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A Population-Based Study of the Incidence and Survival of Anorectal Gastrointestinal Stromal Tumor

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Manuscript Preparation E
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Background: Gastrointestinal stromal tumor (GIST) is the most common type of primary gastrointestinal mesenchymal tumor, but GISTs arising in the anus and rectum are rare. This study aimed to undertake a population-based analysis of the incidence, patient demographics, and survival of patients with anorectal GIST compared with patients with GIST arising from other sites based on the Surveillance, Epidemiology, and End Results (SEER) Program database.

Material/Methods: The SEER database was used to identify all patients diagnosed with GIST and patients diagnosed with anorectal GIST from 2000 to 2015. The incidence of GIST, baseline clinical and demographic data, tumor stage, and patient survival data were analyzed, including overall survival (OS) and cancer-specific survival (CSS).

Results: A total of 277 patients with anorectal GIST were identified, with an incidence of 0.018 per 100,000. The incidence of GIST arising from other sites was 0.719 per 100,000. The median age at diagnosis for anorectal GIST was 57.5 years (range, 26–92 years), median tumor size was 6.55 cm (range, 0.6–20 cm), and surgery, but not chemotherapy, improved OS and CSS. Patients with anorectal GIST had a mean 1-year, 3-year, 5-year, and 10-year OS of 91.1%, 82.5%, 75.2%, and 58.5%, respectively. Patients with GIST arising at other sites had a mean 1-year, 3-year, 5-year, and 10-year OS of 88.3%, 76.4%, 66.5%, and 46.8%, respectively.

Conclusions: Anorectal GIST is a rare tumor that has a better outcome compared with GISTs arising at other sites in the gastrointestinal tract.

MeSH Keywords: Cohort Studies • Gastrointestinal Stromal Tumors • SEER Program

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Background

Gastrointestinal stromal tumor (GIST) is the most common type of primary gastrointestinal mesenchymal tumor and is believed to arise from the gastrointestinal interstitial cell of Cajal [1]. GISTs most commonly occur in the stomach and small intestinal, and anorectal GISTs are rare [2]. GISTs show a spectrum of malignancy from low-grade tumors to high-grade tumors and can present as early-stage tumors confined to the bowel wall, or as late-stage tumors with local invasion and metastases [3]. The prognosis of GIST is influenced by age, tumor size, histological grade, and mitotic index [4]. Gastric GISTs have been shown to have less aggressive malignant behavior when compared with GISTs located in other sites [5]. Therefore, the location of the primary tumor site has prognostic implications for patients with GIST.

Surgical treatment varies in difficulty according to the location of GIST. For anorectal GIST, it is difficult to achieve complete resection due to the complex anatomic structure of the anus and rectum. Surgery is a potentially curative first-line treatment choice for GIST. However, imatinib, a targeted tyrosine kinase inhibitor, has been recommended as effective postoperative adjuvant treatment [6]. Imatinib is effective for the treatment of metastatic or non-resectable GISTs and is used as neoadjuvant therapy [7,8]. Wilkinson et al. [9] showed the effects of imatinib on reducing tumor size, mitotic rate, and sphincter preservation surgery in a cohort of 19 patients with rectal GIST. However, studies on anorectal GISTs are limited and have primarily been case reports or case series with small sample size.

Therefore, this study aimed to undertake a population-based analysis of the incidence, patient demographics, and survival of patients with anorectal GIST compared with patients with GIST arising from other sites in the gastrointestinal tract based on the Surveillance, Epidemiology, and End Results (SEER) Program database.

Material and Methods

Patients

Patients with anorectal gastrointestinal stromal tumor (GIST) from 2000 to 2015 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) Program database using SEER-Stat software (version 8.3.5) (*https://seer.cancer.gov/*). Ethical consent was waived in this study as the SEER database contained anonymized patient data. Based on the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) histological classification, the SEER database was interrogated for GISTs, corresponding to ICD-O-3 code 8936, for all sites. Data on the frequency, incidence, treatment, and survival data of GISTs were retrieved. Patients with an unknown primary site were excluded. Data for every GIST not located in rectum and anus was were compared with anorectal GIST, and referred to as 'other GIST.'

Baseline clinical and demographic patient characteristic data retrieved included age, year of diagnosis, gender, race, and marital status. Data on tumor variables included tumor location, grade, treatment, and stage according to the American Joint Committee on Cancer (AJCC) 7th edition, or the tumor, node, metastasis (TNM) stage. Patient survival time from diagnosis to last follow-up or the date of death were included. Patients with a live vital status or who were lost to follow-up were right censored for overall survival (OS) analysis, and patient death not attributable to GISTs were right censored for the cancer-specific survival (CSS) analysis.

Statistical analysis

Rates were per 100,000 and were age-adjusted according to the 2000 US Standard Population, using the 19 age groups according to the US Census P25-1130 (*www.census.gov/prod/1/pop/p25-1130*). The annual percentage change in incidence was analyzed using yearly endpoints. Survival curves were analyzed using the Kaplan-Meier method by treatment modality and AJCC stage and compared using the log-rank test. Continuous variables were compared using the t-test. Comparison of categorical variables was performed using the chi-squared (χ^2) test. Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc, Chicago, IL, USA) or SEER*Stat 8.3.5 software (National Cancer Institute, Bethesda, MD, USA). P-values were two-sided. $P<0.05$ indicated statistical significance.

Results

Patient and tumor characteristics

The Surveillance, Epidemiology, and End Results (SEER) Program 18 database search identified 277 anorectal GISTs, compared with 9713 cases of GIST arising from other sites in the gastrointestinal tract, or 'other GIST' (Table 1). There were 56 patients with an unknown primary site that were excluded. The baseline characteristics were shown in Table 1. Data analysis showed that 60.65% of anorectal GISTs and 52.35% of other GISTs were diagnosed in male patients, and 39.35% of anorectal GISTs and 47.65%of other GISTs were diagnosed in female patients ($P=0.006$). Caucasian patients comprised 61.37% of anorectal GISTs and 68.97% of other GISTs, African-American patients represented 14.80% of anorectal GISTs and 18.01% of other GISTS, and other ethnic groups accounted for 9.03% of anorectal GISTs and 12.66% of other GISTS ($P<0.001$). Marital status in anorectal GISTs (61.37% were married) and other GISTs

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Table 1. Demographic and clinical data of the patients included in the study.

Characteristic		Anorectal GIST (N=277)	Other GISTS (N=9713)	p-Value
Gender, n (%)	Male	168 (60.65)	5085 (52.35)	0.006
	Female	109 (39.35)	4628 (47.65)	
Ethnicity, n (%)	White	170 (61.37)	6699 (68.97)	<0.001
	Black	41 (4.80)	1749 (18.01)	
	Other	25 (9.03)	1230 (12.66)	
	NA	2 (0.72)	35 (0.30)	
Marital status, n (%)	Married	170 (61.37)	5536 (57.00)	0.18
	Other	90 (32.49)	3675 (37.84)	
	NA	17 (6.14)	502 (5.17)	
Age (years)	Range	26–92	8–101	0.017
	Median	57.5	62	
	Mean	59.23	61.35	
Surgery, n (%)	No surgery	74 (26.71)	2093 (21.55)	0.083
	Surgery	202 (72.92)	7531 (77.54)	
	NA	1 (0.36)	89 (0.92)	
Survival months	Range	0–191	0–191	0.023
	Median	55.5	48	
	Mean	68.72	59.03	
Grade	Grade I	16	1095	0.041
	Grade II	27	900	
	Grade III/IV	29	972	
	NA	205	6746	
Size (cm)	Range	0.6–20	0–99	<0.001
	Median	6.55	7.5	
	Mean	6.98	9.5	
Location, n (%)	Rectum/anus	277	NA	
	Stomach	NA	5626 (57.92)	
	Small intestine	NA	2650 (27.28)	
	Colon	NA	249 (2.56)	
	Esophagus	NA	56 (0.58)	
	Other	NA	1132 (11.65)	
	Unknown	NA	56 (0.58)	
Incidence*		0.018	0.719	
Annual percentage change (2000–2015)		2.747 (P=0.047)	3.816 (P<0.001)	

* Rates are per 100,000 and age adjusted to the 2000 US Standard Population (19 age groups, census P25-1130) standard.

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Table 2. Tumor, node, metastasis (TNM) and (AJCC) staging for gastrointestinal stromal tumors (GISTs).

TNM		Anorectal GISTs (%)	Other GISTs (%)	P-value	AJCC	Anorectal GISTs (%)	Other GISTs (%)	p-Value
T7	T0	0 (0)	5 (0.1)	0.070	I	30 (23.8)	1586 (34.8)	0.151
	T1	20 (15.9)	508 (11.1)		II	14 (11.1)	548 (12.0)	0.825
	T2	36 (28.6)	1235 (27.1)		III	33 (26.2)	560 (12.3)	0.025
	T3	39 (31.0)	1119 (24.6)		IV	11 (8.7)	747 (16.4)	0.124
	T4	10 (7.9)	883 (19.4)		NA	38 (30.2)	1116 (24.5)	
	Tx	14 (11.1)	518 (11.4)		Missing	151	5156	
	NA	7 (5.6)	289 (6.3)					
	Missing	151	5156					
N7	N0	11 5(91.3)	4102 (90.0)	0.934				
	N1	4 (3.2)	166 (3.6)					
	Nx	7 (5.6)	289 (6.3)					
	Missing	151	5156					
M7	M0	110 (87.3)	3598 (79.0)	0.108				
	M1	9 (7.1)	670 (14.7)					
	Mx	7 (5.6)	289 (6.3)					
	Missing	151	5156					

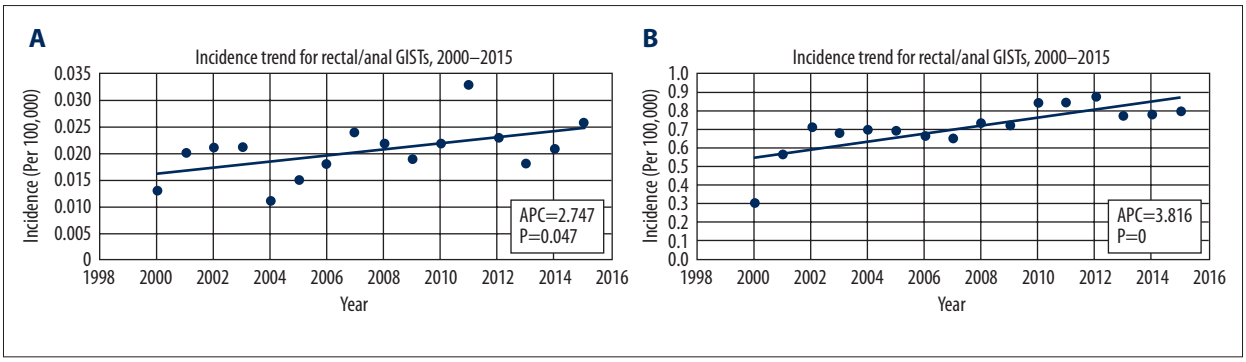

Figure 1. Surveillance, Epidemiology, and End Results (SEER) data show the trend in the incidence of anorectal and other gastrointestinal stromal tumors (GISTs), between 2000 and 2015. (**A**) The trend in the incidence of anorectal gastrointestinal stromal tumor (GIST) between 2000 to 2015. (**B**) The trend in the incidence of other GISTs between 2000 to 2015. APC – annual percentage change.

(57% were married) showed no statistically significant difference (P=0.18). The median (and mean) age at diagnosis was 57.5 years (mean, 59.23 years) for anorectal GIST and 62 years (mean, 61.35 years) for other GISTs. Patient age ranged 26–92 years for anorectal GIST and 8–101 years for other GISTs (P=0.017).

The tumor, node, metastasis (TNM) classification and American Joint Committee on Cancer (AJCC) stage are summarized in Table 2. Staging information was reported in 45% of anorectal GISTs (126/277) and other 55% of GISTs (4557/9713). Anorectal GISTs were stage T2 (28.6%) and stage T3 (27.1%), whereas other GISTs included a larger proportion stage T4 tumors (19.4%) compared with T4 tumors (7.9%) in anorectal GISTs (T1–T3 *vs.* T4; P=0.015). The majority of both anorectal and other GISTs showed no lymph node involvement (91.3% *vs.* 90.0%) and no distant metastases (87.3% *vs.* 79.0%). Patients with anorectal GISTs were most commonly stage III (26.2%), followed by stage I (23.8%), stage II (11.1%), and stage IV (8.7%).

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Table 3. Treatment for gastrointestinal stromal tumors (GISTs).

	Anorectal GISTs (%)	Other GISTs (%)	p-Value
Surgery type			<0.001
No surgery	74 (26.7)	2093 (21.5)	
Local excision	113 (40.8)	1042 (10.7)	
Partial excision	42 (15.2)	4366 (45.0)	
Total excision	2 (0.7)	618 (6.4)	
En block dissection	39 (14.1)	1299 (13.4)	
Surgery NOS	6 (2.2)	206 (2.1)	
Unknown	1 (0.4)	89 (0.9)	
Chemotherapy			<0.001
No chemotherapy	134 (48.4)	5959 (61.4)	
Chemotherapy	143 (51.6)	3754 (38.6)	

For other GISTs, 34.8% were stage I, followed by stage IV (16.4%); and a similar proportion of stage II (12.0%) and stage III (12.3%). The difference was statistically significant for stage III (P=0.025), but not for stage I (P=0.151), stage II (P=0.852) and stage IV (P=0.124). Anorectal GISTs tended to be localized and early stage when compared with other GISTs, according to the analysis of the T-stage and tumor size data.

Incidence, treatment, and survival analysis

Analysis of data from the SEER database showed that between 2000 and 2015 the incidence of anorectal GIST was 0.018 per 100,000, with an annual percentage increase of 2.747% (P=0.047) (Table 1, Figure 1A). The incidence of other GISTs was 0.719 per 100,000, adjusted to the 2000 US standard population (census P25-1130) (Table 1, Figure 1B), and the annual percentage change was 3.816% (P<0.001).

Data on the treatment modality was available in most cases, including 276 anorectal GISTs and 9623 other GISTs (Table 3). Surgery alone was the most commonly chosen treatment in anorectal GISTs (46.4%) and other GISTs (48.0%) (Table 3), followed by the combination of surgery and chemotherapy for anorectal GISTs (26.8%) and other GISTs (30.2%) (Table 3). Local excision was performed most commonly for anorectal GISTs (40.8%), followed by partial excision (15.2%) and en bloc resection (14.1%). In other GISTs, the most frequent surgical procedure was partial excision (45.0%). En bloc resection (13.4%) and local excision (10.7%) were performed much less frequently for other GISTs. Chemotherapy treatment was used significantly more often (51.6%) for patients with anorectal GISTs, compared with patients with other GISTs (38.6%) (P<0.001).

The median (and mean) survival of patients with anorectal GISTs were 55.5 months (mean, 59.23 months), which was a significantly greater than for other GISTs with a median survival of 48 months (mean, 59.03 months) (P=0.023) (Table 1).

For patients with anorectal GIST, the overall survival (OS) at 1 year (91.1%), 3 years (82.5%), 5 years (75.2%), and 10 years (58.5%) and the cancer-specific survival (CSS) at 1 year (96.6%), 3 years (92.3%), 5 years (86.6%), and 10 years (75.6%) were compared with patients with other GISTs, with an OS at 1 year (88.3%), 3 years (76.4%), 5 years (66.5%), and 10 years (46.8%) and CSS at 1 year (94.2%), 3 years (86.9%), 5 years (80.2%), and 10 years (68.2%) (Table 4). The OS and CSS of patients with anorectal GIST were significantly greater compared with patients with other GISTs (Figure 2A, 2B). The 5-year survival rate was used to evaluate the effectiveness of treatment and the impact of treatment modalities on survival, as shown in Table 4. Surgery improved the outcome of patients with anorectal GIST (Table 4), while chemotherapy did not (Table 4). Treatments based on surgery had the best outcome, while patients who underwent chemotherapy showed no difference compared with patients without chemotherapy and surgery.

To compensate for the impact of missing data on survival analysis, survival data were compared for anorectal GISTs and other GISTs in two matched groups, according to early stage (I, II) and advanced stage (III, IV). There was no significant survival difference for early stage anorectal GIST and other GISTs (Figure 2C, 2D), but patients with advanced stage anorectal GIST had a better outcome than patients with other GIST with advanced stage (Figure 2E, 2F).

Discussion

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor originating from the gastrointestinal tract, and

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Table 4. Survival analysis for patients with anorectal gastrointestinal stromal tumors (GISTs) and GISTs arising at other sites in the gastrointestinal site.

	Anorectal GISTs	Other GISTs	p-value
Overall survival (OS) (%)			0.004
1-year	91.1	88.3	
3-year	82.5	76.4	
5-year	75.2	66.5	
10-year	58.5	46.8	
Cancer-specific survival (CSS) (%)			0.041
1-year	96.6	94.2	
3-year	92.3	86.9	
5-year	86.6	80.2	
10-year	75.6	68.2	
5-year overall survival (OS) (%)			
No surgery	48.6		<0.001
Surgery	83.7		
No chemotherapy	75.7		0.954
Chemotherapy	74.8		
Neither surgery or chemotherapy	55.5		Ref.
Chemotherapy alone	53.3		0.347
Surgery alone	82.1		0.001
Chemotherapy + surgery	85.8		<0.001
5-year cancer-specific survival (CSS) (%)			
No surgery	71.2		<0.001
Surgery	90.3		
No chemotherapy	84.7		0.434
Chemotherapy	88.5		
Neither surgery or chemotherapy	71.7		Ref.
Chemotherapy alone	77.6		0.875
Surgery alone	87.9		0.020
Chemotherapy + surgery	93.3		0.040
5-year OS by stage (%)			0.131
Stage I+II (early)	95.3	83.9	
Stage III+IV (late)	82	53.8	
5-year CSS by stage (%)			0.100
Stage I+II (early)	100	96.4	
Stage III+IV (late)	92.3	66.9	

Ref – reference.

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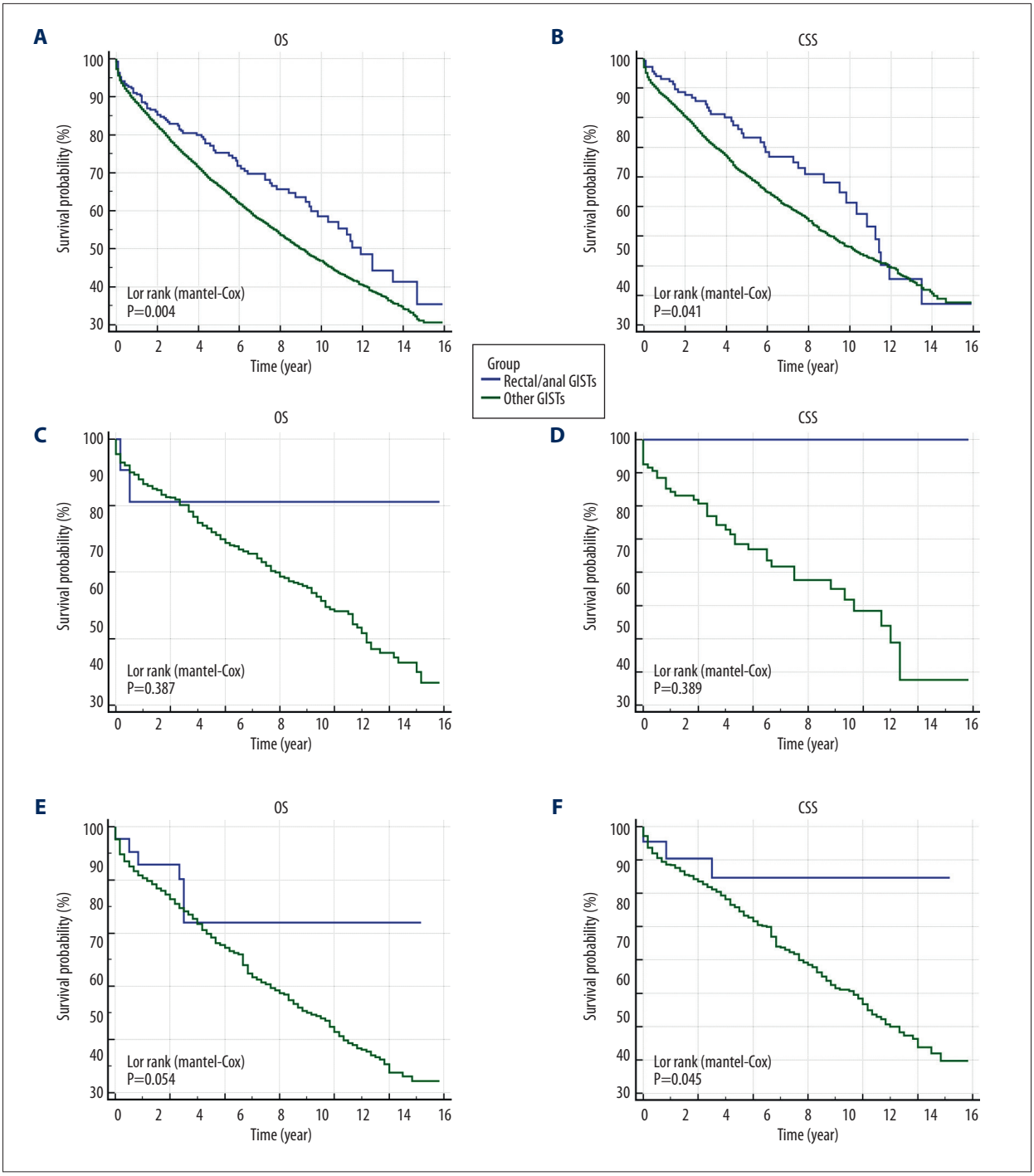

Figure 2. Surveillance, Epidemiology, and End Results (SEER) data show the trend in overall survival (OS) and cancer-specific survival (CSS) for patients with anorectal gastrointestinal stromal tumor (GIST) compared with other GISTS, between 2000 and 2015. (**A**) Overall survival (OS) for anorectal gastrointestinal stromal tumor (GIST) and other GISTs. (**B**) Cancer-specific survival (CSS) for anorectal GIST and other GISTs. (**C**) OS for low stage (I, II) anorectal GIST and other GISTs. (**D**) CSS for low stage (I, II) anorectal GISTs and other GISTs. (**E**) OS for advanced stage (III, IV) anorectal GISTs and other GISTs. (**F**) OS for advanced stage (III, IV) anorectal GISTs and other GISTs.

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most GISTs are found in the stomach and small intestine [10]. Treatment and survival data for the more common types of GIST have been analyzed in previous studies [11–14]. However, because anorectal GISTs are rare, there have been few previous studies that have evaluated the survival data according to patient demographics, stage, and treatment. The findings of the present study showed that the incidence of anorectal GISTs was 0.018 per 100,000 with an increased annual percentage change of 2.747% (Table 1, Figure 1A) and anorectal GISTs comprised 2.8% of all GISTs. Age at diagnosis, male gender, African-American ethnicity, and advanced stage at presentation have previously been reported to be associated with reduced overall survival (OS) for patients with GISTs [15]. The findings of the present study have shown that anorectal GISTs were more common in men, presented at a younger age, and were less common in African-Americans when compared with other GISTs (Table 1). More than half of the anorectal GISTs were stage T2 (28.6%) and T3 (31.0%), while few patients had lymph node involvement (3.2%) and distant metastasis (7.1%) (Table 2). The percentage of cases diagnosed with early stage (I, II) and advanced stage (III, IV) anorectal GIST were almost equal (Table 2).

Ye et al. [16] previously reported that tumor location was not an independent prognostic factor in resectable small GISTs, while other studies identified tumor location as an independent prognostic factor in predicting patient survival [17,18]. In the present study, the 1-year, 3-year, 5-year, and 10-year OS and cancer-specific survival (CSS) were significantly greater in patients with anorectal GIST when compared with patients with other GISTs (Table 4). These findings are consistent with a previously published study [19]. For patients with early-stage tumors, survival rates in patients with anorectal GIST were not significantly different from survival rates in patients with other GISTs (Figure 2C, 2D). In advanced stage anorectal GIST, the OS was higher than other GISTs, but this finding was at the limit of statistical significance (P=0.054) (Figure 2E), whereas the CSS was significantly greater in patients with anorectal GISTs compared with patients with other GISTs (P=0.045) (Figure 2E). Survival analysis showed no significant difference between patients with early stage (I, II) and late stage (III, IV) anorectal GIST (Table 4). Combined with the smaller tumor size (Table 1) and fewer cases of late-stage (T4) tumors, anorectal GIST appeared to be less aggressive that GIST arising from other sites in the gastrointestinal tract (Table 2).

Surgery was commonly used in the treatment of anorectal GISTs and other GISTs (Table 3). More than half of patients with anorectal GIST received chemotherapy, while only 38.6% of patients with other GISTs received chemotherapy (Table 3). Local excision was the most common surgical treatment method in anorectal GISTs, while partial excision was the most common surgical treatment method in other GISTs (Table 3). Surgical resection is the standard treatment for localized GISTs and chemotherapy was preferentially recommended as an effective therapy for advanced GISTs or locoregional disease with a significant risk of relapse [20–22]. As the majority of anorectal GISTs have local recurrence after surgical resection, negative surgical margins were important [23]. However, complete surgical resection can be technically difficult in rectal GISTs because surgery is performed deep in the narrow pelvis and there is a risk of injuring the sphincter muscles or other adjacent organs [24].

In the present study, surgery was found to significantly improve the outcome of patients with anorectal GIST, while chemotherapy did not improve patient outcome (Table 4). The study findings showed that a combination of chemotherapy and surgery resulted in the greatest 5-year OS and CSS from survival analysis (Table 4). In recent decades, imatinib has been shown to be an effective preoperative chemotherapy agent in reducing tumor size and mitotic activity, making radical surgical resection more feasible and increasing the chance of preservation of the anal sphincter [23,25]. Recently, several studies have reported the superiority and advantage of the use of surgery with the combined use of adjuvant imatinib for anorectal GIST [26–28]. However, because of the limited number of only five patients with anorectal GIST included in the study by Kaneko et al. [25], it is difficult to directly compare the findings from the present study. In the present study, chemotherapy was not found to improve the OS and CSS for patients with anorectal GIST (Table 4).

Anorectal cancer comprises about one-third of all colorectal cancer (CRC), which is the second leading cause of cancer death in the United States [29]. More than 90% of anorectal cancers are adenocarcinomas [30]. Because there is no previously published data that compared anorectal GISTs with anorectal adenocarcinoma, a comparison was made as part of the present study on lymph node metastasis, distant metastasis, OS, and CSS between these two groups (Table 5). The anorectal GISTs showed better OS, CSS, less lymph node and distant metastasis than anorectal adenocarcinoma (Table 5).

This study had several limitations. Firstly, due to the analysis of retrospective data from the Surveillance, Epidemiology, and End Results (SEER) Program database, there was likely to be bias arising from data input and also missing data. Second, some treatment data was not obtained, including the specific type and duration of chemotherapy, and data on the adequacy of the surgical resection margin, which is important for survival analysis. Also, for more than half of patients, data on the tumor stage information was missing, which might affect the results and the conclusions made. However, this is the first study on the incidence and survival of anorectal GISTs with large sample size, and the use of the nationally representative SEER database add to the previously limited knowledge

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Table 5. Comparison of the incidence of lymph node (LN) and distant metastasis, overall survival (OS) and cancer-specific survival (CSS) between anorectal gastrointestinal stromal tumors (GISTs) and anorectal adenocarcinoma.

	Anorectal GISTs	Anorectal adenocarcinoma	p-Value
OS, %			<0.001
1 y	91.1	85.8	
3 y	82.5	70.8	
5 y	75.2	61.2	
10 y	58.5	46.7	
CSS, %			<0.001
1 y	96.6	88.9	
3 y	92.3	76.6	
5 y	86.6	69.4	
10 y	75.6	61.7	
Node–, %	91.3	59.9	<0.001
Node+, %	3.2	33.4	
Nx, %	5.6	6.7	
No metastasis, %	87.3	83.5	<0.001
Metastasis, %	7.1	16.5	
Mx, %	5.6	0	

of incidence and survival in patients with anorectal GIST compared with other GISTs.

Conclusions

Anorectal gastrointestinal stromal tumor (GIST) is a rare tumor that has a better outcome compared with GISTs arising at other sites in the gastrointestinal tract. The findings of this population-based study showed that anorectal GIST was more likely to be diagnosed at an earlier stage (T2 and T3), with a lower tumor grade, and with fewer involved lymph nodes and distant metastases compared with other GISTs. Patients with anorectal GIST had a better outcome compared with patients with other GISTs and that surgical treatment, rather than chemotherapy, resulted in improved survival. However, the role of chemotherapy in anorectal GIST requires further large-scale controlled clinical studies.

Acknowledgments

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Ethics approval and consent to participate

Patient consent was not required in this study, as anonymized patient data were analyzed from the Surveillance, Epidemiology, and End Results (SEER) Program database.

Conflict of interest

None

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