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ORIGINAL ARTICLE

Revisiting a dogma: similar survival of patients with small bowel and gastric GIST. A population-based propensity score SEER analysis

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Abstract

Background The objective of the present analysis was to assess whether small bowel gastrointestinal stromal tumor (GIST) is associated with worse cancer-specific survival (CSS) and overall survival (OS) compared with gastric GIST on a population-based level.

Patients and methods Data on patients aged 18 years or older with histologically proven GIST was extracted from the SEER database from 1998 to 2011. OS and CSS for small bowel GIST were compared with OS and CSS for gastric GIST by application of adjusted and unadjusted Cox regression analyses and propensity score analyses.

Results GIST were located in the stomach ($n = 3011$, 59 %), duodenum ($n = 313$, 6 %), jejunum/ileum ($n = 1288$, 25 %), colon ($n = 139$, 3 %), rectum ($n = 172$, 3 %), and extraviscerally ($n = 173$, 3 %). OS and CSS of patients with GIST in the duodenum [OS, HR 0.95, 95 % confidence interval (CI) 0.76–1.19; CSS, HR 0.99, 95 % CI 0.76–1.29] and in the jejunum/ileum (OS, HR 0.97, 95 % CI 0.85–1.10; CSS, HR = 0.95, 95 % CI 0.81–1.10) were similar to those of patients with gastric GIST in multivariate analyses. Conversely, OS and CSS of patients with GIST in the colon (OS, HR 1.40; 95 % CI 1.07–1.83; CSS, HR 1.89, 95 % CI 1.41–2.54) and in an extravisceral location (OS, HR 1.42, 95 % CI 1.14–1.77; CSS, HR = 1.43, 95 % CI 1.11–1.84) were significantly worse than those of patients with gastric GIST.

Conclusions Contrary to common belief, OS and CSS of patients with small bowel GIST are not statistically different from those of patients with gastric GIST when adjustment is made for confounding variables on a population-based level. The prognosis of patients with nongastric GIST is worse because of a colonic and extravisceral GIST location. These findings have implications regarding adjuvant treatment of GIST patients. Hence, the dogma that small bowel GIST patients have worse prognosis than gastric GIST patients and therefore should receive adjuvant treatment to a greater extent must be revisited.

Keywords Gastrointestinal stromal tumors · Surveillance, Epidemiology, and End Results Program · Mortality · Propensity score · Stomach neoplasms · Small bowel neoplasms

Introduction

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal malignancies of the gastrointestinal tract. GIST have their origin in interstitial cells of Cajal, which are pacemaker cells located between the circular and longitudinal muscle layers along the gastrointestinal tract

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and are responsible for gastrointestinal motility. GIST occur most frequently in the stomach and small bowel; other locations such as the esophagus, colon, rectum, and extragastrointestinal tract locations are much rarer [1].

It is a common dogma that intestinal GIST are associated with worse prognosis compared with gastric GIST [1–4]. Additionally to the commonly accepted poor prognostic factors of tumor size and mitotic rate [5], the widely used Armed Forces Institute of Pathology (AFIP) classification of Miettinnen and Lasota [1] added GIST location as a third risk factor. In this risk classification, a location in the jejunum/ileum results in a relevantly higher risk of metastases and tumor-related death compared with a gastric location. These findings have tremendous implications regarding the use of adjuvant therapy in resected GIST patients.

We have previously investigated trends in survival in GIST patients [6]. The objective of the present investigation was to assess whether overall and cancer-specific survival is worse in intestinal GIST patients compared with gastric GIST patients after risk adjustment in multivariate and propensity score analyses.

Methods

Cohort definition

The recent ASCI text data version of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the USA, covering approximately 28 % of cancer cases in the USA, was the source of the present population-based analysis [7]. SEER data were collected and reported with use of data items and codes as documented by the North American Association of Central Cancer Registries (NAACCR) [8]. Primary cancer site and histological features were coded according to criteria in the third edition of the International Classification of Diseases for Oncology (ICD-O-3) [9].

GIST patients were identified by the cancer staging scheme, version 0204, based on the primary site and the ICD-O-3 histological features ($N = 6294$). Patients with cancer diagnosis at autopsy or on the death certificate only as well as patients without histological confirmation were excluded ($N = 65$, NAACCR items 490 and 2180). Patients with other SEER-reportable cancers were excluded unless the GIST was the first diagnosed malignancy ($N = 1058$, NAACCR item 380). Patients younger than 18 years ($N = 24$) and patients with appendiceal ($N = 3$) and esophageal ($N = 29$) GIST were excluded, leaving a total of 5096 patients in the analysis. GIST sizes coded with values exceeding 700.0 mm were considered as missing values because these sizes did not seem plausible.

Statistical analysis

Statistical analyses were performed with R (https://www.r-project.org). A two-sided P value of less than 0.05 was considered statistically significant. Continuous data are expressed as the median and interquartile range. Chi-square statistics and t tests were used to compare proportions and continuous variables, respectively. After descriptive analysis, survival was compared between gastric GIST and GIST in other locations by Kaplan–Meier analysis. P values were computed by likelihood ratio tests based on Cox regression analysis. Multivariate survival analyses were done by Cox regression analyses. The proportional hazards assumption was tested by scaled Schoenfeld residuals and by inspection of the hazard ratio (HR) plots [10]. P values were computed by likelihood ratio tests.

To optimally adjust the data for potential baseline confounding variables, five propensity score analyses as a superior and more refined statistical method for adjustment were performed with the MatchIt R package. In these five analyses, gastric GIST were compared with GIST in the duodenum, jejunum/ileum, colon, rectum, and peritoneum. The propensity score matching was performed as exact matching. In this procedure, each patient with gastric GIST was matched to all possible patients with the counterpart GIST with exactly the same values on all the covariates, forming subclasses such that within each subclass both groups have exactly the same covariate values. Patients with gastric GIST not having a counterpart among the patients with other GIST and vice versa were excluded from this analysis. Finally, overall and cancer-specific survival in patients with gastric GIST and GIST in other locations were assessed in a Cox regression analysis by means of the weights obtained by the matching propensity score analysis.

Subgroup and sensitivity analyses

To preclude a time trend bias, we repeated the entire analysis in two subgroups, the first with diagnosis of the GIST from 1998 to 2004 and the second with diagnosis from 2005 to 2011.

As mitotic count was recorded only after 2009, it was not included in the main analysis. However, a sensitivity analysis was performed including data on mitotic count.

Results

Baseline characteristics

Overall, 5096 patients were included in the analysis. GIST were located in the stomach in 3011 patients (59 %), in the

Table 1 Patients' characteristics

	GIST location							P^a
	Any ($N = 5096$)	Gastric ($n = 3011$)	Duodenal ($n = 313$)	Ileum/jejunum ($n = 1288$)	Colon ($n = 139$)	Rectum ($n = 172$)	Extraintestinal ($n = 173$)	
Size								
≤2 cm	307 (6.0 %)	202 (6.7 %)	17 (5.4 %)	55 (4.3 %)	18 (12.9 %)	14 (8.1 %)	1 (0.6 %)	<0.001
>2 to ≤5 cm	1135 (22.3 %)	718 (23.8 %)	104 (33.2 %)	236 (18.3 %)	21 (15.1 %)	46 (26.7 %)	10 (5.8 %)	
>5 to ≤10 cm	1653 (32.4 %)	944 (31.4 %)	91 (29.1 %)	490 (38.0 %)	41 (29.5 %)	63 (36.6 %)	24 (13.9 %)	
>10 cm	1308 (25.7 %)	732 (24.3 %)	55 (17.6 %)	369 (28.6 %)	29 (20.9 %)	23 (13.4 %)	100 (57.8 %)	
Unknown	693 (13.6 %)	415 (13.8 %)	46 (14.7 %)	138 (10.7 %)	30 (21.6 %)	26 (15.1 %)	38 (22.0 %)	
Metastatic disease								
M0	4173 (81.9 %)	2517 (83.6 %)	262 (83.7 %)	1008 (78.3 %)	107 (77.0 %)	158 (91.9 %)	121 (69.9 %)	<0.001
M1	923 (18.1 %)	494 (16.4 %)	51 (16.3 %)	280 (21.7 %)	32 (23.0 %)	14 (8.1 %)	52 (30.1 %)	
N stage								
N−	4048 (79.4 %)	2425 (80.5 %)	256 (81.8 %)	1010 (78.4 %)	100 (71.9 %)	134 (77.9 %)	123 (71.1 %)	0.009
N+	262 (5.1 %)	147 (4.9 %)	14 (4.5 %)	69 (5.4 %)	15 (10.8 %)	6 (3.5 %)	11 (6.4 %)	
N×	786 (15.4 %)	439 (14.6 %)	43 (13.7 %)	209 (16.2 %)	24 (17.3 %)	32 (18.6 %)	39 (22.5 %)	
Mitotic count[b]								
<2 per 50 HPF	394 (7.7 %)	279 (9.3 %)	27 (8.6 %)	82 (6.4 %)	0 (0 %)	0 (0 %)	6 (3.5 %)	<0.001
2–5 per 50 HPF	171 (3.4 %)	86 (2.9 %)	14 (4.5 %)	65 (5.0 %)	0 (0 %)	0 (0 %)	6 (3.5 %)	
>5 per 50 HPF	159 (3.1 %)	85 (2.8 %)	12 (3.8 %)	61 (4.7 %)	0 (0 %)	0 (0 %)	1 (0.6 %)	
Unknown	4372 (85.8 %)	2561 (85.1 %)	260 (83.1 %)	1080 (83.9 %)	139 (100 %)	172 (100 %)	160 (92.5 %)	
Surgery of primary tumor								
No	851 (16.7 %)	595 (19.8 %)	71 (22.7 %)	67 (5.2 %)	22 (15.8 %)	43 (25 %)	53 (30.6 %)	<0.001
Yes	4245 (83.3 %)	2416 (80.2 %)	242 (77.3 %)	1221 (94.8 %)	117 (84.2 %)	129 (75 %)	120 (69.4 %)	
Period								
1998–2002	1107 (21.7 %)	584 (19.4 %)	60 (19.2 %)	317 (24.6 %)	44 (31.7 %)	48 (27.9 %)	54 (31.2 %)	<0.001
2003–2006	1554 (30.5 %)	927 (30.8 %)	96 (30.7 %)	397 (30.8 %)	39 (28.1 %)	42 (24.4 %)	53 (30.6 %)	
2007–2011	2435 (47.8 %)	1500 (49.8 %)	157 (50.2 %)	574 (44.6 %)	56 (40.3 %)	82 (47.7 %)	66 (38.2 %)	
Sex								
Male	2682 (52.6 %)	1535 (51.0 %)	179 (57.2 %)	688 (53.4 %)	79 (56.8 %)	105 (61.0 %)	96 (55.5 %)	0.026
Female	2414 (47.4 %)	1476 (49.0 %)	134 (42.8 %)	600 (46.6 %)	60 (43.2 %)	67 (39.0 %)	77 (44.5 %)	
Age (years)								
<65	2848 (55.9 %)	1593 (52.9 %)	194 (62.0 %)	788 (61.2 %)	68 (48.9 %)	106 (61.6 %)	99 (57.2 %)	<0.001
65+	2248 (44.1 %)	1418 (47.1 %)	119 (38.0 %)	500 (38.8 %)	71 (51.1 %)	66 (38.4 %)	74 (42.8 %)	
Ethnicity								
Caucasian	3502 (68.7 %)	1896 (63.0 %)	240 (76.7 %)	1029 (79.9 %)	102 (73.4 %)	106 (61.6 %)	129 (74.6 %)	<0.001
African American	914 (17.9 %)	714 (23.7 %)	22 (7.0 %)	107 (8.3 %)	25 (18.0 %)	24 (14.0 %)	22 (12.7 %)	
Other/unknown	680 (13.3 %)	401 (13.3 %)	51 (16.3 %)	152 (11.8 %)	12 (8.6 %)	42 (24.4 %)	22 (12.7 %)	

Table 1 continued

	GIST location							P^a
	Any ($N = 5096$)	Gastric ($n = 3011$)	Duodenal ($n = 313$)	Ileum/jejunum ($n = 1288$)	Colon ($n = 139$)	Rectum ($n = 172$)	Extraintestinal ($n = 173$)	
Marital status								
Married	2975 (58.4 %)	1700 (56.5 %)	202 (64.5 %)	787 (61.1 %)	82 (59.0 %)	105 (61.0 %)	99 (57.2 %)	0.031
Single	830 (16.3 %)	491 (16.3 %)	51 (16.3 %)	207 (16.1 %)	21 (15.1 %)	31 (18.0 %)	29 (16.8 %)	
Other/unknown	1291 (25.3 %)	820 (27.2 %)	60 (19.2 %)	294 (22.8 %)	36 (25.9 %)	36 (20.9 %)	45 (26.0 %)	

GIST gastrointestinal stromal tumor, *HPF* high-power field

[a] Chi-square test

[b] Mitotic count was systematically recorded only after 2009, given in counts per 50 HPF

duodenum in 313 patients (6 %), in the jejunum/ileum in 1288 patients (25 %), in the colon in 139 patients (3 %), in the rectum in 172 patients (3 %), and in extraintestinal locations in 173 patients (3 %). The median follow-up was 37 months (interquartile range 14–74 months). A total of 3520 patients were alive at the end of the follow-up, 1066 had died of GIST, and 510 had died of other causes. The median age was 62 years (interquartile range 52–73 years), with a range of 18–101 years; 47 % of patients were female and 69 % were Caucasian. Table 1 displays the patients' baseline characteristics and compares different GIST locations.

Although mitotic count for patients with colorectal GIST was not recorded, the mean mitotic count was 2.8 ± 3.7 per 50 high power fields (HPF) for gastric GIST, 3.6 ± 3.7 per 50 HPF for duodenal GIST, 4.3 ± 4.2 per 50 HPF for GIST in the jejunum/ileum, and 2.8 ± 3.0 per 50 HPF for extraintestinal GIST locations ($P < 0.001$).

Univariate survival analysis

Three- and 5-year overall and cancer-specific survival estimates for different GIST locations are shown in the overall patient population in Table 2. In univariate analyses, GIST of the colon and in extraintestinal locations were associated with significantly worse overall and cancer-specific survival compared with GIST in the other locations.

In Table 3, 3- and 5-year overall and cancer-specific survival are shown for patients in the adjuvant situation (surgery of the primary tumor performed, no distant metastases) stratified for GIST size and location. Kaplan–Meier curves for the different GIST locations are displayed in Fig. 1. GIST of the colon and peritoneum were associated with significantly worse overall and cancer-specific survival (all $P < 0.001$), whereas the survival of patients with GIST in other locations did not differ relevantly.

Multivariate survival analysis

After adjustment in Cox proportional hazard regression analysis, overall survival for patients with GIST located in the duodenum [HR 0.95, 95 % confidence interval (95 % CI) 0.76–1.19] and jejunum/ileum (HR 0.97; 95 % CI 0.85–1.10) was similar to that patients for with gastric GIST. Similarly, no differences in cancer-specific survival were found for GIST located in the duodenum (HR 0.99; 95 % CI 0.76–1.29) and jejunum/ileum (HR 0.95; 95 % CI 0.81–1.10).

Conversely, GIST in the colon and peritoneum were associated with a worse overall survival (colonic GIST, HR 1.40, 95 % CI 1.07–1.83; extraintestinal GIST, HR 1.42,

Table 2 Univariate Kaplan–Meier survival estimates

Location	3-year survival		5-year survival	
	Overall survival (%)	Cancer-specific survival (%)	Overall survival (%)	Cancer-specific survival (%)
Stomach	77.3 (75.7–79.0)	83.4 (81.9–84.9)	67.6 (65.6–69.6)	77.0 (75.1–78.9)
Duodenum	82.6 (78.2–87.3)	86.8 (82.8–91.0)	74.4 (68.8–80.4)	80.5 (75.3–86.0)
Ileum/jejunum	80.2 (77.8–82.7)	86.1 (84.0–88.3)	72.1 (69.3–75.1)	79.4 (76.7–82.1)
Colon	63.4 (55.4–72.7)	68.9 (61.0–77.8)	56.7 (48.1–66.8)	61.5 (52.9–71.6)
Rectum	86.0 (80.5–91.8)	90.3 (85.6–95.3)	76.5 (69.4–84.4)	82.2 (75.5–89.5)
Peritoneum	55.4 (48.0–63.9)	63.0 (55.6–71.5)	50.2 (42.7–59.1)	57.2 (49.3–66.3)

The 95 % confidence interval is given in parentheses

Table 3 Survival of patients with nonmetastatic gastrointestinal stromal tumor (*GIST*) who underwent primary tumor resection ($N = 3449$)

Size	Location of GIST					
	Stomach	Duodenum	Ileum/jejunum	Colon	Rectum	Peritoneum
All sizes						
Raw mortality	$n = 250/2058$ (12.1 %)	$n = 29/211$ (13.7 %)	$n = 129/902$ (14.3 %)	$n = 22/80$ (27.5 %)	$n = 15/109$ (13.8 %)	$n = 29/89$ (32.6 %)
3-year survival (%)	91.7 (90.3–93.0)	92.0 (87.9–96.2)	89.8 (87.6–92.1)	77.9 (68.8–88.2)	94.7 (90.2–99.4)	75.9 (66.9–86.1)
5-year survival (%)	86.3 (84.4–88.2)	88.2 (83.1–93.7)	85.0 (82.2–87.9)	68.4 (57.8–81.0)	89.0 (82.3–96.2)	68.8 (58.6–80.7)
≤2 cm						
Raw mortality	$n = 13/168$ (7.7 %)	$n = 1/12$ (8.3 %)	$n = 2/45$ (4.4 %)	$n = 3/16$ (18.8 %)	$n = 0/13$ (0 %)	$n = 0/1$ (0 %)
3-year survival (%)	92.3 (87.0–97.9)	100.0 (30.0–100.0)	94.4 (87.0–100.0)	86.5 (70.7–100.0)	100.0 (54.4–100.0)	100.0
5-year survival (%)	90.6 (84.5–97.1)	100.0 (30.0–100.0)	94.4 (87.0–100.0)	75.7 (54.4–100.0)	100.0 (54.4–100.0)	100.0
>2 to ≤5 cm						
Raw mortality	$n = 40/618$ (6.5 %)	$n = 5/88$ (5.7 %)	$n = 13/205$ (6.3 %)	$n = 4/18$ (22.2 %)	$n = 5/38$ (13.2 %)	$n = 2/9$ (22.2 %)
3-year survival (%)	96.0 (94.2–97.7)	97.4 (93.9–100.0)	96.1 (93.0–99.2)	75.7 (57.3–99.8)	90.8 (81.4–100.0)	68.6 (40.3–100.0)
5-year survival (%)	92.6 (90.0–95.3)	97.4 (93.9–100.0)	93.0 (88.6–97.7)	75.7 (57.3–99.8)	90.8 (81.4–100.0)	68.6 (40.3–100.0)
>5 to ≤10 cm						
Raw mortality	$n = 83/768$ (10.8 %)	$n = 14/73$ (19.2 %)	$n = 55/391$ (14.1 %)	$n = 9/26$ (34.6 %)	$n = 6/40$ (15 %)	$n = 5/19$ (26.3 %)
3-year survival (%)	93.1 (91.0–95.1)	86.4 (77.9–95.9)	89.0 (85.5–92.6)	75.6 (60.2–94.8)	96.7 (90.5–100.0)	88.8 (75.3–100.0)
5-year survival (%)	87.9 (85.0–90.8)	83.5 (73.9–94.5)	86.8 (82.9–90.8)	65.5 (48.4–88.5)	93.2 (84.6–100.0)	88.8 (75.3–100.0)
>10 cm						
Raw mortality	$n = 114/504$ (22.6 %)	$n = 9/38$ (23.7 %)	$n = 59/261$ (22.6 %)	$n = 6/20$ (30 %)	$n = 4/18$ (22.2 %)	$n = 22/60$ (36.7 %)
3-year survival (%)	84.4 (80.9–88.0)	88.5 (78.4–99.8)	85.9 (81.3–90.8)	77.5 (60.2–99.9)	87.7 (73.0–100.0)	72.2 (61.1–85.4)
5-year survival (%)	75.6 (71.1–80.4)	78.5 (65.4–94.1)	75.5 (69.4–82.1)	63.4 (43.5–92.5)	65.8 (41.9–100.0)	61.9 (49.4–77.7)

Patients with unknown tumor size ($n = 277$) were excluded. For the 3- and 5-year cancer-specific survival, the 95 % confidence interval is given in parentheses

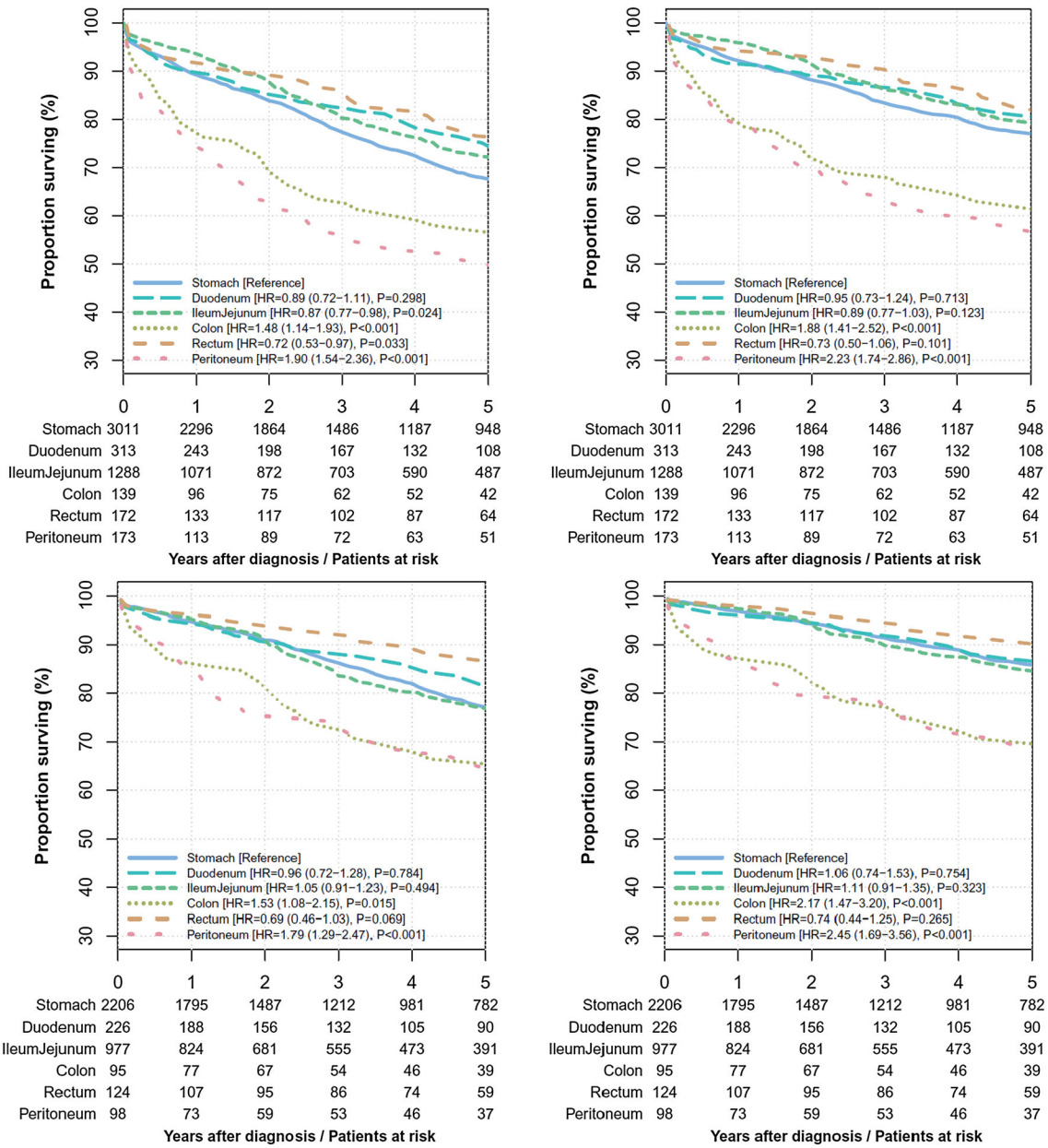

Fig. 1 Kaplan–Meier curves for survival. The *upper panels* display the Kaplan–Meier curves for overall survival (*left*) and cancer-specific survival (*right*) in all patients for different gastrointestinal stromal tumor (GIST) locations. The *lower panels* display the Kaplan–Meier curves for overall survival (*left*) and cancer-specific survival (*right*) in patients with nonmetastatic GIST who underwent GIST resection. The numbers of patients at risk in the two groups are given below the *x*-axis. The hazard ratios (*HR*) and the *P* values indicate the risk of death for a GIST in a particular location compared with gastric GIST (reference category)

95 % CI 1.14–1.77, $P = 0.007$) and cancer-specific survival (colonic GIST, HR 1.89, 95 % CI 1.41–2.54; extraintestinal GIST, HR 1.43, 95 % CI 1.11–1.85, $P < 0.001$).

In addition to GIST location, tumor size greater than 10 cm (HR 2.05, 95 % CI 1.42–2.95, $P < 0.001$), presence of distant metastases (HR 2.43, 95 % CI 2.11–2.79, $P < 0.001$) and lymph node metastases (HR 1.61, 95 % CI 1.29–2.01, $P < 0.001$), older age (HR 1.92, 95 % CI 1.69–2.18, $P < 0.001$), and single marital status (HR 1.40, 95 % CI 1.18–1.66, $P < 0.001$) were associated with worse cancer-specific survival, whereas patients undergoing primary tumor excision (HR 0.43, 95 % CI 0.37–0.50, $P < 0.001$), female patients (HR 0.80, 95 % CI 0.70–0.90, $P < 0.001$), and patients during later time periods ($P < 0.001$) had significantly improved cancer-specific survival (Table 4). Similar results were found for overall survival (Table 4).

Table 4 Multivariate Cox regression survival analysis

	Overall survival				Cancer-specific survival			
	Unadjusted[a]		Cox regression, full model[b]		Unadjusted[a]		Cox regression, full model[b]	
	HR	P^c	HR	P^c	HR	P^c	HR	P^c
Location								
Stomach	Reference	<0.001	Reference	0.007	Reference	<0.001	Reference	<0.001
Duodenum	0.89 (0.72–1.11)		0.95 (0.76–1.19)		0.95 (0.73–1.24)		0.99 (0.76–1.29)	
Ileum/jejunum	0.87 (0.77–0.98)		0.97 (0.85–1.10)		0.89 (0.77–1.03)		0.95 (0.81–1.10)	
Colon	1.48 (1.14–1.93)		1.40 (1.07–1.83)		1.88 (1.41–2.52)		1.89 (1.41–2.54)	
Rectum	0.72 (0.53–0.97)		0.93 (0.69–1.27)		0.73 (0.50–1.06)		0.98 (0.67–1.43)	
Peritoneum	1.90 (1.54–2.36)		1.42 (1.14–1.77)		2.23 (1.74–2.86)		1.43 (1.11–1.84)	
Size								
≤2 cm	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
>2 to ≤5 cm	0.69 (0.53–0.90)		0.69 (0.53–0.91)		0.77 (0.52–1.14)		0.77 (0.52–1.15)	
>5 to ≤10 cm	0.91 (0.71–1.18)		0.86 (0.67–1.11)		1.34 (0.93–1.93)		1.24 (0.86–1.79)	
>10 cm	1.45 (1.13–1.86)		1.23 (0.96–1.59)		2.51 (1.75–3.60)		2.05 (1.42–2.95)	
Unknown	1.76 (1.36–2.28)		1.06 (0.82–1.39)		2.94 (2.03–4.25)		1.54 (1.06–2.25)	
Metastatic disease								
M0	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
M1	2.85 (2.56–3.17)		2.01 (1.79–2.27)		3.73 (3.30–4.23)		2.43 (2.11–2.79)	
N category								
N−	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
N+	2.28 (1.89–2.75)		1.57 (1.29–1.91)		2.73 (2.20–3.38)		1.61 (1.29–2.01)	
NX	1.80 (1.61–2.02)		1.13 (0.99–1.28)		2.09 (1.82–2.39)		1.18 (1.01–1.38)	
Surgery of the primary tumor								
No	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Yes	0.33 (0.29–0.36)		0.48 (0.42–0.55)		0.27 (0.24–0.31)		0.43 (0.37–0.50)	
Period								
1998–2002	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
2003–2006	0.79 (0.70–0.88)		0.75 (0.66–0.84)		0.76 (0.66–0.88)		0.73 (0.63–0.84)	
2007–2011	0.65 (0.56–0.75)		0.62 (0.53–0.71)		0.59 (0.50–0.70)		0.57 (0.48–0.67)	
Sex								
Male	Reference	<0.001	Reference	<0.001	Reference	0.001	Reference	<0.001
Female	0.80 (0.72–0.88)		0.72 (0.65–0.80)		0.82 (0.73–0.93)		0.80 (0.70–0.90)	
Age (years)								
<65	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
65+	2.39 (2.16–2.64)		2.53 (2.27–2.81)		1.81 (1.60–2.04)		1.92 (1.69–2.18)	

Table 4 continued

	Overall survival				Cancer-specific survival			
	Unadjusted[a]		Cox regression, full model[b]		Unadjusted[a]		Cox regression, full model[b]	
	HR	P^c	HR	P^c	HR	P^c	HR	P^c
Ethnicity								
Caucasian	Reference	0.002	Reference	0.034	Reference	0.016	Reference	0.148
African American	1.19 (1.05–1.35)		1.12 (0.98–1.28)		1.15 (0.99–1.34)		1.02 (0.86–1.19)	
Other/unknown	0.87 (0.74–1.01)		0.88 (0.75–1.03)		0.83 (0.69–1.01)		0.83 (0.69–1.01)	
Marital status								
Married	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Single	1.19 (1.03–1.36)		1.38 (1.19–1.59)		1.30 (1.11–1.54)		1.40 (1.18–1.66)	
Other/unknown	1.50 (1.34–1.67)		1.34 (1.19–1.52)		1.45 (1.26–1.67)		1.32 (1.14–1.53)	

The 95 % confidence interval is given in parentheses

HR hazard ratio

[a] Univariate Cox regression analysis

[b] Multivariate full model Cox regression analysis

[c] Likelihood ratio tests

Propensity score matching

To further corroborate the findings from univariate and multivariate Cox proportional hazards regression analyses, propensity-score-matched analyses were performed as described in "Statistical analysis." Table 5 shows the patients' characteristics in each of the cohorts for the five comparisons. No differences between gastric GIST and its counterparts were observed (all $P = 1.0$), demonstrating perfect matching. When overall and cancer-specific survival of patients with gastric GIST (the reference category) were compared with those for patients with GIST in the other five locations, only colonic and extraintestinal GIST differed significantly from gastric GIST. Figure 2 displays the Kaplan–Meier curves and HR for cancer-specific survival after weighted exact propensity score matching. When gastric GIST was compared with GIST of the duodenum, jejunum/ileum, and rectum in cohorts with similar baseline characteristics, no relevant difference was observed.

Subgroup analyses for 1998–2004 and 2005–2011

To preclude a time trend bias, we repeated the entire analysis in two subsamples of patients with diagnosis of the GIST from 1998 to 2004 and from 2005 to 2011. Both analyses yielded similar results as the main analysis, demonstrating worse cancer-specific and overall survival in patients with colonic and extraintestinal GIST (data not shown).

A sensitivity analysis was performed including data on mitotic count. No relevant differences regarding GIST location (primary predictor variable) were found between the model with and without inclusion of mitotic counts (see the electronic supplementary material).

Discussion

The present population-based study including more than 5000 patients provides compelling evidence that intestinal GIST patients have outcomes similar to those of gastric GIST patients. Indeed, overall and cancer-specific survivals were comparable even after risk adjustment in multivariate and propensity score analysis. These findings are contrary to common belief and current guidelines. We thus suggest that the dogma that patients with intestinal GIST have worse prognosis than patients with gastric GIST should be revisited. Hence, the decision for or against an adjuvant imatinib treatment should rely primarily on mitotic rate and size for intestinal GIST, not on location.

Risk classification after GIST resection is of key importance as it enables the patient to be counseled

Table 5 Patients' characteristics after paiwise weighted exact propensity score matching against gastric gastrointestinal stromal tumor (GIST; see the electronic supplementary material)

	Stomach vs duodenum			Stomach vs ileum/jejunum			Stomach vs colon			Stomach vs rectum			Stomach vs peritoneum		
	Stomach (%)	Duodenum (%)	P^a	Stomach	Ileum/ Jejunum	P^a	Stomach	Colon	P^a	Stomach	Rectum	P^a	Stomach	Peritoneum	P^a
Baseline															
All patients	3011 (100 %)	313 (100 %)	–	3011 (100 %)	1288 (100 %)	–	3011 (100 %)	139 (100 %)	–	3011 (100 %)	172 (100 %)	–	3011 (100 %)	173 (100 %)	–
Propensity score analysis															
Patients excluded	1929 (64.1 %)	73 (23.3 %)	–	1228 (40.8 %)	280 (21.7 %)	–	2496 (82.9 %)	41 (29.5 %)	–	2177 (72.3 %)	50 (29.1 %)	–	2479 (82.3 %)	60 (34.7 %)	–
Patients included	1082 (35.9 %)	240 (76.7 %)		1783 (59.2 %)	1008 (78.3 %)		515 (17.1 %)	98 (70.5 %)		834 (27.7 %)	122 (70.9 %)		532 (17.7 %)	113 (65.3 %)	
Size															
≤2 cm	49 (4.5 %)	10.9 (4.5 %)	1.0	74 (4.2 %)	41.8 (4.2 %)	1.0	52 (10.1 %)	9.9 (10.1 %)	1.0	41 (4.9 %)	6 (4.9 %)	1.0	3 (0.6 %)	0.6 (0.6 %)	1.0
>2 to ≤5 cm	391 (36.1 %)	86.7 (36.1 %)		483 (27.1 %)	273.1 (27.1 %)		140 (27.2 %)	26.6 (27.2 %)		286 (34.3 %)	41.8 (34.3 %)		77 (14.5 %)	16.4 (14.5 %)	
>5 to ≤10 cm	428 (39.6 %)	94.9 (39.6 %)		671 (37.6 %)	379.3 (37.6 %)		170 (33.0 %)	32.3 (33.0 %)		336 (40.3 %)	49.2 (40.3 %)		179 (33.6 %)	38 (33.6 %)	
>10 cm	166 (15.3 %)	36.8 (15.3 %)		453 (25.4 %)	256.1 (25.4 %)		136 (26.4 %)	25.9 (26.4 %)		145 (17.4 %)	21.2 (17.4 %)		246 (46.2 %)	52.3 (46.2 %)	
Unknown	48 (4.4 %)	10.6 (4.4 %)		102 (5.7 %)	57.7 (5.7 %)		17 (3.3 %)	3.2 (3.3 %)		26 (3.1 %)	3.8 (3.1 %)		27 (5.1 %)	5.7 (5.1 %)	
Metastatic disease															
M0	1034 (95.6 %)	229.4 (95.6 %)	1.0	1666 (93.4 %)	941.9 (93.4 %)	1.0	496 (96.3 %)	94.4 (96.3 %)	1.0	824 (98.8 %)	120.5 (98.8 %)	1.0	507 (95.3 %)	107.7 (95.3 %)	1.0
M1	48 (4.4 %)	10.6 (4.4 %)		117 (6.6 %)	66.1 (6.6 %)		19 (3.7 %)	3.6 (3.7 %)		10 (1.2 %)	1.5 (1.2 %)		25 (4.7 %)	5.3 (4.7 %)	
N category															
N−	1041 (96.2 %)	230.9 (96.2 %)	1.0	1661 (93.2 %)	939 (93.2 %)	1.0	494 (95.9 %)	94 (95.9 %)	1.0	812 (97.4 %)	118.8 (97.4 %)	1.0	505 (94.9 %)	107.3 (94.9 %)	1.0
N+	8 (0.7 %)	1.8 (0.7 %)		16 (0.9 %)	9 (0.9 %)		4 (0.8 %)	0.8 (0.8 %)		3 (0.4 %)	0.4 (0.4 %)		1 (0.2 %)	0.2 (0.2 %)	
NX	33 (3.0 %)	7.3 (3.0 %)		106 (5.9 %)	59.9 (5.9 %)		17 (3.3 %)	3.2 (3.3 %)		19 (2.3 %)	2.8 (2.3 %)		26 (4.9 %)	5.5 (4.9 %)	
Surgery of primary tumor															
No	61 (5.6 %)	13.5 (5.6 %)	1.0	52 (2.9 %)	29.4 (2.9 %)	1.0	16 (3.1 %)	3 (3.1 %)	1.0	37 (4.4 %)	5.4 (4.4 %)	1.0	43 (8.1 %)	9.1 (8.1 %)	1.0
Yes	1021 (94.4 %)	226.5 (94.4 %)		1731 (97.1 %)	978.6 (97.1 %)		499 (96.9 %)	95 (96.9 %)		797 (95.6 %)	116.6 (95.6 %)		489 (91.9 %)	103.9 (91.9 %)	
Period															
1998–2002	139 (12.8 %)	30.8 (12.8 %)	1.0	311 (17.4 %)	175.8 (17.4 %)	1.0	105 (20.4 %)	20 (20.4 %)	1.0	102 (12.2 %)	14.9 (12.2 %)	1.0	72 (13.5 %)	15.3 (13.5 %)	1.0
2003–2006	285 (26.3 %)	63.2 (26.3 %)		521 (29.2 %)	294.5 (29.2 %)		226 (43.9 %)	43 (43.9 %)		177 (21.2 %)	25.9 (21.2 %)		160 (30.1 %)	34 (30.1 %)	
2007–2011	658 (60.8 %)	146 (60.8 %)		951 (53.3 %)	537.6 (53.3 %)		184 (35.7 %)	35 (35.7 %)		555 (66.5 %)	81.2 (66.5 %)		300 (56.4 %)	63.7 (56.4 %)	
Sex															
Male	603 (55.7 %)	133.8 (55.7 %)	1.0	931 (52.2 %)	526.3 (52.2 %)	1.0	344 (66.8 %)	65.5 (66.8 %)	1.0	535 (64.1 %)	78.3 (64.1 %)	1.0	291 (54.7 %)	61.8 (54.7 %)	1.0
Female	479 (44.3 %)	106.2 (44.3 %)		852 (47.8 %)	481.7 (47.8 %)		171 (33.2 %)	32.5 (33.2 %)		299 (35.9 %)	43.7 (35.9 %)		241 (45.3 %)	51.2 (45.3 %)	
Age (years)															
<65	655 (60.5 %)	145.3 (60.5 %)	1.0	992 (55.6 %)	560.8 (55.6 %)	1.0	223 (43.3 %)	42.4 (43.3 %)	1.0	434 (52.0 %)	63.5 (52.0 %)	1.0	316 (59.4 %)	67.1 (59.4 %)	1.0
65+	427 (39.5 %)	94.7 (39.5 %)		791 (44.4 %)	447.2 (44.4 %)		292 (56.7 %)	55.6 (56.7 %)		400 (48.0 %)	58.5 (48.0 %)		216 (40.6 %)	45.9 (40.6 %)	
Ethnicity															
Caucasian	917 (84.8 %)	203.4 (84.8 %)	1.0	1341 (75.2 %)	758.1 (75.2 %)	1.0	430 (83.5 %)	81.8 (83.5 %)	1.0	696 (83.5 %)	101.8 (83.5 %)	1.0	459 (86.3 %)	97.5 (86.3 %)	1.0
African American	65 (6.0 %)	14.4 (6.0 %)		262 (14.7 %)	148.1 (14.7 %)		70 (13.6 %)	13.3 (13.6 %)		58 (7.0 %)	8.5 (7.0 %)		39 (7.3 %)	8.3 (7.3 %)	

Table 5 continued

	Stomach vs duodenum			Stomach vs ileum/jejunum			Stomach vs colon			Stomach vs rectum			Stomach vs peritoneum		
	Stomach (%)	Duodenum (%)	P^a	Stomach	Ileum/Jejunum	P^a	Stomach	Colon	P^a	Stomach	Rectum	P^a	Stomach	Peritoneum	P^a
Other/unknown	100 (9.2 %)	22.2 (9.2 %)		180 (10.1 %)	101.8 (10.1 %)		15 (2.9 %)	2.9 (2.9 %)		80 (9.6 %)	11.7 (9.6 %)		34 (6.4 %)	7.2 (6.4%)	
Marital status															
Married	810 (74.9 %)	179.7 (74.9 %)	1.0	1153 (64.7 %)	651.8 (64.7 %)	1.0	379 (73.6 %)	72.1 (73.6 %)	1.0	635 (76.1 %)	92.9 (76.1 %)	1.0	359 (67.5 %)	76.3 (67.5 %)	1.0
Single	96 (8.9 %)	21.3 (8.9 %)		209 (11.7 %)	118.2 (11.7 %)		48 (9.3 %)	9.1 (9.3 %)		70 (8.4 %)	10.2 (8.4 %)		59 (11.1 %)	12.5 (11.1 %)	
Other/unknown	176 (16.3 %)	39 (16.3 %)		421 (23.6 %)	238 (23.6 %)		88 (17.1 %)	16.7 (17.1 %)		129 (15.5 %)	18.9 (15.5 %)		114 (21.4 %)	24.2 (21.4 %)	

[a] Weighted chi-square test in pairwise comparisons of gastric GIST versus GIST at other locations

regarding prognosis and guides decision making regarding adjuvant imatinib treatment. The first risk classification by Fletcher and et al. [5] used GIST size and mitotic rate and categorized patients into four groups (very low risk, low risk, intermediate risk, and high risk) . In 2006, Miettinen and Lasota [1] published the widely used AFIP risk classification. This risk classification is based on approximately 2000 patients and provides estimates of recurrence for GIST subsets based on size, mitotic rate and location. The AFIP risk classification was even incorporated in the 2012 European Society of Medical Oncology guidelines [3]. In the AFIP risk classification, intestinal GIST patients are claimed to have significantly worse prognosis than gastric GIST patients, particularly if the GIST size exceeds 5 cm. Furthermore, worse outcomes are found for duodenal and rectal GIST location. For instance, in patients with a GIST size greater than 10 cm and a mitotic rate equal to or less than five per 50 HPF, the risk of metastases or tumor-related death is 12 % in gastric GIST patients, but 52 % in jejunal/ileal GIST patients, 34 % in duodenal GIST patients, and even 57 % in rectal GIST patients. Similarly, in patients with a GIST size from 2 to 5 cm and a mitotic rate above five per 50 HPF, the risk of metastases or tumor-related death is 16 % in gastric GIST patients, but 73 % in jejunal/ileal GIST patients, 50 % in duodenal GIST patients, and 52 % in rectal GIST patients. Our results strongly differ from those of the AFIP risk classification. Most importantly, neither statistically significant nor clinically relevant overall and cancer-specific survival differences can be found between gastric GIST patients and patients with intestinal or rectal GIST. Conversely, in the present analysis, patients with colonic and extravisceral GIST have significantly worse outcomes than gastric GIST patients. The fact that nongastric GIST is associated with worse prognosis than gastric GIST is thus due to colonic and extraintestinal GIST, and not because of location in the small bowel or rectum.

The large discrepancy regarding patient outcomes between the AFIP risk classification and our results is concerning as the estimated risk of recurrence serves as the main criterion for the use of adjuvant imatinib treatment. The question arises whether patients with intestinal GIST are overtreated. It is not clear why this difference exists between the data from Miettinen and colleagues—who undoubtedly did outstanding pioneer work regarding the understanding of pathophysiology and treatment of GIST—and the SEER data. It may be due to different time periods in which the patients were enrolled. The patients on which the AFIP risk classification is based were enrolled from 1970 to 1996, but our study includes a patient population from 1998 to 2011. It is also known that virtually none of the patients enrolled in the studies of Miettinen and colleagues were treated with imatinib, as the relevant

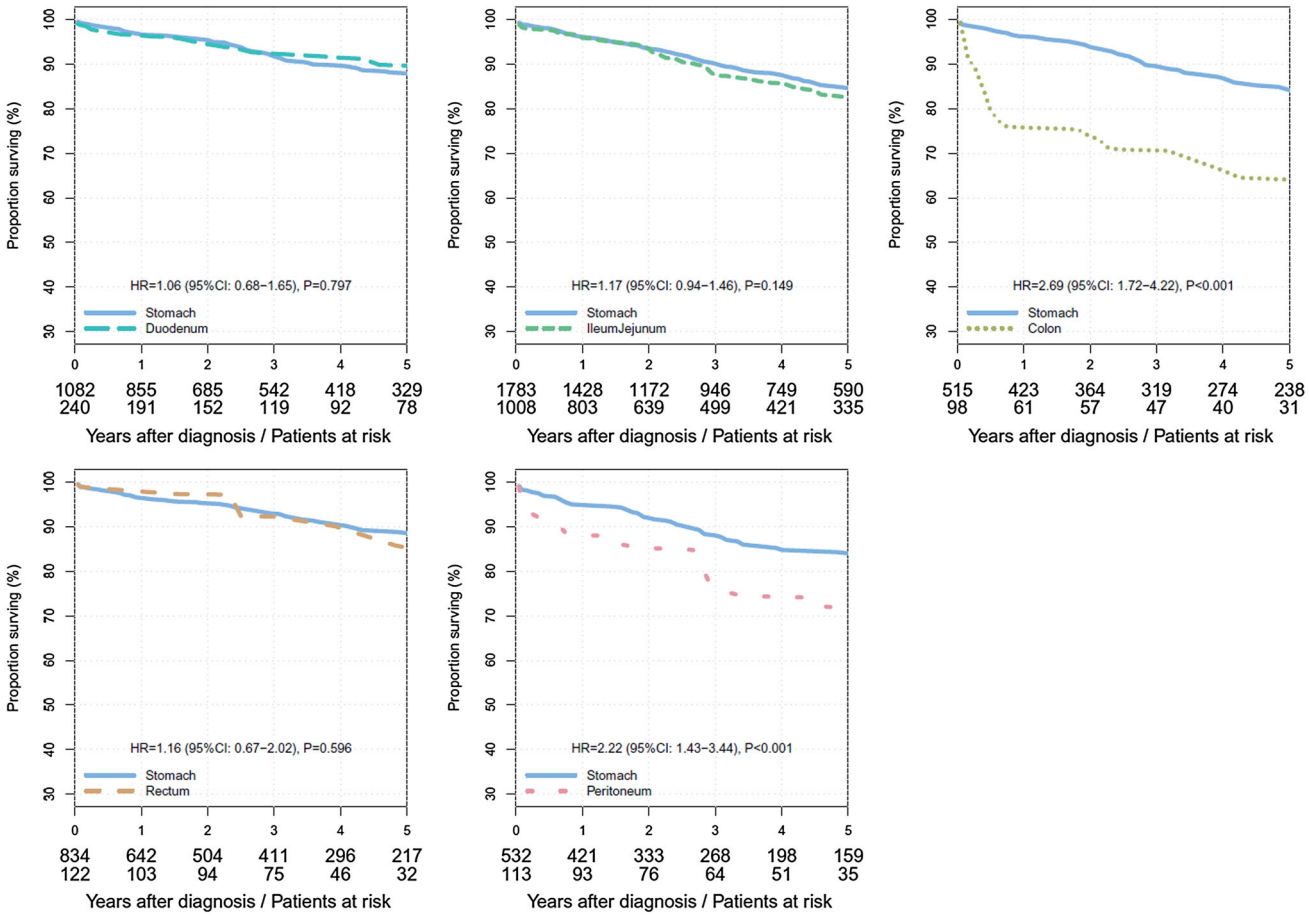

Fig. 2 Kaplan–Meier curves for cancer-specific survival after exact weighted pairwise propensity score matching. Each location is compared with gastric location (reference category). The hazard ratios (*HR*) and the *P* values indicate the risk of death for a gastrointestinal stromal tumor in a particular location compared with gastric gastrointestinal stromal tumor. The numbers of patients at risk in the two groups are given *below* the *x*-axis. *CI* confidence interval

period was before the conduct of randomized controlled trials in the advanced setting [11, 12] and the adjuvant setting [13, 14] and FDA approval. Second, it is possible that imatinib treatment in patients with intestinal and rectal GIST in our study compensates for the worse prognosis. However, in subset analysis of the early (1998–2004) versus the late (2005–2011) period, our results are robust regarding the prognosis of patients with intestinal GIST compared with patients with gastric GIST. This appears to be a strong argument against potential confounding due to imatinib intake. Regardless, there is no doubt that a risk categorization of continuous biological variables such as size and mitotic rate is problematic. In this regard, prognostic contour maps as described by Joensuu et al. [15] are helpful in assessing the risk of recurrence in GIST patients. The main advantage of these contour maps is that minor changes in size and mitotic rate do not result in major changes in the individual patient's risk estimation.

Small bowel GIST were described as being different from gastric GIST. For instance, the rate of *KIT* exon 9 mutation, which is known to be associated with poorer prognosis compared with a mutation in *KIT* exon 11, is clearly higher in intestinal GIST than in gastric GIST [16, 17]. In this regard, our findings are surprising. However, on a population-based level, molecular differences between gastric and intestinal GIST do not seem to relevantly impact overall and cancer-specific survival.

In the present analysis, patients with colonic and extraintestinal GIST had significantly worse overall and cancer-specific survival compared with patients with gastric or intestinal GIST. This may be explained by a later time point of diagnosis in these locations and hence larger tumor size, which, however, was only found in the present analysis for extraintestinal GIST. Furthermore, it is well known that some peritoneal GIST metastases are misclassified as primary extraintestinal GIST, which then of course is associated with worse prognosis [1].

We acknowledge the limitations of this study. The main drawback of this analysis is the lack of information on mitotic rate, which was only systematically collected in the

SEER database after 2009. However, a sensitivity analyses including information on mitotic counts showed similar findings (see the electronic supplemental material). Moreover, if intestinal GIST patients indeed had a worse prognosis than gastric GIST patients, this should become evident in a large US cohort even without having the information on mitotic rate. Second, information on tyrosine kinase inhibitors used, pathologic findings such as ulceration, tumor necrosis, and type of *KIT* or *PDGFR* mutations, comorbidities, performance status, and the site and number of metastases is not available in the SEER database. Despite these limitations, the present study has a variety of strengths. First, the population-based nature of the registry mirrors the real-world outcomes for GIST patients and is associated with a high degree of generalizability. It is key to evaluate to what extent findings in often highly selected patients in single-institution studies can be found in the overall patient population. Second, the large sample size is associated with a high degree of power. Third, the adjustment for confounding factors was performed not only with conventional multivariate analysis but also with propensity score matching.

In conclusion, contrary to common belief, overall survival and cancer-specific survival of patients with small bowel GIST are not different from those of patients with gastric GIST when adjustment is made for confounding variables on a population based-level. These findings have relevant implications in the decision making for adjuvant treatment of small bowel GIST patients.

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Compliance with ethical standards

Ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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