Number (n = 2085)	Percentage (%)	Mean ± SD
Gender			
Male	1369	66.7	
Female	716	34.3	
Age, years	2085	100	54.8 ± 11.5
Location of tumor			
Lower third	1270	60.9	
Middle third	631	30.3	
Upper third	184	8.8	
Tumor size (mm)	2085	100	30.5 ± 19.1
Retrieved lymph node	2085	100	25.0 ± 12.7
Gastrectomy			
Subtotal	1850	88.7	
Total	235	11.3	
Depth of invasion			
Mucosa	1033	49.5	
Submucosa	1052	50.5	
Macroscopic finding			
Superficial	1752	84.0	
Protruded	119	5.7	
Excavated	214	10.3	
Histopathologic type			
Papillary adenocarcinoma	8	0.4	
Tubular adenocarcinoma	1705	81.8	
Well differentiated	480	23.0	
Moderately differentiated	574	27.5	
Poorly differentiated	651	31.2	
Signet ring cell carcinoma	345	16.5	
Mucinous adenocarcinoma	26	1.2	
Lymph node metastasis			
No	1829	87.7	
Yes	256	12.3	
Tumor recurrence			
No	1990	95.4	
Yes	95	4.6	
Stage			
I	1829	87.7	
II	156	7.5	
III	75	3.6	
IV	25	1.2	
Adjuvant chemotherapy			
No	1963	94.1	
Yes	122	5.9	

SD, standard deviation.

(24.2%) of GC progression, 81 (63.3%) of a GC-unrelated cause, and 16 (12.5%) from an unknown cause. Younger female patients had a higher proportion of GC-related deaths than younger male patients (Figure 5A). However, there was a similar proportion of GC-related

Table 2. Multivariate analysis of factors influencing survival using a cox proportional hazards model.

Characteristics	OS		RFS	
	Hazards ratio (95% CI)	*p* value		
Sex				
Male	1		1	
Female	0.65 (0.53–0.80)	<0.05	0.93 (0.62–1.44)	NS
Age, years				
⩽50	1		1	
>50	0.55 (0.38–0.79)	<0.05	1.29 (0.84–1.98)	NS
Tumor size				
⩽3 cm	1		1	
>3 cm	1.13 (1.42–2.37)	NS	0.83 (0.53–1.27)	NS
Lymphovascular invasion				
No	1		1	
Yes	1.17 (0.87–1.57)	NS	1.62 (0.95–2.77)	NS
Lymph node metastasis				
No	1		1	
Yes	1.84 (1.42–2.37)	<0.05	6.25 (3.94–10.01)	<0.05
Depth of invasion				
Mucosa	1		1	
Submucosa	1.28 (0.04–1.57)	<0.05	1.67 (0.98–1.27)	NS
Histology				
WD-TUB	1		1	
MD-TUB	0.74 (0.58–0.95)	<0.05	0.59 (0.32–1.10)	NS
PD-TUB	0.88 (0.63–1.12)	NS	0.69 (0.38–1.24)	NS
SRC	0.55 (0.38–0.79)	<0.05	0.72 (0.34–1.54	NS

CI, confidence interval; MD-TUB, moderately differentiated tubular adenocarcinoma; NS, nonspecific; PD-TUB, poorly differentiated tubular adenocarcinoma; SRC, signet ring cell carcinoma; WD-TUB, well-differentiated tubular adenocarcinoma.

deaths among older male and older female patients (Figure 5B, $p > 0.05$).

Risk factors for lymph node metastasis in GC patients according to sex and age

In our present study, we found that lymph node metastasis was the most important prognostic factor (Table 2). We further found that female sex, larger tumor size, deeper tumor invasion, and lymphovascular invasion were independent risk factors for lymph node metastasis in a logistic regression model (Table 5). We evaluated risk factors according to sex (Table 6) and found that all categories, except histologic types, were risk factors for lymph node metastasis in men. In women, however, tumor size was excluded and histologic type was added to the risk factors. Female sex, large tumor size, lymphovascular invasion, submucosal cancer, and PD-TUB were identified as independent risk factors for lymph node metastasis in younger patients (Table 7). However, sex was not a risk factor in older patients.

Discussion

As has been well established previously [Kitamura *et al.* 1997; Katai *et al.* 2000; Roviello *et al.* 2006; Kim *et al.* 2014], lymph node metastasis was the most important risk factor for survival outcomes in our current study. However, it was not determined to be a risk factor for survival among the female GC patients in our analysis. The survival of patients with EGC confined to the mucosa is usually better than that of patients with EGC confined to the submucosa [Folli *et al.* 1995; Pertl *et al.* 1999; Saragoni *et al.* 2000; Popiela *et al.* 2002]. In contrast, some authors have reported

Table 3. Multivariate analysis of factors influencing survival using a cox proportional hazards model.

Characteristics	Male		Female	
	Hazards ratio	*p* value	Hazards ratio	*p* value
Age				
⩽55	1		1	
>55	4.46 (3.95–5.87)	<0.05	2.9 (1.53–3.45)	<0.05
Tumor size				
⩽3 cm	1		1	
>3 cm	1.15 (0.92–1.44)	NS	1.15 (0.80–1.65)	NS
Lymphovascular invasion				
No	1		1	
Yes	1.39 (0.99–1.99)	NS	0.72 (0.35–1.32)	NS
Lymph node metastasis				
No	1		1	
Yes	1.34 (0.96–1.84)	NS	3.33 (2.14–5.04)	<0.05
Depth of invasion				
Mucosa	1		1	
Submucosa	1.35 (1.06–1.71)	<0.05	1.11 (0.78–1.72)	NS
Histology				
WD-TUB	1		1	
MD-TUB	0.73 (0.53–0.92)	<0.05	0.95 (0.54–1.69)	NS
PD-TUB	0.83 (0.63–1.10)	NS	1.01 (0.61–1.68)	NS
SRC	0.50 (0.39–0.83)	<0.05	0.69 (0.37–3.45)	NS

NS, nonspecific; MD-TUB, moderately differentiated tubular adenocarcinoma; PD-TUB, poorly differentiated tubular adenocarcinoma; SRC, signet ring cell carcinoma; WD-TUB, well-differentiated tubular adenocarcinoma.

that depth of infiltration does not influence long-term outcome in patients with EGC [Baba *et al.* 1995; Jentschura *et al.* 1997; Tsujitani *et al.* 1999; Piso *et al.* 2001]. Popiela and colleagues [Popiela *et al.* 2002] showed that age was an independent prognostic factor for EGC, which has not been consistently reported by others [Baba *et al.* 1995; Folli *et al.* 1995; Everett and Axon, 1997]. These discrepancies could depend on whether OS or disease-related survival is analyzed. In our current study, age was not found to be an independent risk factor for OS but was for RFS. However, there have been some conflicting results regarding other prognostic factors, and undifferentiated, diffuse, and larger tumors have been associated with poor survival outcomes [Hioki *et al.* 1990; Inoue *et al.* 1991; Baba *et al.* 1995; Everett and Axon, 1997; Jentschura *et al.* 1997; Ishigami *et al.* 1999; Pertl *et al.* 1999; Saragoni *et al.* 2000]. We found in our present analysis that the prognostic factors differed according to the sex and age of the GC patients. It is well known that older men have a poorer OS than older women because they generally have more comorbidities than similarly aged women [Lim *et al.* 2014; Lee *et al.* 2016]. In our present study, the men indeed had a poorer OS than the women. However, we found no statistically significant difference between the RFS of the men and women in our GC cohort.

The prime consideration for EGC treatment is whether the patient has a lymph node metastasis. EGC with lymph node metastasis, or a probability of lymph node metastasis, should not be treated using endoscopic resection. Hence, many studies attempted to predict a nodal involvement for EGC and reported that the presence of a nodal involvement is related to submucosal invasion, tumor size, poor differentiation, and lymphatic invasion [Maehara *et al.* 1992; Folli *et al.* 1995; Seto *et al.* 1997; Hochwald *et al.* 1999; Saragoni *et al.* 2000]. The Japanese Gastric Cancer Association thus recommended that endoscopic resection be indicated as the standard treatment for the following tumor type: a differentiated adenocarcinoma without ulcerative findings, with a depth of invasion clinically diagnosed as T1a and a diameter of ⩽2 cm

Table 4. Multivariate analysis of factors influencing survival using a cox proportional hazards model.

Characteristics	⩽ 55 years		> 55 years	
	Hazards ratio	*p* value	Hazards ratio	*p* value
Sex				
Male	1		1	
Female	1.03 (0.68–1.55)	NS	0.54 (0.42–0.69)	<0.05
Tumor size				
⩽3 cm	1		1	
>3 cm	1.55 (1.03–2.28)	<0.05	1.02 (10.7–1.27)	NS
Lymphovascular invasion				
No	1		1	
Yes	1.12 (0.62–2.02)	NS	1.17 (0.83–1.65)	NS
Lymph node metastasis				
No	1		1	
Yes	2.97 (1.86–4.75)	<0.05	1.45 (1.07–1.98)	<0.05
Depth of invasion				
Mucosa	1		1	
Submucosa	1.43 (0.93–2.21)	NS	1.26 (1.00–1.59)	NS
Histology				
WD-TUB	1		1	
MD-TUB	0.64 (0.34–1.20)	NS	0.76 (0.58–0.99)	<0.05
PD-TUB	0.71 (0.40–1.27	NS	0.93 (0.71–1.22)	NS
SRC	0.63 (0.32–1.55)	NS	0.54 (0.42–0.69)	<0.05

NS, nonspecific; MD-TUB, moderately differentiated tubular adenocarcinoma; PD-TUB, poorly differentiated tubular adenocarcinoma; SRC, signet ring cell carcinoma; WD-TUB, well-differentiated tubular adenocarcinoma.

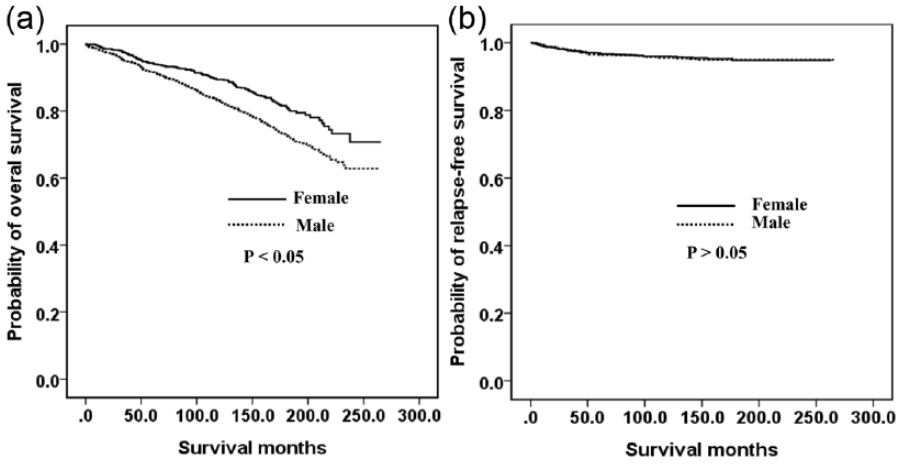

Figure 1. Kaplan–Meier survival curves according to sex: (a) overall survival; (b) relapse-free survival.

[Japanese Gastric Cancer Association, 2011]. In our current study, we found that the risk of nodal metastasis for EGC differed according to sex and age. Female sex was identified as an independent risk factor for lymph node metastasis. In addition, an age younger than 55 years was found to be a risk factor for lymph node metastasis in women (odds ratio, 2.27). We think the reasons young females could be a prognostic factor in GC are as follows; first, females had larger

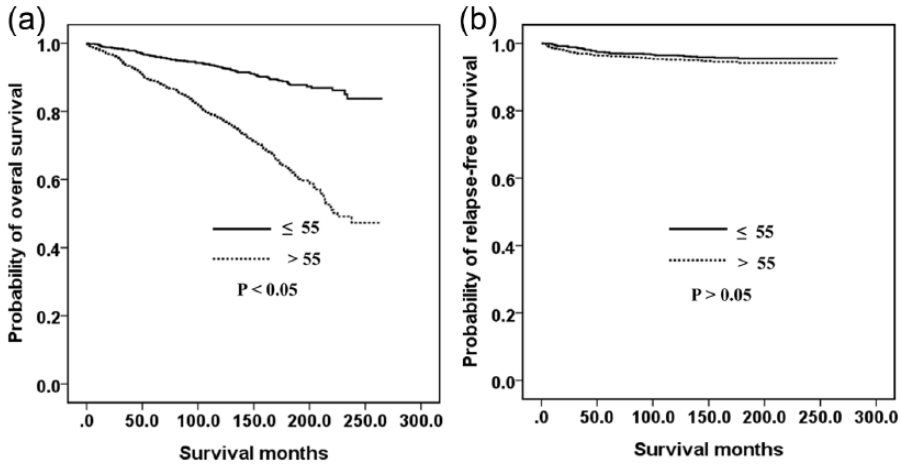

Figure 2. Kaplan–Meier curves according to according to age: (a) overall survival; (b) relapse-free survival.

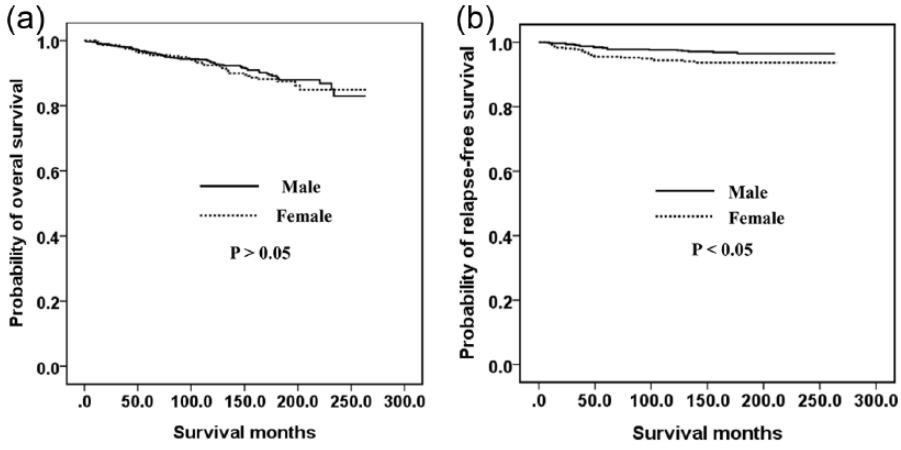

Figure 3. Kaplan–Meier survival curves according to sex in younger patients (⩽55 years): (a) overall survival; (b) relapse-free survival.

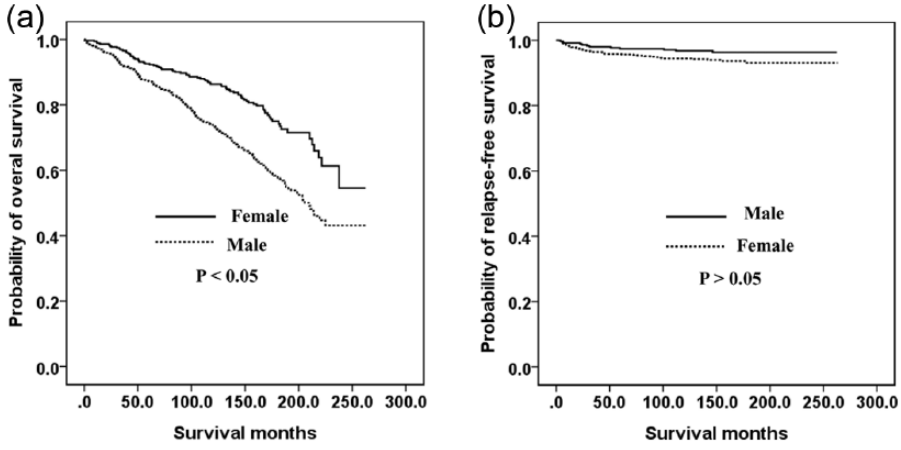

Figure 4. Kaplan–Meier survival curves according to sex in older patients (>55 years): (a) overall survival; (b) relapse-free survival.

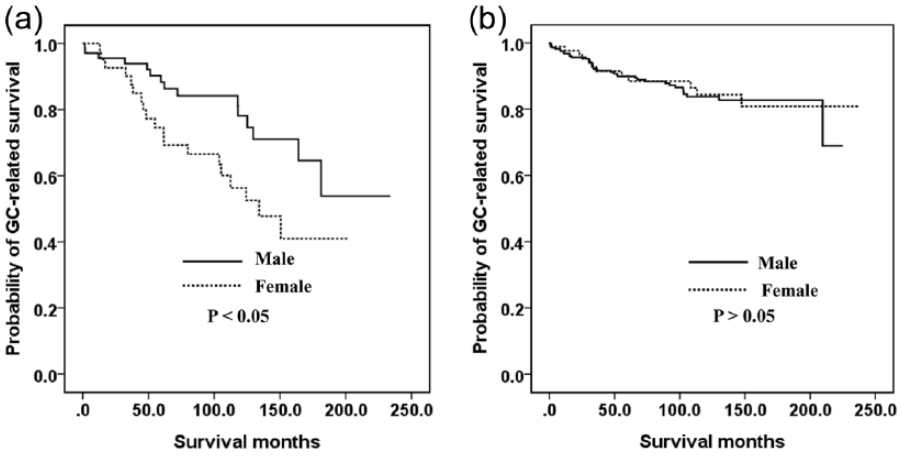

Figure 5. Kaplan–Meier survival curves for gastric cancer-related survival: (a) in younger patients (⩽55 years); (b) in older patients (>55 years).

Table 5. Analysis of lymph node metastasis using the chi-square test and a logistic regression model.

Characteristics	Univariate		Multivariate	
	Number (%)	*p* value	Odds ratio (95% CI)	*p* value
Sex		<0.05		
Male (*n* = 1,369)	606			
Female (*n* = 716)	110		1.44 (1.07–1.94)	<0.05
Tumor size		<0.05		
⩽3 cm (*n* = 1,039)	111			
>3 cm (*n* = 779)	145		1.71 (1.28–2.30)	<0.05
Lymphovascular invasion		<0.05		
No (*n* = 1,887)	176			
Yes (*n* = 198)	80		3.79 (2.29–5.42)	<0.05
Depth of invasion		<0.05		
Mucosa (*n* = 1,033)	38			
Submucosa (*n* = 1,052)	218		4.43 (3.04–6.47)	<0.05
Histology		<0.05		
WD-TUB (*n* = 480)	25			
MD-TUB (*n* = 574)	74		1.38 (0.83–2.29)	NS
PD-TUB (*n* = 651)	118		2.20 (1.37–3.54)	<0.05
SRC (*n* = 345)	31		1.46 (0.85–2.06)	NS

CI, confidence interval; NS, nonspecific; MD-TUB, moderately differentiated tubular adenocarcinoma; PD-TUB, poorly differentiated tubular adenocarcinoma; SRC, signet ring cell carcinoma; WD-TUB, well-differentiated tubular adenocarcinoma.

tumors and a higher proportion in disuse type, PD-TUB and SRC than males ($p < 0.05$). Second, females had a lower proportion in WD-TUB or MD-TUB. Likewise, in younger patients, females had larger tumors and a higher proportion in diffuse type, PD-TUB and SRC than males ($p < 0.05$). In addition, females had a lower proportion in WD-TUB or MD-TUB in younger patients ($p < 0.05$). The odds ratio of this group was higher than that of the tumor size or depth of invasion categories. We contend therefore that women younger than 55 years with EGC would not be indicated for endoscopic resection.

Table 6. Analysis of lymph node metastasis according to sex using a logistic regression model.

Characteristics	Male		Female	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Tumor size				
⩽3 cm	1		1	
>3 cm	2.07 (1.41–3.02)	<0.05	1.34 (0.85–2.11)	NS
Lymphovascular invasion				
No	1		1	
Yes	4.10 (2.62–6.40)	<0.05	3.42 (1.86–6.27)	<0.05
Depth of invasion				
Mucosa	1		1	
Submucosa	4.48 (2.67–7.52)	<0.05	4.51 (2.58–7.86)	<0.05
Histology				
WD-TUB		1	1	
MD-TUB	1.31 (0.72–2.39)	NS	1.14 (0.59–3.79)	NS
PD-TUB	1.69 (0.93–6.05)	NS	3.19 (1.37–7.45)	<0.05
SRC	1.58 (0.75–3.59)	NS	1.58 (0.61–4.11)	NS

CI, confidence interval; NS, nonspecific; MD-TUB, moderately differentiated tubular adenocarcinoma; PD-TUB, poorly differentiated tubular adenocarcinoma; SRC, signet ring cell carcinoma; WD-TUB, well-differentiated tubular adenocarcinoma.

Table 7. Analysis of lymph node metastasis using a logistic regression model according to age.

Characteristics	⩽55 years		>55 years	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Sex				
Male	1	<0.05	1	
Female	2.27 (1.42–3.30)		0.98 (0.64–1.52)	NS
Tumor size				
⩽3 cm	1	<0.05	1	
>3 cm	1.92 (1.27–2.90)		1.61 (1.06–2.43)	<0.05
Lymphovascular invasion				
No	1	<0.05	1	
Yes	4.01 (2.35–6.86)		3.66 (2.24–5.98)	<0.05
Depth of invasion				
Mucosa	1	<0.05	1	
Submucosa	2.17 (1.42–3.30)1		5.12 (2.85–9.17)	<0.05
Histology				
WD-TUB	1	NS	1	
MD-TUB	2.70 (0.99–7.32)	<0.05	0.95 (0.51–1.77)	NS
PD-TUB	2.71 (1.02–7.14)	NS	2.17 (1.22–3.85)	<0.05
SRC	2.99 (0.83–6.64)		0.86 (0.22–2.29)	NS

CI, confidence interval; NS, nonspecific; MD-TUB, moderately differentiated tubular adenocarcinoma; PD-TUB, poorly differentiated tubular adenocarcinoma; SRC, signet ring cell carcinoma; WD-TUB, well-differentiated tubular adenocarcinoma.

There are some limitations of this study. First, this is a retrospective analysis, and we evaluated data from electronic medical records (EMRs). Second, we did not evaluate data for chemotherapy because the aim of this study was to confirm that sex and age influence survival and lymph node metastasis, and that sex and age could be categories of EMR/ESD treatment for EGC (T1) patients at the time of diagnosis. Third, we adopted two systems; treatment guidelines and macroscopic (endoscopic) findings were classified according to the JGCA guidelines [Japanese Gastric Cancer Association, 2011] because there are no macroscopic (endoscopic) classifications and treatment guidelines for EGC in the AJCC TNM system. Others, including pathologic factors, were classified according to AJCC TNM 7th edition or WHO.

In conclusion, male sex and age are independent prognostic factors for OS but not for RFS in GC patients. In younger patients ($\leqslant$55 years), there is no significant difference between the RFS and OS outcome of men and women with GC. However, older men have a poorer OS and older women (>55 years) have a poorer RFS. In addition, younger female GC patients have a higher proportion of GC-related deaths than younger male patients. We found from our current analysis that female sex is an independent risk factor for nodal involvement in younger GC patients. Hence, young women with EGC should be more intensively treated and monitored than other patient groups with GC and should not be treated by endoscopic resection.

Ethical Standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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