Comparison of Disease-Specific Survival in the United States and Korea After Resection for Early-Stage Node-Negative Gastric Carcinoma

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Background and Objectives: Disease-specific survival (DSS) for GC patients differs in Eastern and Western countries. The aim is to compare outcomes of US and Korean patients following resection of early-stage, node-negative gastric carcinoma (GC).

Methods: All patients (1995–2005) with T1N0 gastric carcinoma, excluding gastroesophageal tumors, were evaluated. DSS was compared by adjusting for prognostic variables from an internationally validated GC nomogram.

Results: The cohort included 598 Korean patients and 159 US patients. Age and BMI were significantly higher in US patients. Distal tumor location was more frequent in Korea (60% vs. 52%) and proximal location in the US (19% vs. 5%, $P < 0.0001$). Five-year DSS did not differ significantly between Korea and the US. After multivariate analysis, DSS of Korean patients persisted, with no significant differences when compared to US patients (HR = 1.2, 95% CI: 0.3–5.2, $P = 0.83$).

Conclusions: Despite widespread speculations that GC differs in the East and West, when we compare similarly staged, node-negative GC patients, survival did not differ significantly between Korea and the US. This suggests that GC is a heterogeneous disease and when similar subtypes of gastric cancer are compared, these differences disappear. This study suggests more similarities than previously hypothesized between US and Korean GC patients.

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KEY WORDS: gastric carcinoma; early gastric cancer; Eastern and Western

INTRODUCTION

Gastric carcinoma remains the second leading cause of cancer-related deaths in the world, with the highest incidence in Japan, Korea, China, Latin America, and Eastern Europe. In the United States, the incidence is 22,000 per year [1–3]. Many studies, including our own recent analysis, have noted lower 5-year survival after curative-intent gastrectomy for gastric cancer in the West compared to the East. Many hypotheses have been proposed to explain these differences, including differences between US and Korean patients in genetics, incidence of proximal versus distal cancers, environmental exposures, surgical factors, and neoadjuvant/adjuvant treatment protocols [4–10]. However, the many differences between East and West make clear comparisons of gastric cancer survival difficult. One difference in surgical factors is extended lymph node dissection, which is routinely practiced in the East, and typically more lymph nodes are retrieved or identified by pathologists in the East [11]. Because extended lymph node dissection may lead to both stage migration and better cancer control, this practice is frequently hypothesized to explain the survival differences. Another important factor is location and subtype of tumor, as most Eastern gastric cancers are distal, intestinal-type tumors, whereas more Western gastric cancers are in a proximal location with more diffuse-type tumors than in the East [11].

In a prior analysis from our two institutions [11], we compared patients undergoing curative intent resections for gastric cancer over a 10-year period. Due to treatment practice differences, we excluded patients receiving neoadjuvant chemotherapy (only in the US cohort). Comparisons were made by applying a gastric cancer nomogram, which is a mathematically derived tool that accurately predicts 5- and 9-year disease-specific survival for patients undergoing

curative gastric resection [12]. This nomogram, developed by our institution, combines the factors of gender, age, tumor location, Lauren classification, tumor size, number of positive and negative nodes, as well as depth of invasion and T stage. The nomogram has been independently validated in the United States, Germany, and the Netherlands and found to be both reliable and accurate [12–14]. After multivariate analysis adjusting for factors in the nomogram, the DSS of Korean gastric cancer patients persisted as significantly better than that of US patients (HR = 1.3; 95% CI: 1.0–1.6; $P = 0.008$). Results were essentially the same when the analysis was repeated with the inclusion of patients who received neoadjuvant chemotherapy. Nevertheless, the US and Korean cohorts had disparities, including the significantly higher incidence of tumors of the gastroesophageal junction (GEJ) in the US cohort and the significantly higher number of lymph nodes resected or identified in Korean patients. These factors led us to conclude that multiple unmeasured covariates could explain observed differences in survival [11].

The aim of this study is to compare survival between two high-volume gastric cancer centers in the US and Korea by comparing only early-stage, node negative tumors that have been adequately staged (majority ≥ 15 nodes sampled). In addition, this analysis

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excludes GEJ tumors, which predominate in the West, and excludes patients receiving neoadjuvant and adjuvant treatment. Because very few T1 tumors are node positive, comparing this more well-matched cohort minimizes issues of stage migration. Disease-specific mortality was compared between the US and Korea, with multivariate analysis incorporating the nomogram variables to test for an independent effect of East versus West and to analyze factors that predict differences.

PATIENTS AND METHODS

In prospectively maintained gastric cancer databases at the two participating institutions, we identified all patients diagnosed with gastric adenocarcinoma from 1995 through 2005 and eligible for curative (R0) resections: 1,751 at Seoul St. Mary's Hospital and 1,027 at Memorial Sloan-Kettering Cancer Center. This analysis included patients who underwent a curative intent R0 resection with no other cancer history. Patients were excluded if they underwent neoadjuvant chemotherapy, if they underwent wedge resection or endoscopic mucosal resections, or if final pathology revealed a positive margin or metastatic disease. From this group, all patients with T1N0 gastric carcinomas were identified. Patients with GEJ, diffuse whole body tumors, or unknown tumor location were also excluded, since almost all such patients were in the US cohort with no comparable number in the Korean cohort. This left 687 Korean patients and 159 US patients with T1N0 tumors. Among these, adjuvant chemotherapy had been administered to 72 Korean patients but no US patients, so these 72 Korean patients were excluded from the analysis, as were 17 Korean patients whose adjuvant treatment status was unknown. Patients were compared for demographics, surgical and pathologic factors, and survival. Cox regression using nomogram variables was applied to generate univariate and multivariable analyses. Approval for this study was obtained from institutional review boards at both centers.

Surgical Technique

Prior to initiation of this study, a gastric surgeon from each cancer center observed operations at the other institution. Differences noted were the omission of dissection of lymph node #14v for patients in the US compared to Korea. Otherwise, techniques and methods of lymph node dissections were confirmed as similar.

Korean Patients

Patient data were collected from "The Gastric Cancer Patients Registry" from the Seoul St. Mary's Hospital in Seoul, South Korea. Follow-up evaluation consisted of the patient's history, physical examination, laboratory tests including tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9), chest radiography, endoscopy, computed tomography (CT), and bone scintigraphy. These assessments were repeated every 6 months until the third postoperative year, then every year thereafter for at least 5 years. Magnetic resonance imaging, CT of the brain or chest, barium enema, and positron emission tomography (PET) were performed only when indicated.

US Patients

Data were collected from an IRB-approved gastric cancer database from Memorial Sloan-Kettering Cancer Center, New York, NY and included the demographic characteristics, clinicopathologic findings, surgical characteristics, complications, and follow-up status. Follow-up evaluation consisted of the patient's history, physical examination, laboratory tests, endoscopy, and CT. These assessments were repeated every 3–6 months until the third postoperative year,

then every year thereafter for at least 5 years. Magnetic resonance imaging, CT of the brain or chest, and PET were performed only when indicated.

Statistical Analysis

Patient, tumor, and treatment variables were compared between the two countries using the chi square test, the Wilcoxon rank sum test, and/or the Cochran–Armitage trend test. The primary endpoint was disease-specific survival (DSS), defined as the time from resection to death due to disease, with patients censored at date of last follow-up. Other endpoints included recurrence-free survival (RFS), defined as the time from resection to first recurrence, and overall survival (OS), defined as the time from resection to death from any cause or last follow-up. Survival was estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. A competing risk survival analysis was used to estimate and compare the cumulative incidence of disease-specific death, with death due to other or unknown cause treated as a competing factor. Gray's method was used to compare the cumulative incidence curves predicting the probability of death due to gastric cancer. Multivariate competing risk regression analysis [15] was used to assess the effect of country on disease-specific survival after controlling for important prognostic factors identified in an internationally validated nomogram [12]. A P -value of ≤ 0.05 was considered statistically significant in all analyses. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC) or the cmprsk package in R (www.r-project.org).

RESULTS

Patient and Disease Characteristics

Over a 10-year period, 598 Korean patients and 159 US patients were available for the analysis of T1N0 carcinomas after inclusion and exclusion criteria were applied. Patients' characteristics are outlined in Table I. A majority in both cohorts were male (68% in Korea and 57% in the US). The proportion of female patients and median age and body mass index (BMI) were significantly higher in the US cohort (Table I). The US cohort had significant racial diversity. A family history of gastric cancer was reported by twice as many US patients as Korean patients, although in both cohorts most patients had no known family history.

Operative and Perioperative Characteristics

The Korean and US cohorts were similar in the proportions undergoing distal gastrectomy (87% vs. 86%, respectively) and total gastrectomy (13% vs. 14%). The US cohort had more proximal cancers, a higher percentage of differentiated and intestinal tumors, and smaller median tumor size. A significantly higher number of patients in the Korean group underwent $\geq D2$ lymphadenectomy (84% vs. 75%, Table I). No patients underwent adjuvant treatment. Complication data were collected in both countries; however, inherent differences in collection systems made direct comparison challenging. Therefore, as a surrogate measure for major complications, we used 30-day postoperative mortality; this was similar between the two groups (0.3% vs. 1%; $P = 0.20$). Because of differences in societal approach, length of stay cannot be used as a surrogate for complications.

Pathologic Characteristics

Table II summarizes pathologic features of interest. The majority of patients in both centers had tumors in the distal stomach (60% in

TABLE I. Clinical and Surgical Characteristics of Patients in the Study

	Country		<i>P</i> -value ^a
	Korea	United States	
No. of patients	598	159	
Male	404 (67.6%)	90 (56.6%)	0.01
Age, years (range)	58 (21–91)	69 (29–90)	<0.0001
BMI, kg/m ² (range) ^b	22.9 (15.2–35.2)	26.9 (15.1–46.5)	<0.0001
Race			
Caucasian	0	107 (66%)	
Black	0	14 (9%)	
Asian	598 (100%)	23 (14%)	
Hispanic	0	15 (11%)	
Family history			0.007
Yes	39 (7%)	20 (13%)	
No	559 (93%)	132 (83%)	
Unknown	0	7 (4%)	
Operation			0.83
Total gastrectomy	79 (13%)	22 (14%)	
Distal subtotal gastrectomy	519 (87%)	137 (86%)	
Lymphadenectomy			0.01
D1	96 (16%)	39 (25%)	
D2/D3	502 (84%)	119 (75%)	
Unknown	0	1 (1%)	
30-day postoperative mortality			0.20
Yes	2 (0.3%)	2 (1%)	
No	596 (99.7%)	157 (99%)	

Data are number (%) or median (range).

BMI, body mass index.

^aChi-square test used for categorical or binary variables; Wilcoxon rank sum test used for continuous variables. The statistical tests are based on available data.

^bn = 551 for Korea and n = 140 for US.

Korea and 52% in the US), although more US patients had upper 1/3 tumors (19% vs. 5% in Korea; $P < 0.0001$). More US patients had well-differentiated tumors and more Korean patients had diffuse tumors. The median tumor size was similar between the groups. However, the lymph node retrieval was significantly greater in the Korean group, with 15 or more lymph nodes examined in 96% of Korean patients versus 72% of the US patients ($P < 0.0001$).

Survival Analysis

Median follow-up in both countries was 5.7 years (range, 1.1–13.2 in Korea and 0.04–12.9 in the US). Five-year recurrence-free survival was 98% for both Korean and US patients (Table III). Overall survival was significantly higher for Koreans at 96% compared to 88% for US patients, consistent with age and comorbidities. To account for variations in co-morbidities and age in the two cohorts, probability of death due to gastric cancer was evaluated for all patients at 5 years. There was no significant difference, with 2% for Korean patients compared to 3% for US patients ($P = 0.13$ by Gray's test; Table III). This is represented graphically in Figure 1, showing overall survival, and in Figure 2, showing probability of death from disease in relation to months of follow-up. Figure 3 shows the disease-specific mortality separately for stages T1a and T1b.

To account for differences between Korean and US patients in prognostically significant variables, we performed a multivariate analysis including both country and the variables used in our internationally validated nomogram (Table IV). In this analysis, the two countries demonstrated no significant difference in disease-specific

survival, with an adjusted hazard ratio of 1.2 ($P = 0.83$), suggesting that, after adjusting for clinically significant prognostic factors, patients in Korea with node-negative early stage gastric cancer demonstrate similar disease-specific survival to patients in the United States.

The analysis using nomogram variables (Table IV) demonstrates both univariate and multivariate factors of importance in the T1N0 subgroup. In multivariate analysis, the only factor that remained significant was depth of tumor invasion ($P = 0.05$). In addition, we compared the univariate estimates for our prior publication [11] with the same factors applied to our subgroup analysis of patients with T1N0 gastric adenocarcinoma (Table V), demonstrating that country of origin is no longer a statistically significant factor.

DISCUSSION

The cause of disparities in gastric cancer outcomes among patients in Asian and Western countries is debated. It remains unclear whether such differences are related to disease variables such as a discrepancy in the incidence of proximal versus distal cancers, inherent genetic differences in gastric cancer of Asians compared to the Caucasians, disparities in environmental exposures, or surgical factors and neoadjuvant/adjuvant treatment protocols. Gastric carcinoma is a heterogeneous disease, demonstrating poorer survival for GEJ tumors compared to distal tumors, making it highly relevant that US patients present with far more GEJ tumors and Korean patients with far more distal tumors [2,16–18]. In addition, the nodal harvest/identification in Korean patients is much higher than in the US patients [19,20], raising the issue of staging accuracy and stage migration. To obviate such differences and compare a more similar group of patients, we analyzed outcomes from similarly staged, non-GEJ, node-negative gastric carcinomas treated by surgical resection alone. Within this group, disease-specific survival of Korean and US patients did not significantly differ.

The 598 Korean patients and 159 US patients in this study had significant differences in demographic, clinical, and pathologic characteristics, even with these similarly staged tumors. The post-operative mortality rate was no different. However, the lymph node retrieval/identification was significantly higher in Korean patients, with 15 or more lymph nodes retrieved in 96% of Korean patients compared to 72% in the US. All of these findings suggest that the presentation and pattern of early gastric cancer between the two cohorts continue to differ.

Overall survival remained significantly different in our study (96% for Korean vs. 88% for US patients), likely attributable to the greater age and more frequent comorbidities of the US cohort. However, the probability of death due to gastric cancer showed no significant difference ($P = 0.13$). This emphasizes the importance of comparing disease-specific survival, rather than overall survival, when making comparisons among different cohorts of patients. Although disease-specific mortality was not statistically different between the countries, the HR was higher in univariate analysis (2.2; 95% CI: 0.8–6.0) than in multivariate analysis (1.2; 95% CI: 0.3–5.2). This suggests that one or more of the factors that the multivariate analysis adjusted for (age and tumor size and depth) may contribute to higher survival for the Korean patients. Conversely, the absence of significant differences in the multivariate analysis suggests that, after adjusting for clinically significant prognostic factors, patients in Korea with node-negative, early stage gastric cancer demonstrate similar disease-specific survival to their counterparts in the US.

The lack of a survival difference between Korea and the US contrasts with the results of a prior analysis by our two institutions, in which we compared all curative intent gastrectomies from the same

TABLE II. Pathologic Characteristics for Patients in the Study

Variable	Country				P-value ^a
	Korea (N = 598)		United States (N = 159)		
	No. of pts.	%	No. of pts.	%	
Depth					0.0006
T1a	337	56%	60	38%	
T1b	261	44%	88	55%	
Unknown	0	0	11	7%	
Location of tumor					<0.0001
Upper	31	5%	31	19%	
Middle	209	35%	46	29%	
Lower	358	60%	82	52%	
Differentiation					0.02
Differentiated	341	57%	105	66%	
Undifferentiated	249	42%	49	31%	
Unknown	8	1%	5	3%	
Lauren classification					0.04
Diffuse	184	31%	40	25%	
Intestinal	334	56%	105	66%	
Mixed	60	10%	9	6%	
N/A or unknown	20	3%	5	3%	
Median tumor size, cm (range)	n = 596		n = 151		0.002
Overall	2.0 (0.1–12.0)		1.8 (0.0–9.7)		
By location					
Upper	2.0 (0.3–12.0)		2.2 (0.4–8.5)		
Middle	2.5 (0.3–9.0)		1.5 (0.0–7.5)		<0.0001
Lower	2.0 (0.1–9.0)		1.7 (0.0–9.7)		
Lymph node retrieval					
0–14	25	4%	45	28%	
15–30	174	29%	71	45%	
>30	399	67%	43	27%	

N/A, not applicable; Pts, patients.

^aChi-square test used for categorical or binary variables; Wilcoxon rank sum test used for continuous variables. Statistical tests are based on available data.

two centers and found consistently better survival for patients from Korea compared to the United States [11]. The Korean patients had a significant 20% improvement in disease-specific survival stage for stage, even after adjusting for the nomogram variables. In general, operative characteristics differed more between the two groups than they did in our current analysis. It is likely that the Korean patients' lower node positivity (the most powerful predictor of outcome) and earlier stage were dominant factors in the survival difference.

This point is further emphasized by comparing univariate estimates from our prior comparison, which included all patients with surgically resectable gastric carcinoma [11], to those in our current series including only patients with T1N0 disease (Table V). Most of the factors that were significant predictors of disease-specific death in our prior analysis (including country, tumor location, Lauren

classification, and size) were non-significant in the present analysis. This suggests that when comparisons are made between adequately staged gastric cancers of similar types (as defined by location and differentiation), the differences previously observed disappear. There are many possible explanations for this result, including the heterogeneous nature of gastric cancer which may allow us to compare more similar types of gastric cancer (non-GEJ, node-negative tumors).

Other studies have also addressed the influence of ethnicity on gastric cancer outcomes, attempting to investigate the factors that may explain observed differences. In a comparison of Japanese and US gastric cancer patients, one study found that 5-year survival for Japanese patients averaged 6–13% higher for all stages evaluated, although authors concluded that the more favorable outcomes could

TABLE III. Recurrence-Free, Overall, and Disease-Specific Survival for Patients With T1N0 gastric Adenocarcinoma, 1995–2005

	Country						<i>P</i> -value
	Korea			United States			
	No. of pts.	5-year probability (%)	95% CI	No. of pts.	5-year probability (%)	95% CI	
Recurrence-free survival	546	98.3	96.6–99.1	159	97.6	92.7–99.2	0.05
Overall survival	584	96.3	94.1–97.7	159	88.0	81.1–92.6	<0.0001
Probability of death	577			159			
Due to gastric cancer		1.6	0.4–2.9		3.2	0.1–6.3	0.13
Due to other causes		1.3	0.2–2.3		8.8	3.9–13.6	<0.0001

CI, confidence interval; Pts, patients.

Fig. 1. Overall survival of patients with T1N0 gastric carcinoma undergoing curative intent resection. *P*-value represents log-rank analysis of survival.

be explained by differences in tumor location, stage, and accuracy of staging [4]. A cohort study of 3,770 patients in the United States examined differences in presentation and survival for Asian, Hispanic, Caucasian, and African American patients [21]. Asians were more likely to have node-negative, localized disease (OR 1.61, 95% CI: 1.23–2.10), less likely to have proximal tumors (OR 0.22, 95% CI: 0.15–0.31), and less likely to be over 50 years old (OR 0.58, 95% CI: 0.43–0.77). The 5-year survival rate for Asian patients was 21% compared to 10% for Caucasians. Other studies comparing gastric cancer survival in Brazil, Italy, Japan, and the US have similarly found differences in survival, although these authors also conclude that the disparity is not explained by ethnicity-related differences in tumor biology [22,23].

An interesting study from the United States aimed to address the issue of differences in tumor biology by comparing overall survival

Fig. 2. Probability of death from disease for patients with T1N0 gastric carcinoma undergoing curative intent resection. *P*-value represents Gray's test analysis of survival.

among patients of different ethnicities who underwent surgical resection for gastric cancer in the United States. Overall survival was better for Asian Americans than for all other US ethnic groups, even after multivariate analysis. This study allowed for disparities in surgical technique and neo/adjvant treatment to be equalized; however, they reported overall survival rather than disease-specific survival [24]. Known differences in age and comorbidities between Asian and non-Asian populations developing gastric cancer make conclusions from this study subject to further debate.

This current study is unique in that it attempts to address disease-specific survival after obviating differences in surgical factors (such as extent of lymphadenectomy) and treatment practice by comparing two pure cohorts of non-GEJ, lymph-node—negative gastric carcinomas treated with surgical monotherapy. Patients with T1 tumors have a relatively low incidence of lymph node positivity: roughly 2–11%

Fig. 3. Comparison of disease-specific mortality in US versus Korea by stage (a, T1a, and b, T1b). *P*-value represents Gray's test analysis of survival.

TABLE IV. Cox Regression for Disease-Specific Death Using Nomogram Variables

Variable	Levels	Univariate ^a		Multivariate ^b (N = 819) ^c	
		Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Country	Korea	1.0	0.13	1.0	0.83
	United States	2.2 (0.8–6.0)		1.2 (0.3–5.2)	
Tumor depth	T1a	1.0	0.01	1.0	0.05
	T1b	5.1 (1.4–18.0)		3.7 (1.0–13.5)	
Sex	Female	1.0	0.42		
	Male	1.6 (0.5–4.9)			
Age		1.08 (1.02–1.13)	0.004	1.06 (0.99–1.14)	0.09
Tumor location	Upper	1.0	0.72		
	Middle	1.8 (0.2–14.9)			
	Lower	1.2 (0.2–10.1)			
Lauren	Diffuse	1.0	0.23		
	Intestinal	1.5 (0.4–5.7)			
	Mixed	3.8 (0.8–18.5)			
Tumor size		1.2 (1.0–1.4)	0.08	1.1 (0.9–1.4)	0.26
Lymph nodes retrieved		1.00 (0.98–1.03)	0.74		

CI, confidence interval; HR, hazard ratio.

^aOne variable from the nomogram, number of positive lymph nodes, was not included in the model because the analysis includes only N0 patients.

^bThere were fewer events (disease-specific deaths) in the T1N0 subgroup, and so we have tighter restrictions on the number of variables that should be in the multivariate model. However, most variables were not significant in univariate analysis, suggesting that multivariate analysis may not be necessary. Lauren classification and tumor size were not included because those two variables were not significant in the prior analysis that included patients with GE junction tumors.

^cn = 159 US; n = 660 Korea.

for T1a carcinomas and 22–25% for T1b carcinomas [25–28], thus minimizing the potential for understaging in the US, even though fewer lymph nodes were examined in the US cohort. A limitation the study is that the size of the study cohort limited the statistical power of the analyses. Although our multivariate analysis yielded a non-significant HR of 1.2 for country as a predictor of disease-specific-death, the 95% confidence interval (0.3–5.2) means that we still cannot with certainty exclude the possibility that outcome is still influenced by factors not accounted for, such as less aggressive tumor biology in Korean patients. Nevertheless, our analysis demonstrates that early node-negative gastric carcinomas have similar survival outcomes in Korea and the US. Thus, our comparison, unlike other reports, suggests that differences between Eastern and Western patients are not as marked as once believed.

This conclusion, however, raises an interesting question: is the higher survival in Asia reported in other studies related to differences in site, age, extent of lymphadenectomy, genetic variations in patterns of progression to lymph node metastases, or varying epidemiologic/environmental factors?

In summary, this analysis demonstrates that when comparing similarly staged, non-GEJ gastric cancers where lymph node status is a minor contributing factor, the disease-specific survival for patients with gastric cancer in the US and Korea is more similar than previously believed. Although the possibility of inherent biologic differences cannot be fully excluded by this analysis, it is a valid and coherent attempt to demonstrate that observed survival differences may be predominantly related to differences in node positivity, tumor location, and stage.

TABLE V. Comparison of Univariate Estimates for Disease-Specific Death for Patients With All Stages of Resectable Gastric Carcinoma (From Prior Publication [11]) Versus the Current Cohort of Only Those Patients With T1N0 Gastric Adenocarcinoma

Variable	Levels	All stages, n = 2,357		T1N0 subgroup, n = 757	
		Unadjusted HR (95% CI)	P-value	Unadjusted HR (95% CI)	P-value
Country	Korea	1.0	<0.0001	1.0	0.13
	US	2.1 (1.8–2.5)		2.2 (0.8–6.0)	
Sex	Female	1.0	0.76	1.0	0.42
	Male	1.0 (0.9–1.2)		1.6 (0.5–4.9)	
Age		1.02 (1.01–1.03)	<0.0001	1.08 (1.02–1.13)	0.004
Tumor location	Upper	1.0	<0.0001	1.0	0.72
	Middle	0.7 (0.5–0.9)		1.8 (0.2–14.9)	
	Lower	0.6 (0.4–0.7)		1.2 (0.2–10.1)	
Lauren	Diffuse	1.0	<0.0001	1.0	0.23
	Intestinal	0.6 (0.5–0.7)		1.5 (0.4–5.7)	
	Mixed	1.1 (0.9–1.4)		3.8 (0.8–18.5)	
Tumor size		1.21 (1.18–1.24)	<0.0001	1.2 (1.0–1.4)	0.08
Lymph nodes retrieved		0.998 (0.993–1.002)	0.34	1.00 (0.98–1.03)	0.74

In terms of country, the point estimate (HR) is lower for the T1N0 subgroup analysis compared with the HR for the full cohort analysis [11] (CI is wider in the subgroup analysis due to smaller number of patients). There are also clear differences in point estimates for sex, tumor location, and Lauren.

CI, confidence interval; HR, hazard ratio.

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