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Gastrointestinal Cancer

Aggressive Histology and Extensive Metastasis Characteristic of Very Young Gastric Cancer (Less Than 30 Years): A Retrospective Clinical Audit

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Abstract

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Objectives Gastric cancer (GC) is an aggressive disease and remains one of the most common causes of cancer-related mortality worldwide. Incidence of gastric cancer in young (GCY) varies between 2 and 8%. GCY faces unique challenges such as biological variation, diagnosis at an advanced stage, issues related to fertility preservation, and psychosocial considerations. This study aimed to find the differences in clinical characteristics and treatment outcomes of GCY compared to gastric cancer in older adults (GCO).

Material and Methods This is a retrospective study from a tertiary care center. We screened records from 2015 to 2020, identified 33 records of GCY (less than 30 years), and compared the data with GCO (greater than 30 years) during 2015 and 2018.

Results We identified 33 patients with GCY with a median age of 28 years (21–30) and a female to male ratio of 2:1. In GCY, 60% of patients presented with metastatic disease. Diffuse-type histology was more common in the GCY than in GCO (66.7% vs. 41.7%, $p = 0.001$). In patients with metastasis, multiple metastases were common in GCY compared to GCO (45% vs. 15%, $p = 0.003$). The median duration of follow-up for all patients was 27 (24–29) months. In GCY, the median OS was not reached for patients treated with curative intent, and it was 13 months for those treated with palliative intent.

Conclusion The incidence of GCY in our study was like the western literature. Female patients with aggressive diffuse histology and multiple extensive metastases were characteristic of GCY. The survival outcomes were identical to GCO.

Keywords
- young gastric cancer
- aggressive histology
- gastric adenocarcinoma

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Introduction

Gastric cancer (GC) is a very aggressive disease and remains one of the most common causes of cancer-related mortality worldwide. The age-standardized incidence rate for gastric cancer is 4.5 per 1 lakh population. Two-thirds of the patients present at an advanced stage due to non-specific symptoms at presentation, finally ending in palliative treatment.[1]

Across the literature, variation exists in the specific cut-offs used to define gastric cancer in young (GCY) adult patients. Most studies used an age cut-off of less than 40 years for GCY. Our study described GCY as all diagnosed gastric adenocarcinoma patients aged up to 30 years. Gastric cancer in older adults (GCO) includes all GC patients aged above 30 years. Our study's median age of GC is one decade less than that seen in western countries, so in our research, we defined GCY as less than 30 years.[2]

Various studies have reported the incidence of GCY between 2 and 8%.[3–6] The age-adjusted incidence rate in GCY from the SEER database was 0.9 per 1 lakh. The incidence of GC has decreased worldwide, but the incidence of GCY has increased over the past decade.[6] A single-center study from India reported the incidence of GCY as 18%, which was high compared to the literature data.[7]

GCY faces challenges such as biological tumor variation, advanced-stage diagnosis, treatment adherence, fertility preservation problems, and psychosocial considerations.[4,6,7] This study aimed to find the differences in clinical characteristics and treatment outcomes of GCY compared to GCO.

Materials and Methods

Study Population

This is a retrospective study in a tertiary care center in Southern India. We screened records from 2015 to 2020 and identified 33 records of GCY. To provide comparative data, we used the retrospective data of GCO from 2015 to 2018, which was available. Of the 505 patients, who presented with GC to our department from January 2015 to December 2018, 469 patients were >30 GCO with adenocarcinoma histology. The consort diagram of inclusion criteria and age is represented in ►Fig. 1.

Statistical Analysis

Categorical data are expressed in proportion, and a median described the continuous data with a range. The association between GCY and GCO patients was studied using a chi-square test. Overall survival (OS) was defined as the time from the date of diagnosis to death. For the patients alive at the last follow-up, OS was censored at the last follow-up or April 30, 2021, whichever came first. The Kaplan–Meier method was used to estimate the survival curves, and the

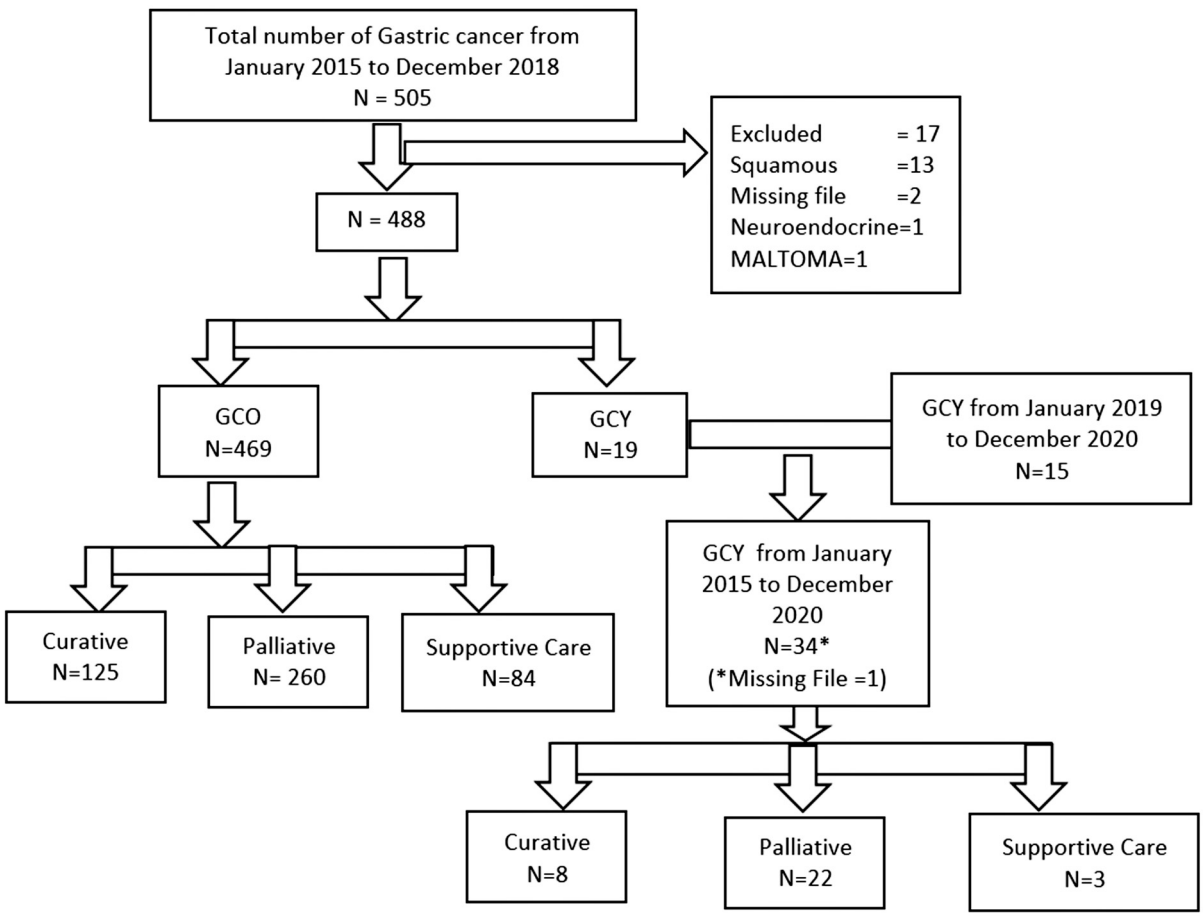

Fig. 1 Consort flow diagram of study participants.

log-rank test was used to compare survival data. IBM SPSS ver.19 was used for the analysis of the data. A p-value < 0.05 was considered statistically significant.

Results

From our records, we identified 33 patients with GCY from 2015 to 2020. The median age was 28 years (21–30), with a male to female ratio of 1:2. The most common symptom at presentation was abdomen pain, followed by weight loss and vomiting. Gastric outlet obstruction at presentation was seen in 22%. ►Table 1 describes the baseline characteristics. Distal GC were seen more often than proximal cancers. In GCY, 60% of patients presented with metastatic disease and 40% with nonmetastatic disease. Among the 40% of patients with non-metastatic disease, most (61%) were locally advanced (T4a and T4b). Nearly all patients had nodal involvement. In patients with metastasis, peritoneum, liver, and nonregional nodes were the most common sites of metastasis. Tumor characteristics of all patients are reported in ►Table 2.

A comparison of the clinical and pathological parameters between GCY and GCO is shown in ►Tables 1 and 2. Males were predominant in GCO (68%), whereas in the GCY group, females were predominant (67%). No patients in GCY had a family history of GC. GCY had good performance status (PS 1) compared to GCO (90.9% vs. 68.7%, p-value 0.02). Both groups had distal gastric cancers more often than proximal cancers, and GCY had less incidence of gastric outlet obstruction than GCO (21% vs. 40%, p-value 0.04). Diffuse-type tumor histology was seen more in the GCY than in GCO (66.7% vs. 41.7%, p-value 0.001). In patients with metastasis, multiple metastases were common in GCY compared to GCO (45% vs. 15%, p-value 0.003).

Table 1 Baseline comparison of clinical and demography characteristics of GCY and GCO

S. No.	Variable	Category	Gastric cancer in young (GCY) ($n = 33$)	Gastric cancer in old (GCO) ($n = 469$)	p-Value
1.	Age (y)	Median (range)	28 (21-30)	55 (31-86)	
2.	Gender	Female	22 (66.7)	148 (31.6)	<0.001
		Male	11 (33.3)	321 (68.4)	
3.	BMI	Underweight	23 (74.2)	207 (56.1)	0.06
		Non-underweight	8 (25.8)	162 (43.9)	
		Missing data	2	100	
4.	ECOG	0-1	30 (90.9)	322 (68.7)	0.02
		2	3 (9.1)	124 (26.4)	
		3-4		23 (4.9)	
5.	Co-morbidity	Yes	2 (6.1)	80 (17.1)	0.09
6.	Type of comorbidities	Diabetes Mellitus	0 (0.0)	32(40)	
		Hypertension	0 (0.0)	18 (22.5)	
		DM and Hypertension	0 (0.0)	12 (15)	
		Chronic Obstructive Pulmonary Disease	0 (0.0)	5 (6.3)	
		others	2 (100)	13 (16.2)	
7.	Albumin	Median (range)	4.1 (2.3-4.7)	3.5 (1.2-4.9)	0.002
8.	Duration of symptoms (months)	Median (range)	2 (0.10-12)	3 (0.1–24)	0.32
9.	Type of symptoms	Abdominal pain	23 (69.7)	301 (64.2)	
		Vomiting	25 (75.8)	269 (57.4)	
		Loss of weight	21 (63.6)	262 (55.9)	
		Loss of appetite	23 (69.7)	213 (45.4)	
		Dyspepsia	11 (33.3)	47 (10)	
		Melena	6 (18.2)	81 (17.3)	
		Abdominal distension	2(6.1)	43(9.2)	
		Hematemesis	1 (3.0)	30 (6.4)	
		Mass abdomen	1(3.0)	21(4.5)	
10.	Gastric outlet obstruction	Positive	7 (21.2)	101 (40.2)	0.04

Abbreviations: BMI, body mass index; ECOG, Eastern cooperative group.

Table 2 Baseline comparison of tumor characteristics of GCY and GCO

S. No.	Variable	Category	GCY ($n = 33$)	GCO ($n = 469$)	*p*-Value
1.	Site of tumor	GEJ/cardia	9 (27.3)	97 (22.2)	0.53
		Fundus and body	6 (18.2)	60 (13.8)	
		Antrum and Pylorus	18 (54.5)	262 (60.1)	
		Linitis plastica	0 (0.0)	17 (3.9)	
2.	Stage	Early	1 (3.0)	6 (1.3)	0.43
		Locally advanced	12 (36.4)	216 (46.1)	
		Metastasis	20 (60.6)	247 (52.7)	
3.	TNM staging (early and locally advanced)				
	T status	T1-3	5 (38.5)	71 (32.9)	0.41
		T4a	6 (46.2)	74 (34.3)	
		T4b	2 (15.4)	71 (32.9)	
	N status	N0-N1	9 (69.2)	131 (61.2)	0.77
		N2-N3	4 (30.8)	83 (38.8)	
		Missing		2	
4.	Metastasis	Single	11(55.0)	207 (84.8)	0.003
		Multiple	9[a] (45.0)	37 (15.2)[b]	
		Missing data		3	
5.	Site of single metastasis	Organ metastates	9 (81.8)	155 (74.9)	
		Liver	1 (9.1)	65 (31.4)	
		bone	0 (0.0)	3 (1.4)	
		lung	0 (0.0)	5 (2.4)	
		Omental	2 (18.2)	0 (0.0)	
		Adrenal	0 (0.0)	4 (1.9)	
		Peritoneal	2 (18.2)	69 (33.3)	
		Ovary	4 (36.4)	7 (3.4)	
		Kidney	0 (0.0)	1 (0.5)	
		Skin	0	1(0.5)	
		Nonregional nodal metastases	2(18.2)	52(25.1)	
6.	Histopathology subtype	Diffuse	22 (66.7)	186 (41.7)	0.001
		a. Signet	10 (45.5)	65 (14.6)	
		b. Nonsignet	12 (54.5)	121 (27.1)	
		Intestinal	8 (24.2)	259 (58.1)	
		Mixed		1 (0.2)	
		Missing data	3	23	
7.	Treatment				
	Surgery	Curative	6 (18.2)	102 (28.3)	0.17
		Palliative	7 (21.2)	118 (32.8)	
	Chemotherapy	NACT	5 (15.2)	62 (13.2)	0.46
		Adjuvant	3 (9.1)	63 (13.4)	
		Palliative	22 (66.7)	260 (55.4)	
		No chemo	3 (9.1)	84 (17.9)	

[a]**GCY** = Site of multiple metastasis (9):1 (liver, bone); 2 (liver, peritoneal); 1 (peritoneal, kidney); 2 (peritoneal, mediastinal); 2 (nodal, peritoneal) and 1 (ovary, nodal).

[b]**GCO** = Site of multiple metastasis (37): 4 (liver, nodal); 1 (liver, nodal, and bone); 3 (liver, nodal, peritoneal) ; 1 (liver, nodal, and ovary), 1 (liver and bone); 1 (liver, bone, lungs); 7 (liver and peritoneal); 3 (liver and lungs); 9 (nodal and peritoneal); 1 (nodal, lungs); 2 (bone and peritoneal); 3 (peritoneal and ovary); 1 (bone and adrenal).

Table 3 Gastric cancer treatment modality in GCY and GCO

S. No.	Chemotherapy	Subcategory	Gastric cancer in young (GCY) ($n=30$)			Gastric cancer in old (GCO) ($n=385$)		
			NACT ($N=5$)	Adjuvant ($N=3$)	Palliative ($N=22$)	NACT ($N=62$)	Adjuvant ($N=63$)	Palliative ($N=260$)
1	First line	FLOT	2 (40)		3 (13.6)			
		EOX	3 (60)		13 (59.2)	55 (88.7)	15 (23.8)	183 (70.3)
		CAP-CIS		1 (33.3)			16 (25.4)	1 (0.4)
		CAPOX		1 (33.3)	2 (9.1)	2 (3.2)	15 (23.8)	24 (9.2)
		Capecitabine			3 (13.6)	5 (8.1)	13 (20.6)	47 (18.1)
		others		1 (33.3)	1(4.5)		4(6.4)	1 (2.0)
1a	Dose modification		2 (40)		4 (18.2)	11 (17.7)	7 (11.1)	18 (6.9)
1b	Dose delay[a]		3 (60)	2 (66.7)	3 (13.6)	20 (32.3)	17 (27)	77(29.6)
2	Second line	Docetaxel	1 (20)	1 (33.3)		7 (11.3)	2 (3.2)	41 (15.8)
		EOX	1 (20)					2 (0.8)
		Capecitabine			3 (13.6)			5 (1.9)
		CAPOX						1 (0.4)
		FOLFIRI						1 (0.4)
2a	Dose modification[b]					2 (3.2)		10 (3.8)
2b	Dose delay					2 (3.2)		2 (0.8)
3	Third line	Capecitabine	1 (20)					1 (0.4)
		FOLFIRI						1 (0.4)
		Irinotecan						2 (0.8)

Abbreviations: EOX, epirubicin, oxaliplatin, and capecitabine; CAPOX, capecitabine and oxaliplatin; CAP-CIS, capecitabine and cisplatin; FLOT, 5FU, leucovorin, oxaliplatin, and docetaxel; FOLFIRI, 5FU, oxaliplatin, leucovorin, irinotecan.
[b]Dose modification in GCY($n=6$) [reason: poor performance status ($n=3$), grade 3 diarrhea ($n=2$), grade 4 thrombocytopenia ($n=1$)].
aDose delay in GCY ($n=8$) [reason: patients defaulted ($n=3$), grade 3 neutropenia ($n=1$), grade 3 diarrhea ($n=3$), grade 4 thrombocytopenia ($n=1$)].

Of the 33 patients in GCY, 8 (24%) patients received curative-intent treatment (including perioperative chemotherapy with surgery), 22 (67%) received palliative chemotherapy, and 3 (9%) received best supportive care. The commonest chemotherapy regimen used in the curative setting was the EOX regimen in 38%. Among those patients treated with curative intent in GCY, dose modification was done in two patients (25%) due to chemotoxicity in the previous cycle, and delay in the chemotherapy was recorded in five patients (75%). The commonest chemotherapy regimen used in the palliative setting was the EOX regimen in 59% of GCY. Of the 22 patients who received first-line palliative chemotherapy on progression, only three were fit to receive second-line chemotherapy in the GCY group. The reasons for dose modification and delay in chemotherapy in GCY are detailed in ►Table 3.

Overall, 68% of patients could complete more than three cycles of chemotherapy. Various treatment modalities in both groups have been compared and represented in ►Table 3. The percentage of patients receiving curative-intent chemotherapy was similar in GCY and GCO. In patients receiving curative intent therapy, the choice of chemotherapy regimen, dose modification, and dose delay were identical in both groups. The commonest chemotherapy regimen used in the palliative setting was the EOX regimen in 59% of GCY and 70% of GCO. A similar number of patients received first- and second-line palliative chemotherapy in both groups.

The median duration of follow-up for all patients was 27 (range, 24–29) months. The median OS of the entire population was 11 (range, 10–12) months. In GCY, the median OS was not reached for patients treated with curative intent, and it was 13 months for those treated with palliative intent. Similarly, in GCO on curative intent therapy, the median OS was 22 months (range, 17.01–26.99), and of those treated with palliative intent, the median OS was 9 months (7.87–10.14). Survival curves are shown in ►Fig. 2.

Univariate analysis and multivariate analysis for OS in GCY is shown in ►Table 4. There was no statistically significant difference in the 2-year survival of the variables analyzed. However, numerically, males had better 2-year OS than females (47.4% vs. 22.1%), and GCY with intestinal histology had better 2-year OS than those with diffuse histology (62% vs. 19%).

Discussion

Over the past few decades, we have seen significant changes in GC's biology, incidence, and outcomes worldwide.[1,8,9]

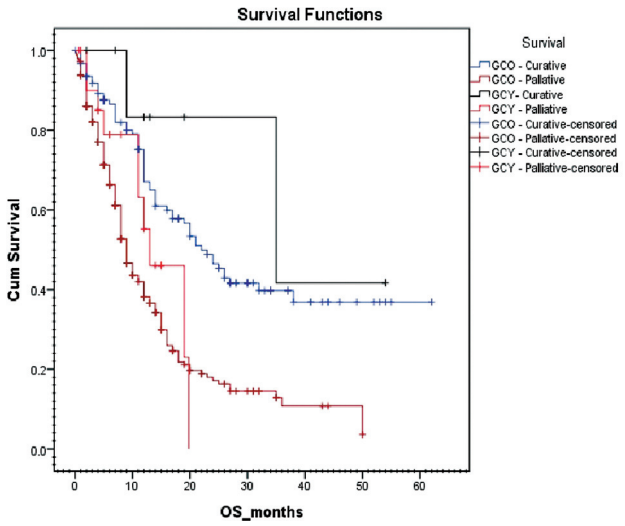

Fig. 2 Kaplan–Meier survival estimate for overall survival of gastric cancer in young (GCY) and gastric cancer in old (GCO) treated with curative and palliative intent.

Change in lifestyle, addiction, and food habits, rampant use of antacids and proton-pump inhibitors, early detection and treatment of *Helicobacter pylori*-induced gastritis, availability and increased accessibility of treatment and newer therapies are a few reasons behind this change.[8,10,11] These reasons vary with a person's age, and the risk of developing cancer changes with underlying genetic vulnerability and cumulative pressure from exposure to risk factors throughout one's lifetime. Sparse data are available in GC patients less than 30 years of age. Our study reports the clinical characteristics, treatment, and survival of GC patients less than 30 years of age compared to > 30 years of age.

Most studies used an age cut-off of less than 40 years for GCY. Our research's median age of GC is one decade less than that seen in western countries (55 years vs. 68 years), so we defined GCY as less than 30 years.[2] Contrary to the GCO, the incidence of GCY is rising. Various studies reported the incidence of GCY between 2 and 8%.[3–6] Our study had 4.6% of GCY among the registered GC cases, similar to that reported in the literature.

In our study, GCY is more common in females (67%) than males. A higher female proportion is the most common finding reported in the literature for GCY, indicating that sex hormones, especially estrogen, may play an essential role in GCY development.[5,6] Zhou et al and Matsuyama et al showed that ER-beta expression rather than ERα expression correlated with young age and advanced cancer stages in GCY.[12,13] For males, exposure to environmental risk factors, such as smoking and alcohol intake, involves a sequence of preneoplastic lesions, contributing to increased GC incidence later in life.

The proximal GC incidence increases in the developed world concordance with esophageal cancers, suggesting that these might have similar risk factors and pathologies. However, in India, the distal GC is still the most common, as reported in the literature.[14] In our study, antrum and pylorus were the most common sites in GCY (55%) and GCO (60%).

Diffuse type gastric cancer (DGC) histology was more common in GCY than GCO (66.7% vs. 41.7%, 0.001). This is in concordance with the various studies from the literature, where DGC was more commonly detected in younger individuals.[6,7,15–18] This disproportion may be primarily genetically determined, mainly alterations in the *CDH1* gene, predisposing individuals to DGC at a younger age. Pathogenicity of DGC involves multiple factors of cell signaling pathways, cell–cell adhesion, and *H. pylori* infection. The E-cadherin and cell-signaling pathways are vital in maintaining cell integrity and normal cell function. The alterations in E-cadherin have been known as a factor strongly associated factor with DGC.[6,19] None of the GCY patients had a family history of cancer, and due to logistics, genetic, and molecular studies were not done in our patients.

The difference in the stage at presentation between GCY and GCO was found in most studies. GCY mainly presented with locally advanced and node or distant metastatic disease.[5,6,17,18,20] In addition to the aggressive diffuse histology type, delay in diagnosis is also a reason for the advanced stage at presentation. The main reason for the delay in diagnosis is that GC was not considered a differential diagnosis in young patients presenting with gastrointestinal symptoms and was not assigned to routine endoscopic screening.[6] Despite no delay in the diagnosis in our study, 60% of GCY had metastases at presentation, indicating the aggressive biology of the disease. Though GCY presented in the advanced stage, there was no difference in the literature's incidence of multiple site metastases in GCY and GCO. However, in our study, the incidence of multiple metastases (two or more sites) was more common in GCY than in the GCO.

While some studies demonstrated poorer outcomes in young patients, the majority reported a better prognosis than older individuals, and some still have no differences in survival based on age.[6,21–24] Even though GCY had more diffuse-type histology and aggressive presentation, they had better performance status, less comorbidity, and similar[18] tolerance to chemotherapy, which resulted in similar survival compared to GCO. Our study also showed no difference in survival between the two groups. In our research (GCY), male sex and intestinal type histology had better survival but did not reach statistical significance due to the small sample size and short follow-up.

The strength of this study is that we are comparing the data with GCO from the same population. Limitations are retrospective data, small sample size, and different comparison periods. Unique challenges in GCY, such as fertility preservation and psychosocial problems, could not be analyzed as we did not have the data.

Conclusion

GCY is more common in females and has aggressive diffuse-type histology with multiple metastases than GCO. Even though GCY had more diffuse-type histology and aggressive presentation, they had better performance status, fewer comorbidities, and similar OS compared to GCO. A separate

Table 4 Univariate and multivariate analyses for overall survival in GCY

S. No.	Parameter	*N*	Median OS (months)	Univariate analysis		Multivariate analysis	
				HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
1	Gender ($n=33$)				1.00		0.12
	Male	11	13 (0.0-29.9)	Reference		Reference	
	Female	22	19(4.4-33.6)	1.00 (0.30-3.33)		0.22 (0.03-1.45)	
2	ECOG ($n=33$)				0.39		0.55
	1	30	19.8(11.1-28.4)	Reference		Reference	
	>1	3	11.0 (6.2-15.8)	1.97 (0.42-9.35)		0.50 (0.05-4.82)	
3	Histology ($n=30$)				0.34		0.25
	Intestinal	8	Not reached	Reference		Reference	
	Diffuse	22	19 (7.4-30.6)	1.88 (0.51-6.90)		3.70 (0.40-34.20)	
4	Site of tumor ($n=33$)				0.49		0.64
	GEJ/cardia	9	Not reached	Reference		Reference	
	Fundus and body	6	11 (6.7-15.3)	3.07 (0.48-19.69)		3.89 (0.24-64.13)	
	Antrum and pylorus	18	19 (11.5-26.5)	1.71 (0.36-8.21)		1.99 (0.25-15.69)	
5	GOO ($n=33$)				0.16		0.07
	Yes	7	Not reached	0.23 (0.03-1.79)		0.10 (0.01-1.22)	
	No	26	13 (5.6-20.4)	Reference		Reference	
6	Stage ($n=33$)				0.09		0.36
	Nonmetastasis	13	35 (2.6-67.4)	Reference		Reference	
	Metastasis	20	19 (10.1-27.9)	3.09 (0.81-11.76)		2.53 (0.35-18.22)	
7	Metastasis ($n=20$)				0.23		0.43
	Single	11	11 (2.4-19.6)	Reference		Reference	
	Multiple	9	Not reached	0.36 (0.07-1.81)		1.96 (0.36-10.57)	

Abbreviations: ECOG, Eastern cooperative group; GEJ, gastroesophageal junction; GOO, gastric outlet obstruction; OS, overall survival.

registry for this unique subset of patients to study the detailed genetic factors, etiology, clinical characteristics, treatment adherence, sexual health, and psychosocial problems would help understand the pathogenesis, treatment response, and outcomes

Data Availability Statement

Data will be available on request.

Ethical Approval

Institute Ethics approval was taken before commencement of the study.

Funding

None.

Conflict of Interest

None declared.

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