Original Article

Comparable prognosis of early gastric cancer between intestinal type and diffuse type in patients of age 75 and older: a SEER-based cohort study

Ping Yin[1#], Rencheng Cai[2#], Xiaohua Zhou[3#], Xuemin Yao[4], Qiufen Yang[4], Yuehong Jin[4], Xuehua Jiao[5], Chengjie Lu[6], Zhenguo Qiao[4]

[1]Department of Traditional Chinese Medicine, Wujiang Fifth People's Hospital, Suzhou, China; [2]Department of Geriatrics, Gaochun People's Hospital, Nanjing, China; [3]Department of General Surgery, Gaochun People's Hospital, Nanjing, China; [4]Department of Gastroenterology, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, Suzhou, China; [5]Department of Endocrinology, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, Suzhou, China; [6]Department of Traditional Chinese Medicine, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, Suzhou, China

Contributions: (I) Conception and design: C Lu, Z Qiao; (II) Administrative support: X Zhou; (III) Provision of study materials or patients: R Cai; (IV) Collection and assembly of data: Y Jin, X Yao; (V) Data analysis and interpretation: Q Yang, X Jiao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Chengjie Lu, MD. Department of Traditional Chinese Medicine, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, No. 2666 Ludang Road, Suzhou 215200, China. Email: patzhifeiji@163.com; Zhenguo Qiao, MD. Department of Gastroenterology, Suzhou Ninth People's Hospital, Suzhou Ninth Hospital Affiliated to Soochow University, No. 2666 Ludang Road, Suzhou 215200, China. Email: qzg66666666@163.com.

Background: The prognostic significance of Lauren's classification in elderly early gastric cancer (EGC) patients remains largely unknown. We aim to investigate the characteristics and clinical implications of Lauren's classification in elderly EGC patients.

Methods: Patients were collected from the Surveillance, Epidemiology, and End Results (SEER) database based on the inclusion and exclusion criteria. Univariate and multivariate Cox regression, propensity score matching, inverse-probability-weighted analysis, and propensity-score adjustment were utilized to evaluate the association between Lauren's classification and cancer-specific survival (CSS) in elderly EGC patients. Stratification and interaction analyses were used to reveal the effects of confounding factors on the association between Lauren's classification and CSS.

Results: The diffuse type (median, 41.0 months) showed a similar survival (37.0 months), and was mainly distributed in female group (62.5% *vs.* 42.2%) with poorly differentiated or undifferentiated components (89.1% *vs.* 27.0%) compared with intestinal type in elderly EGC patients. Analyses of univariate and multivariate Cox regression, propensity score matching, inverse-probability-weighted analysis, and propensity-score adjustment showed that Lauren's classification was not significantly CSS in elderly EGC patients (P>0.05). Subgroup and interaction analyses confirmed the stability of the results.

Conclusions: Diffuse type was mainly distributed in female patients with more poorly differentiated/undifferentiated components and similar prognosis compared with intestinal type in age 75 and older EGC patients. No significant association was observed between diffuse type and CSS of the elderly EGC patients.

Keywords: Early gastric cancer (EGC); Lauren classification; prognosis; Surveillance, Epidemiology, and End Results database (SEER database)

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Introduction

Gastric cancer (GC) is one of the most prevalent malignancies, remaining the fifth leading cause of cancer-related death (1). Since most of the patients are diagnosed at advanced stages, the 5-year survival rate of this malignancy remains <30% (2). However, if early gastric cancer (EGC) is diagnosed and then undergo curative resection, the 5-year survival rate can be >95% (3). Therefore, it is rather meaningful to diagnose and resect EGC to improve the prognosis of GC.

More than a third of new GC cases are patients aged 75 years and older (4). Several previous studies have reported that elderly GC patients often show a poorer survival than that of younger patients (5,6). Notably, studies have also found that the overall survival of elderly patients is significantly worse than that of younger patients after gastrectomy (7,8). This is partly caused by the fact that older age is closely associated with more organ dysfunction, longer hospitalization duration, and poorer nutrition (7). In recent years, endoscopic resection has been wildly practiced in the minimally invasive treatment of EGC, which shows comparable prognosis, fewer complications, and shorter hospitalization time compared with surgical resection (9,10). This indicates that endoscopic resection may be more suitable and benefitable for elderly EGC patients. Therefore, it is essential to reveal risk factors that may be associated with differential prognosis to unveil endoscopic-resection candidates in elderly EGC patients.

The histological classification proposed by Lauren, including intestinal type and diffuse type, is commonly used for prognostic prediction of GC (11). According to previous reports, the diffuse type is more common in younger GC patients, and associated with a worse prognosis than the intestinal type (12,13). Recent several studies have revealed that the prognostic significance of Lauren's classification is varied in patients of different ages and T stages. For example, Tang *et al.* found that diffuse type was a protective factor of prognosis in early-onset EGC patients [hazard ratio (HR): 0.64; 95% confidence interval (CI), 0.50 to 0.83] (14). Li *et al.* reported that diffuse type was not significantly associated with cancer-specific survival (CSS) in EGC patients (HR: 0.95; 95% CI, 0.77 to 1.18) (15). Interestingly, Tanaka *et al.* revealed that diffuse type was an independent risk factor for overall survival in advanced GC patients (HR: 2.40; 95% CI, 1.30 to 4.49) (16). However, the prognostic implications of Lauren's classification in elderly EGC patients remain largely unknown.

In the present study, we investigated the characteristics of different Lauren's classifications in elderly EGC patients. We also explored the effect size of Lauren's classification on the prognosis in elderly EGC patients, which may provide evidence for the precision treatment of elderly EGC patients. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1681/rc).

Highlight box

Key findings

- Endoscopic resection may be a better choice for elderly patients at or over 75 years old with early gastric cancer (EGC), especially those who cannot tolerate surgery.

What is known and what is new?

- The incidence of elderly patients with gastric cancer is increasing, and there are few data on the treatment and prognosis of gastric cancer in patients over 75 years old. Lauren's classification is wildly used in predicting prognosis of gastric cancer (GC). However, the prognostic implications of Lauren's classification in elderly EGC patients remain largely unknown.
- Our study was designed to assess treatment patterns and prognosis in this segment of old patients (≥75 years) with gastric cancer. Our objective was to investigate the characteristics and clinical implications of Lauren's classification in elderly EGC patients.

What is the implication, and what should change now?

- Our results were somewhat different from previous study. We found that diffuse type was mainly distributed in female patients with more poorly differentiated/undifferentiated components and similar prognosis compared with intestinal type in age 75 and older EGC patients. Therefore, endoscopic resection may be suitable for both diffuse and intestinal type in elderly EGC patients. This has certain significance for guiding clinical treatment.

Methods

Patients

This study is a retrospective cohort study. The study was performed following the Declaration of Helsinki (revised in 2013). Patients with EGC were collected from the Surveillance, Epidemiology, and End Results (SEER) database via SEER*Stat software (version 8.3.9; www.seer.cancer.gov). Since the SEER database is available publicly with de-identified data, informed consent or institutional review was not required.

Patients with GC from 2004 to 2017 were included in this study in accordance with previous reports (N=92,554). The following patients were excluded: (I) GC was not the

first diagnosed primary tumor (N=22,618); (II) surgery status unknown or without positive pathology or without tumor (N=39,318); (III) other pathological types except intestinal or diffuse type (N=7,965); (IV) no complete dates of follow-up were available (N=3,253); (V) death with unknown reasons (N=254); (VI) age younger than 75 years old (N=13,905); (VII) not EGC with metastasis (N=3,887). In the current study, EGC was defined as GC invading no more deeply than the submucosa, irrespective of lymph node metastasis as described before (17,18). The intestinal type included histologically diagnosed carcinoma [not otherwise specified (NOS); M8010], adenocarcinoma (NOS; M8140), tubular (M8211), and intestinal type (M8144), and diffuse type consisted of signet-ring cell carcinoma (M8490), diffuse carcinoma (M8145), and linitis plastica (M8142) (15).

Variables and outcomes

The following clinical and pathological variables were retrieved from the SEER database: age, sex, race, T stage, N stage, tumor size, regional nodes examined, year of diagnosis, primary site, strategy of operation, radiotherapy, chemotherapy, and marital status. The age was classified into two groups of <85 and ≥85 years. The race was divided into five groups: White, Asian or Pacific Islander, Black, American Indian/Alaska Native, and Unknown. T stage was recorded as T1a (mucosa), T1b (submucosa), and T1NOS. N stage was classified into six groups: N0, N1, N2, N3a, N3b, and NX based on the American Joint Committee on Cancer (AJCC) 7th Edition of Gastric Cancer. Tumor size consisted of five groups, including T ≤2, 2< T ≤3, 3< T ≤5, T >5, and Unknown. Regional nodes examined were classified into <15, ≥15, and Unknown groups according to previous reports (15). Year of diagnosis was recorded as 2004–2007, 2008–2011, 2012–2015, and 2016–2017. Primary tumor site was classified into nine groups: cardia, fundus of stomach, lesser curvature of stomach, greater curvature of stomach, body of stomach, gastric antrum, pylorus, stomach (NOS), and overlapping lesion of stomach. The primary outcome was the CSS, which was defined as death caused by EGC. Patients were recorded as censored with alive at the latest follow-up date.

Statistical analyses

For categorical variables, data were presented with frequencies and percentages. For continuous variables with Gaussian distribution, data were presented with the mean and the standard deviation. For continuous variables with non-normal distribution, the median and interquartile range were utilized. For data comparison in different groups, the Student's *t*-test was used for continuous variables with Gaussian distribution, the nonparametric Kruskal-Wallis rank-sum test was implemented for continuous variables with non-normal distribution, and the chi-squared test was utilized for categorical variables. Kaplan-Meier analysis was used for time-event data, and compared with a log-rank test.

The association between the included variables and CSS was evaluated with univariable Cox proportional-hazards regression. To adjust potential confounders, a multivariable Cox regression model was used to evaluate the independent association between Lauren's classification and CSS including all the potential confounders. In consideration of the unbalanced sample size of the intestinal and diffuse group, propensity-score methods were used to control the effects of potential confounders. The propensity of different Lauren's classifications was calculated with a multivariable logistic regression model including all the potential confounders. Three propensity-score methods were used to evaluate the independent effect of Lauren's classification on CSS with the Cox regression model. The first method was propensity-score matching, and the nearest-neighbor method was used to establish 1:1 matched samples. The second was inverse-probability-weighted analysis by using stabilized inverse-probability-weighting weight according to previous reports. The third was propensity-score adjustment by setting the propensity score as a covariate to be adjusted in the multivariable Cox regression model.

In addition, subgroup and interaction analyses were used to evaluate the association between Lauren's classification and CSS in different ages, sexes, tumor sizes, T stages, N stages, and grades to validate the stability of the effect size. All the missing data were presented as a separate group in all the variables, and combined to a similar effect-size group when conducting subgroup analysis. All the statistical analyses were performed using R statistical software (version 4.1.2, The R Foundation) with R studio (version 2022.02.0, https://www.rstudio.com). The statistical significance was set with a two-sided P<0.05.

Results

Baseline characteristics in elderly patients with EGC

After exclusion as described above, 1,354 EGC patients with age 75 years and older were included in the present analysis (*Figure 1*). Among these patients, 1,170 patients

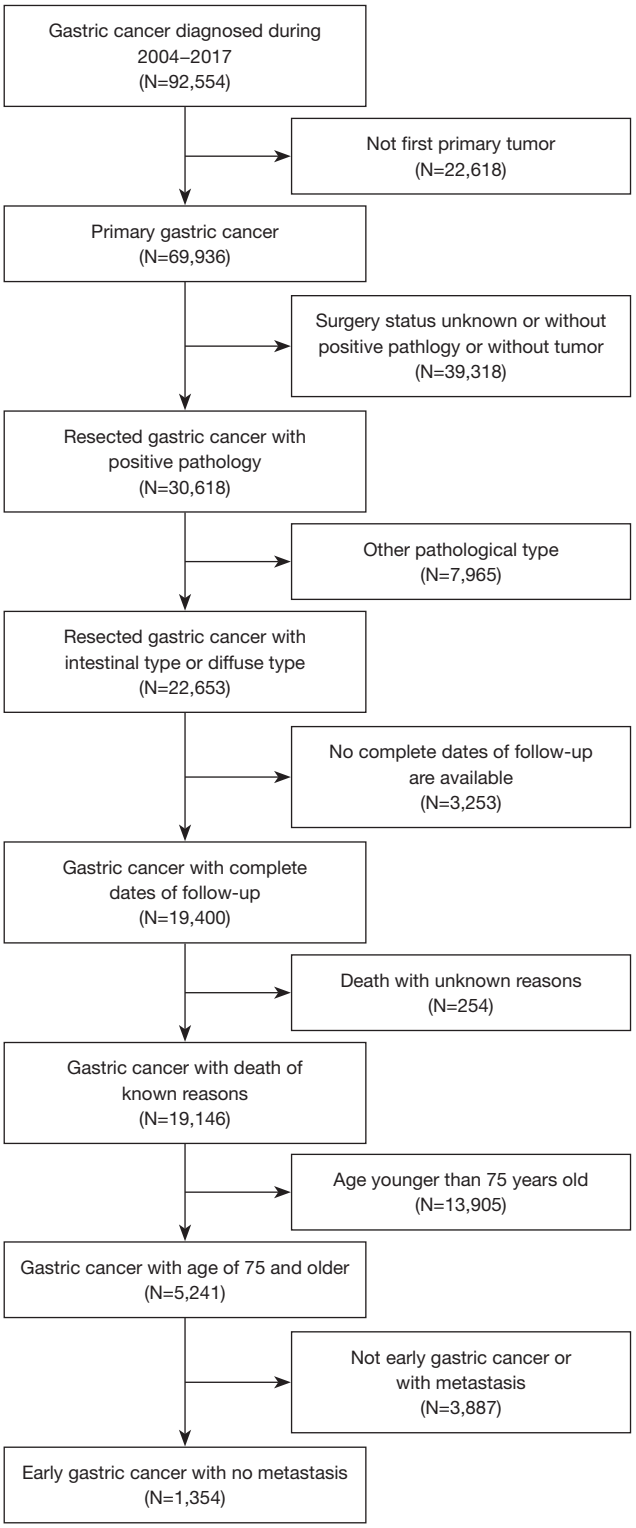

Figure 1 Flowchart of selection of EGC patients of age 75 and older with intestinal type or diffused type in the SEER database. EGC, early gastric cancer; SEER, Surveillance, Epidemiology, and End Results.

were intestinal-type EGC and 184 were diffuse type. The diffuse type (41.0, interquartile range, 10.8–76.5 months) showed a similar survival compared with intestinal type (37.0, interquartile range, 14.0–71.0 months; P=0.978; *Table 1*). The diffuse type was mainly distributed in female group (62.5% *vs.* 42.2%), and was more commonly located in lesser curvature (15.2% *vs.* 10.4%), body of stomach (17.4% *vs.* 12.7%), pylorus (7.6% *vs.* 2.3%) compared with intestinal type (*Table 1*). The poorly differentiated or undifferentiated EGC accounted for 89.1% in diffuse type, but this proportion was only 27.0% in intestinal type (*Table 1*). More patients with diffuse type accepted surgical resection (92.9% *vs.* 79.6%) and chemotherapy (12.5% *vs.* 7.0%) compared with intestinal type (*Table 1*). Other variables including age, year of diagnosis, T stage, N stage, radiotherapy, tumor size, race, regional nodes examined, and marital status showed no statistical significance in the intestinal and diffuse group (*Table 1*). Collectively, although diffuse-type EGC showed a higher percentage of poorly differentiated or undifferentiated compartments, the stage and survival of diffuse-type EGC were comparable to those of intestinal type in age 75 years and older patients.

Survival analysis between intestinal and diffuse type EGC

Firstly, Kaplan-Meier curves were used to perform survival analysis. In the total cohort, the overall survival rate was comparable in intestinal-type and diffuse-type patients (*Figure 2A*, P=0.65). The CSS rate was also similar in intestinal-type and diffuse-type patients (*Figure 2B*, P=0.4). In different subgroups, the diffuse type exhibited comparable CSS with intestinal type in different stratification factors of tumor size, T stage, and N stage (*Figure 3*, P>0.05). These results validated that the survival of diffuse type was in common with that of intestinal type in age 75 years and older EGC patients.

The association between Lauren's classification and CSS

Initially, we analyzed the association of Lauren's classification and CSS with univariable Cox regression. The results of univariable regression analysis showed that age (P<0.001), year of diagnosis (2012–2015; P<0.001), gastric antrum (P<0.001), poorly differentiated or undifferentiated (P=0.002), T stage (P<0.001), N stage (P<0.05), radiotherapy (P=0.040), tumor size (P<0.05), Asian or Pacific Islander (P<0.001), and regional nodes examined (≥15; P=0.004) were associated with CSS (*Table 2*).

Table 1 Baseline characteristics of the included patients

Characteristics	All patients (N=1,354)	Intestinal (N=1,170)	Diffuse (N=184)	P value
Age				0.728
<85 years	1,051 (77.6)	910 (77.8)	141 (76.6)	
≥85 years	303 (22.4)	260 (22.2)	43 (23.4)	
Sex				<0.001
Male	745 (55.0)	676 (57.8)	69 (37.5)	
Female	609 (45.0)	494 (42.2)	115 (62.5)	
Year of diagnosis				0.87
2004–2007	420 (31.0)	366 (31.3)	54 (29.3)	
2008–2011	369 (27.3)	320 (27.4)	49 (26.6)	
2012–2015	378 (27.9)	322 (27.5)	56 (30.4)	
2016–2017	187 (13.8)	162 (13.8)	25 (13.6)	
Primary site				<0.001
Cardia	287 (21.2)	278 (23.8)	9 (4.9)	
Fundus of stomach	37 (2.7)	30 (2.6)	7 (3.8)	
Lesser curvature of stomach	150 (11.1)	122 (10.4)	28 (15.2)	
Greater curvature of stomach	58 (4.3)	46 (3.9)	12 (6.5)	
Body of stomach	181 (13.4)	149 (12.7)	32 (17.4)	
Gastric antrum	433 (32.0)	383 (32.7)	50 (27.2)	
Pylorus	41 (3.0)	27 (2.3)	14 (7.6)	
Stomach, NOS	110 (8.1)	91 (7.8)	19 (10.3)	
Overlapping lesion of stomach	57 (4.2)	44 (3.8)	13 (7.1)	
Grade				<0.001
Moderately differentiated or well differentiated	720 (53.2)	714 (61.0)	6 (3.3)	
Poorly differentiated or undifferentiated	480 (35.5)	316 (27.0)	164 (89.1)	
Unknown	154 (11.4)	140 (12.0)	14 (7.6)	
T stage				0.26
T1a	567 (41.9)	500 (42.7)	67 (36.4)	
T1b	679 (50.1)	579 (49.5)	100 (54.3)	
T1 NOS	108 (8.0)	91 (7.8)	17 (9.2)	
N stage				0.221
N0	1,151 (85.0)	1,003 (85.7)	148 (80.4)	
N1	112 (8.3)	92 (7.9)	20 (10.9)	
N2	45 (3.3)	38 (3.2)	7 (3.8)	
N3a	10 (0.7)	7 (0.6)	3 (1.6)	
N3b	2 (0.1)	1 (0.1)	1 (0.5)	
NX	34 (2.5)	29 (2.5)	5 (2.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All patients (N=1,354)	Intestinal (N=1,170)	Diffuse (N=184)	P value
Operation				<0.001
Endoscopy	252 (18.6)	239 (20.4)	13 (7.1)	
Surgery	1,102 (81.4)	931 (79.6)	171 (92.9)	
Radiotherapy				0.357
None/unknown	1,278 (94.4)	1,107 (94.6)	171 (92.9)	
Yes	76 (5.6)	63 (5.4)	13 (7.1)	
Chemotherapy				0.01
No/unknown	1,249 (92.2)	1,088 (93.0)	161 (87.5)	
Yes	105 (7.8)	82 (7.0)	23 (12.5)	
Tumor size (cm)				0.728
T ≤2	637 (47.0)	549 (46.9)	88 (47.8)	
2< T ≤3	211 (15.6)	178 (15.2)	33 (17.9)	
3< T ≤5	192 (14.2)	165 (14.1)	27 (14.7)	
T >5	67 (4.9)	59 (5.0)	8 (4.3)	
Unknown	247 (18.2)	219 (18.7)	28 (15.2)	
Race				0.413
White	855 (63.1)	743 (63.5)	112 (60.9)	
Asian or Pacific Islander	369 (27.3)	310 (26.5)	59 (32.1)	
Black	118 (8.7)	106 (9.1)	12 (6.5)	
American Indian/Alaska Native	5 (0.4)	5 (0.4)	0 (0.0)	
Unknown	7 (0.5)	6 (0.5)	1 (0.5)	
Regional nodes examined				0.061
<15	952 (70.3)	836 (71.5)	116 (63.0)	
≥15	377 (27.8)	314 (26.8)	63 (34.2)	
Unknown	25 (1.8)	20 (1.7)	5 (2.7)	
Marital status				0.685
Married	717 (53.0)	628 (53.7)	89 (48.4)	
Divorced or separated	76 (5.6)	67 (5.7)	9 (4.9)	
Widowed	390 (28.8)	330 (28.2)	60 (32.6)	
Single (never married)	109 (8.1)	92 (7.9)	17 (9.2)	
Unmarried or domestic partner	3 (0.2)	3 (0.3)	0 (0.0)	
Unknown	59 (4.4)	50 (4.3)	9 (4.9)	
Survival months	38.0 (14.0–72.0)	37.0 (14.0–71.0)	41.0 (10.8–76.5)	0.978

Data are presented as number (percentage) or median (interquartile range). NOS, not otherwise specified.

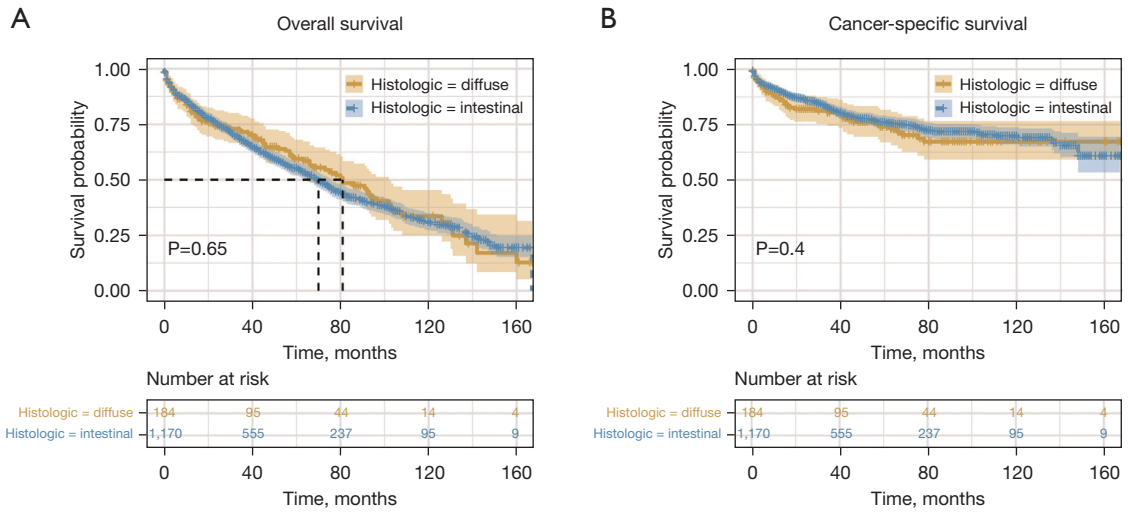

Figure 2 Survival analysis of EGC older patients based on Lauren's classification. (A) Kaplan-Meier analysis of overall survival based on Lauren's classification. (B) Kaplan-Meier analysis of cancer-specific survival based on Lauren's classification. EGC, early gastric cancer.

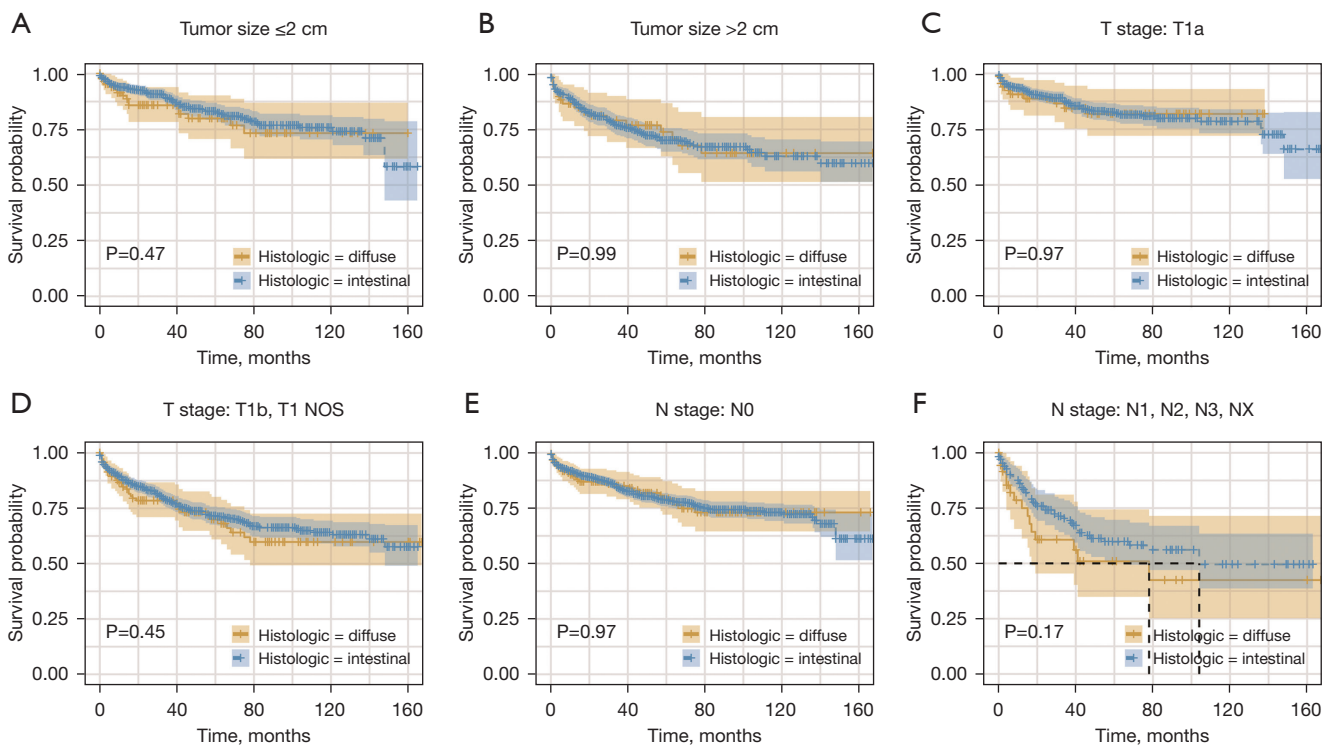

Figure 3 Subgroup CSS analysis of EGC older patients based on Lauren's classification. (A) Kaplan-Meier analysis of CSS based on Lauren's classification in the group of tumor size ≤2 cm. (B) Kaplan-Meier analysis of CSS based on Lauren's classification in the group of tumor size >2 cm. (C) Kaplan-Meier analysis of CSS based on Lauren's classification in the group of T1a. (D) Kaplan-Meier analysis of CSS based on Lauren's classification in the group of T1b and T1NOS. (E) Kaplan-Meier analysis of CSS based on Lauren's classification in the group of N0. (F) Kaplan-Meier analysis of CSS based on Lauren's classification in the group of N1, N2, N3, and NX. EGC, early gastric cancer; CSS, cancer-specific survival; NOS, not otherwise specified.

The crude analysis showed that diffuse type marginal association with CSS compared with intestinal type in age 75 years and older EGC patients (HR: 1.15; 95% CI, 0.83 to 1.58, P=0.400). Subsequently, we used multivariable Cox regression and three propensity-score methods to reduce the effects of potential confounders to evaluate the independent association between Lauren's classification and CSS. The results of multivariable Cox regression showed that patients with diffuse type exhibited no significant association with CSS after adjusting all the potential confounders (HR: 1.04; 95% CI, 0.72 to 1.50, P=0.837, *Table 3*). The analysis of propensity-score matching also validated that there was no significant association between diffuse type and CSS in age 75 and older EGC patients (HR: 1.09; 95% CI, 0.71 to 1.68, P=0.682, *Table 3*). The analyses of inverse-probability-weighted analysis (HR: 1.27; 95% CI, 0.77 to 2.10, P=0.343, *Table 3*) and propensity-score adjustment (HR: 1.07; 95% CI, 0.72 to 1.59, P=0.750, *Table 3*) also showed consistent results.

Next, we conducted stratification and interaction analyses to further validate our findings. The results of stratification analysis confirmed that no significant association was observed in different ages, sexes, tumor sizes, T stages, N stages, and grades in age 75 years and older EGC patients (*Figure 4*). In addition, there was no significant interaction between subgroups (*Figure 4*, P>0.05). These results showed that there was no significant association between diffuse type and CSS in age 75 years and older EGC patients with comprehensive methods to control the effects of potential confounders.

Discussion

Elderly EGC patients present with distinct clinical and prognostic features compared with younger patients (7). In the present study, we investigated the clinical significance of Lauren's classification in CSS in age 75 and older EGC patients. We found that diffuse type showed a similar CSS rate compared with intestinal type in these patients. The subsequent univariable Cox regression analysis, multivariable Cox analysis, propensity-score analyses, and subgroup analysis demonstrated that there was no significant association between diffuse type and CSS compared with intestinal type. These results confirmed the similarly prognostic implication of intestinal type and diffuse type, which may indicate that endoscopic resection is benefitable and promising in age 75 and older diffuse-type

Table 2 Univariable Cox regression analysis for cancer-specific survival in older patients with EGC

Variables	HR (95% CI)	P value
Age		
<85 years	Reference	
≥85 years	1.66 (1.28–2.15)	<0.001
Sex		
Male	Reference	
Female	0.81 (0.64–1.02)	0.076
Year of diagnosis		
2004–2007	Reference	
2008–2011	1.07 (0.82–1.39)	0.625
2012–2015	0.54 (0.38–0.76)	<0.001
2016–2017	0.38 (0.19–0.76)	0.006
Primary site		
Cardia	Reference	
Fundus of stomach	1.46 (0.81–2.64)	0.205
Lesser curvature of stomach	0.82 (0.55–1.23)	0.339
Greater curvature of stomach	0.72 (0.39–1.33)	0.301
Body of stomach	0.78 (0.53–1.17)	0.229
Gastric antrum	0.56 (0.41–0.78)	<0.001
Pylorus	1.21 (0.64–2.29)	0.548
Stomach, NOS	0.94 (0.61–1.47)	0.793
Overlapping lesion of stomach	0.74 (0.39–1.40)	0.353
Grade		
Moderately differentiated or well differentiated	Reference	
Poorly differentiated or undifferentiated	1.48 (1.16–1.88)	0.002
Unknown	0.80 (0.51–1.24)	0.314
Histologic type		
Intestinal	Reference	
Diffuse	1.15 (0.83–1.58)	0.400
T stage		
T1a	Reference	
T1b	1.61 (1.24–2.09)	<0.001
T1 NOS	2.49 (1.69–3.66)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	HR (95% CI)	P value
N stage		
N0	Reference	
N1	1.78 (1.25–2.54)	0.001
N2	1.98 (1.15–3.39)	0.014
N3a	4.77 (2.12–10.74)	<0.001
N3b	17.74 (4.37–71.93)	<0.001
NX	2.67 (1.49–4.78)	<0.001
Operation		
Endoscopy	Reference	
Surgery	1.22 (0.87–1.71)	0.243
Radiotherapy		
None/unknown	Reference	
Yes	1.55 (1.02–2.36)	0.040
Chemotherapy		
No/unknown	Reference	
Yes	1.32 (0.90–1.96)	0.158
Tumor size (cm)		
T ≤2	Reference	
2< T ≤3	1.48 (1.05–2.08)	0.026
3< T ≤5	1.72 (1.23–2.42)	0.002
T >5	2.61 (1.66–4.11)	<0.001
Unknown	1.74 (1.27–2.38)	<0.001
Race		
White	Reference	
Asian or Pacific Islander	0.54 (0.40–0.73)	<0.001
Black	1.08 (0.74–1.60)	0.682
American Indian/Alaska Native	0.78 (0.11–5.60)	0.809
Unknown	0.00 (0.00–Inf)	0.988
Regional nodes examined		
<15	Reference	
≥15	0.66 (0.49–0.88)	0.004
Unknown	1.13 (0.53–2.40)	0.753

Table 2 (*continued*)

Variables	HR (95% CI)	P value
Marital status		
Married	Reference	
Divorced or separated	1.17 (0.72–1.91)	0.521
Widowed	1.04 (0.80–1.36)	0.761
Single (never married)	1.24 (0.82–1.88)	0.311
Unmarried or domestic partner	2.07 (0.29–14.82)	0.468
Unknown	0.79 (0.42–1.49)	0.465

EGC, early gastric cancer; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

Table 3 Associations between Lauren's classification and cancer-specific survival in older patients with EGC in the crude analysis, multivariable analysis, and propensity-score analyses

Analysis	HR (95% CI)	P value
Crude analysis		
Intestinal	Reference	
Diffuse	1.15 (0.83–1.58)	0.400
Multivariable Cox analysis*		
Intestinal	Reference	
Diffuse	1.04 (0.72–1.50)	0.837
Propensity-score analyses		
Intestinal	Reference	
Diffuse		
With matching#	1.09 (0.71–1.68)	0.682
With inverse probability weighting	1.27 (0.77–2.10)	0.343
Adjusted for propensity score	1.07 (0.72–1.59)	0.750

*, adjusted variables: age, sex, year of diagnosis, primary site, grade, T stage, N stage, operation, radiation, chemotherapy, tumor size, race, regional nodes examined, marital status. #, propensity-score matching factors: age, sex, year of diagnosis, primary site, grade, T stage, N stage, operation, radiation, chemotherapy, tumor size, race, regional nodes examined, marital status. After matching, 184 intestinal and 184 diffuse patients were used for analysis. EGC, early gastric cancer; HR, hazard ratio; CI, confidence interval.

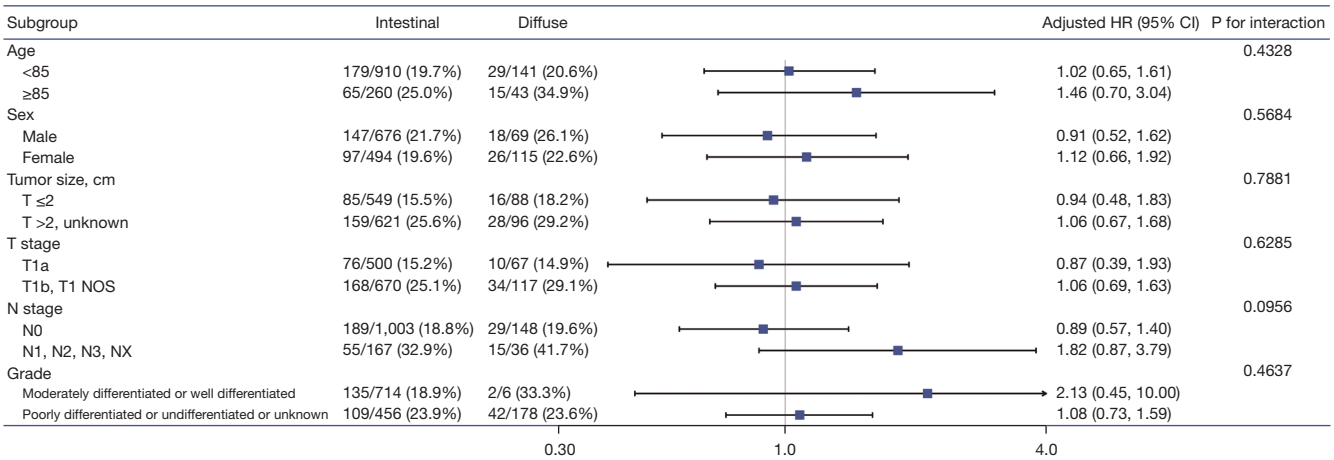

Figure 4 Subgroup and interaction analyses of the association between Lauren's classification on CSS in different groups of age, sex, tumor size, T stage, N stage, and grade. All the potential variables were adjusted except the stratified variable. CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

EGC patients.

Lauren's classification is wildly used in predicting prognosis of GC. According to previous studies, the clinical significance of Lauren's classification is diverse in patients of different ages and T stages (14-16). Here, we investigated the clinical characteristics of Lauren's classification in age 75 and older diffuse-type EGC patients. In consistence with previous reports, our results also showed that diffuse type was mainly distributed in female patients with more poorly differentiated/undifferentiated components (19). Several studies found that diffuse type contained more T1a-stage tumor compared with intestinal type in EGC patients (14,15). Our results showed that T1a-stage was comparable in the intestinal and diffuse type in elderly EGC patients. This may be explained by the heterogeneous features of EGC in elderly patients. More large-sample studies need to be conducted to validate the findings.

Age is a key risk factor that influenced the prognosis of EGC with different Lauren's classification. In early-onset patients (patients aged ≤45 years), diffuse type is not remarkably associated with prognosis of resectable GC patients (HR: 0.47; 95% CI, 0.18 to 1.22) (20). In another report, it was found that diffuse type was a protective factor of prognosis in early-onset EGC patients (HR: 0.64; 95% CI, 0.50 to 0.83) (14). Interestingly, it has been revealed that diffuse type is not significantly associated with prognosis in a study contained both early-onset and elderly EGC patients (HR: 0.95; 95% CI, 0.77 to 1.18) (15). This indicated that diffuse type may have similar effect on the prognosis in elderly EGC patients, which has not been reported before. Here, we revealed that diffuse type was also not significantly associated with prognosis with multiple comprehensive methods to reduce the effects of potential confounders. This may provide data support for selecting the appropriate therapeutic strategies in these elderly patients.

T stage also plays a fundamental role in predicting prognosis of GC with Lauren's classification. In studies involving both early and advanced GC, diffuse type is demonstrated to be controversially association with the prognosis. Tang *et al.* found that diffuse type was apparently related to worse survival of GC with multiple Cox regression (HR: 1.20; 95% CI, 1.15 to 1.20) (13). Another study manifested that diffuse type was a protective factor of GC survival using propensity score matching (HR: 0.56; 95% CI: 0.45 to 0.78) (21). Notably, in advanced GC patients, Tanaka *et al.* revealed that diffuse type was an independent risk factor for overall survival (HR: 2.40; 95% CI, 1.30 to 4.49, P=0.005) (16). The contradicting results may be explained by different variables and statistical methods involved in different studies. Here, we investigated the effects of Lauren's classification in EGC. In accordance with most studies, we also found that diffuse type showed a similar effect on the prognosis of EGC. To validate our results, we included variables as many as possible and used multiple comprehensive methods to control the effects of the potential confounders. The analysis of multivariable Cox regression and three propensity-score methods showed

similar results. Consistently, the analyses of stratification and interaction also confirmed the correctness of the results.

Elderly GC patients often exhibit a worse survival than that of younger patients even after surgical resection due to more organ dysfunction, longer hospitalization duration, and poorer nutrition (7). Recently, endoscopic resection manifests advantages of comparable prognosis, fewer complications, and shorter hospitalization time in comparison with surgical resection (9). According to the latest guidelines, endoscopic resection is more suitable for intestinal-type EGC than diffuse type (22). However, our results revealed that diffuse type showed a similar effect on the prognosis of EGC and this may indicate that endoscopic resection may be suitable for elderly EGC patients, which may further improve the therapeutic effectiveness of operation in these patients.

However, several limitations should be noticed in the present study. Firstly, due to data limitations, we did not analyze the effect of mixed type in the study. We will collect related clinical data in our hospital to perform further analysis in the following studies. Secondly, the characteristics of EGC in SEER database may be different from that in China, where most GC were caused by Helicobacter pylori infection. This indicated that the conclusions should be treated with the consideration of the race and nation. More studies included other races and nations should be conducted to further validate the results.

Conclusions

In conclusion, we found that diffuse type was mainly distributed in female patients with more poorly differentiated/undifferentiated components and similar prognosis compared with intestinal type in age 75 and older EGC patients. Multiple comprehensive analyses demonstrated that no significant association was observed between diffuse type and CSS of the elderly EGC patients. Endoscopic resection may be suitable for both diffuse and intestinal type in elderly EGC patients, which may further improve the therapeutic effectiveness of operation in these patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1681/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1681/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1681/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed following the Declaration of Helsinki (revised in 2013). Patients with EGC were collected from the SEER database via SEER*Stat software (version 8.3.9; www.seer.cancer.gov). Since the SEER database is available publicly with de-identified data, informed consent or institutional review was not required.

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