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Clinicopathological characteristics and prognostic factors of gastrointestinal stromal tumors treated with curative surgery

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Abstract

Aim: In this study, we aimed to present our experience with Gastrointestinal Stromal Tumors (GIST).

Material and Methods: All GIST cases in the archived files of the pathology database of Adana City Hospital for the period between January 2010 and December 2019 were reviewed. Patients were grouped according to their mitotic index: Group1: ≤5 and, Group2: >5; the two groups were compared for clinical symptoms, preoperative tests, treatments, pathological characteristics and follow-up data; and univariate and multivariate survival analyses were performed.

Results: This study included 106 patients, who were divided in Group 1 (61 patients) and Group 2 (45 patients). The most common tumor location was the stomach (54.7%), the mean tumor size was 7.45 cm The tumor size was greater in Group 2 (5 vs. 8 cm, p<0.001), the margins were irregular in Group 2 (14.8% vs. 35.6%, p:0.013), the high-risk group according to NIH Guidelines was Group 2 (24.6% vs. 88.9%, p<0.001), and necrosis (p:0.002) and invasion (p<0.001) were more common in Group 2. Among the patients who developed recurrence, the time to recurrence was longer in Group 1 (61 vs. 48 months, p:0.037). The metastatic growth rate was higher in Group 2 (4.9% vs. 24.4%, p:0.003). While disease-free survival was shorter in Group 2 (126 vs. 98, p:0.020). Multivariate analyses showed that emergency operations, a Ki67 index of >5, presence of tumor necrosis, S100 positivity and recurrence at follow-up were all associated with reduced survival.

Discussion: This study provides information on the clinicopathological characteristics and epidemiology of GISTs. Patients with a high mitotic index are associated with poor histopathological and oncological outcomes.

Keywords

Gastrointestinal Stromal Tumors (GISTs), Prognostic Factors, Survival

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Introduction

Gastrointestinal stromal tumors (GISTs) are relatively rare neoplasms that are believed to originate from the mesenchymal elements of the intestines. The GIST histogenesis, diagnostic criteria, prognosis and terminology have been a matter of debate for many years. The current epidemiology suggests that the overall incidence of GIST in the United States is 0.70 per 100,000 people per year, with a tendency to increase each year [1]. Most GISTs originate in the stomach (60%) or the small intestine, including the jejunum or ileum (30%), but may also originate in the duodenum (4–5%), colon and appendix (1–2%), or esophagus (1%), and occasionally outside the gastrointestinal tract [2,3].

The main treatment for primary, localized, resectable gastrointestinal stromal tumors (GISTs) is radical resection with negative margins. That said, almost all GISTs have some degree of recurrence risk. Identifying the risk factors for recurrence after primary surgery is important for the establishment of an appropriate prognosis and follow-up program, and most importantly, to identify patients who will best benefit from adjuvant therapy and thus reduce disease recurrences [4-8]. According to the latest versions of the clinical guidelines, including NCCN, ESMO/EURACAN and the French Intergroup Clinical Practice guidelines, mitotic rate, tumor size and tumor site, including tumor rupture, are all widely accepted prognostic factors. These four established prognostic factors, however, have continued to be researched and improved upon in recent years [3-5]

Extensive experience is required to understand the behavior of tumors and to predict disease outcomes, although this can be difficult due to the low incidence and uncommon locations of GISTs. Furthermore, the rarity of these neoplasms has prevented the adoption of a strong statistical approach in all but a few studies, and series reported in the literature have provided limited information due to the low number of patients [6,7]

Although this issue has been addressed in several studies, the heterogeneity of the patient population and the variety in clinical presentation, anatomical location and morphological characteristics have complicated analyses. We present here the findings of our assessment of the effects of a wide range of factors on survival in those who have undergone curative surgery for Gastrointestinal Stromal Tumors, including patient and tumor characteristics, immunohistochemical results, pathological findings, metastasis or recurrence, and tumor location.

Material and Methods

Study population

The study included all cases of GIST retrieved from the pathology database at Adana City Training and Research Hospital between January 2010 and December 2019. Currently, diagnoses of GISTs are based on two factors: a) the presence of spindle, epithelioid, or mesenchymal tumor cells on histopathological examination; and b) CD117 expression with or without CD34 expression via immunohistochemical staining. All patients in the study were diagnosed based on these two criteria. This study was approved by the Adana City Hospital Local Ethics Committee (No 25.03.2020 772/53.).

Data Collection

Data were collected from the individual patient medical case notes, electronic patient records and pathology reports. Gender, age, tumor location, tumor size, presenting complaints, laboratory parameters, type of surgery, mitotic index, Ki67 index, intratumoral necrosis, tumor cell types and borders, National Institutes of Health (NIH) risk category, histological type, and mitotic rate determined by hematoxylin and eosin staining, were recorded. Immunohistochemical analyzes of patients were studied using standard protocols, including CD117, CD34, Desmin, S100, SMA and DOG-1 antibodies. Overall survival (OS) was defined as the time from surgical resection to the date of the last follow-up visit or death. Disease-free survival (DFS) was calculated as the time from the date of surgery to the date of the first evidence of local and/or distant recurrence, or the date of the latest visit for patients lost to follow-up. Progression-free survival (PFS) was first calculated in patients with metastases at the time of diagnosis. The patients were grouped according to their mitotic index: Group 1: ≤5 and, Group 2: > 5, and the two groups were compared. Mitotic activity was assessed by counting the number of cells undergoing mitosis per x 50 high-power fields (HPF). The Ministry of Health Death Notification System was accessed to obtain information about the latest status of the patients.

Surgeons at our institution share the GIST treatment philosophy that emphasizes the complete removal of the tumor. Resections are classified as incomplete if the tumor is unresectable at the time of discovery or if there is substantial residual disease following resection. A complete resection is considered the excision of all gross diseases, regardless of microscopic margins. Resection of metastases is performed in selected patients when the primary tumor has been controlled.

Statistical Assessment

IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. was used for the statistical analysis of the data. Along with the descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) for the evaluation of the study data, the Mann-Whitney U test was used for non-normally distributed parameters when analyzing quantitative data. Categorical data were compared using Pearson's Chi-square test and Fisher's Exact test, while a multiple logistic regression was used for multivariate assessments. A Kaplan-Meier analysis and a Log-Rank test were used for the analysis of survival. A p-value of <0.05 was considered statistically significant in the analyses.

Results

This study included 106 patients, of which 60.4% were female, and the mean age was 59 years. The most common tumor location was the stomach (54.7%), the mean tumor size was 7.45 cm, and the mean mitotic index was 6.55.

Patients with a mitotic index of ≤5 were classified as Group 1 and those with a mitotic index of > 5 as Group 2. The gender distribution and mean age in the two groups were similar. Patients in Group 2 received neoadjuvant imatinib more frequently (0% vs. 6.7%, p 0.041). The presenting symptom and localization differed between the groups. The results are

presented in Table 1.

Tumor size was greater in Group 2 (5 vs. 8 cm, p<0.001), the margins were irregular in Group 2 (14.8% vs. 35.6%, p: 0.013), the high-risk group according to the NIH risk criteria was Group 2 (24.6% vs. 88.9%, p<0.001), and necrosis (p: 0.002) and invasion (p<0.001) were more common in Group 2. The Ki67 index was higher in Group 2 (3 vs. 10, p<0.0001). The results are presented in Table 2.

Concerning immunohistochemical markers, the rate of S100 positivity was higher in Group 1 (50.8% vs. 31.1%, p: 0.042), while other markers were similar in the groups. The results are presented in Table 2.

The length of follow-up was similar in the groups (67 vs. 49 months, p: 0.546). Among the patients who developed recurrence, the time to recurrence was longer in Group 1 (61 vs. 48 months, p: 0.037). In Group 2, all patients received imatinib, and postoperative chemotherapy was administered more frequently in Group 2 (1.6% vs. 15.6%, p: 0.007), and the metastatic growth rate was higher in Group 2 (4.9% vs. 24.4%, p: 0.003). The rate of patients who developed mortality in their follow-up (18% vs 20% p:0.798) and the rate of recurrence (6.6% vs 17% p:0.072) were similar in the groups.

While overall survival was similar in the groups (105 vs. 98 months, p: 0.843), disease-free survival was shorter in Group 2 (126 vs. 98, p: 0.020).

Independent risk factors associated with reduced survival were identified as emergency operations, a Ki67 index of >5, cell pattern, borders, cell type, presence of necrosis, S100 positivity, development of recurrence and postoperative chemotherapy. The results are presented in Table 3.

Table 1. Demographic and clinical characteristics

	Group 1	Group 2	p*
	n (%)	n (%)	
Gender			
Female	39 (63.9)	25 (55.6)	0.383
Male	22 (36.1)	20 (44.4)	
Age	58 (33-90)	60 (18-88)	0.472
Symptoms			
Anemia	1 (1.6)	0 (0.0)	0.018
Incidental	12 (19.7)	0 (0.0)	
Hemorrhage	9 (14.8)	8 (17.8)	
Abdominal pain	19 (31.1)	21 (46.7)	
Abdominal mass	8 (13.1)	11 (24.4)	
Prolapsus	0 (0.0)	1 (2.2)	
Jaundice	1 (1.6)	0 (0)	
Obstruction	11 (18.0)	4 (8.9)	
Group localization			
Gastric	34 (55.7)	24 (53.3)	0.806
Non-gastric	27 (44.3)	21 (46.7)	
Localization			.
Caecum	1 (1.6)	0 (0)	0.033
Duodenum	5 (8.2)	0 (0)	
Ileum	9 (14.8)	1 (2.2)	
Jejunum	8 (13.1)	9 (20.0)	
Colon	1 (1.6)	2 (4.4)	
Mesocolon	0 (0)	1 (2.2)	
Stomach	34 (55.7)	24 (53.3)	
Omentum	1 (1.6)	0 (0.0)	
Pelvic	1 (1.6)	5 (11.1)	
Rectum	1 (1.6)	3 (6.7)	
Emergency operation	11 (18.0)	8 (17.8)	NA
Neoadjuvant imatinib			
Absent	61 (100)	42 (93.3)	0.041
Present	0 (0)	3 (6.7)	

Discussion

In the present study, the prognostic factors and survival of a group of patients diagnosed with gastrointestinal stromal tumors who underwent surgery in a Turkish clinic over a 10-year period were assessed retrospectively. Patient survival was associated with the type of surgery, Ki67 index, S100 positivity, postoperative chemotherapy and recurrence, and these findings are largely in agreement with previous studies. In contrast, no association was identified between survival and tumor size or NIH risk in the present study. The evaluation of the factors influencing the prognosis of GISTs is a highly relevant topic, and previous single and multicenter studies have described the association between survival and various factors.

Gastrointestinal stromal tumors are usually asymptomatic and are often detected incidentally, while the most common symptom is abdominal pain. Accompanying symptoms may include non-specific gastrointestinal symptoms such as loss of appetite, early satiety,

weakness, weight loss, abdominal distension, nausea and vomiting. Such tumors, however, may lead to serious gastrointestinal complications with high morbidity and mortality, such as intestinal obstruction, perforation, obstructive jaundice and gastrointestinal bleeding [9,10]. The patient series of our study had symptoms similar to those reported in the literature. Symptoms varied with tumor localization, therefore, despite varying clinical findings, GISTs should be considered in the differential diagnosis, especially in patients with subclinical gastrointestinal symptoms.

Fletcher et al. in 2002 proposed the NIH standard, which is based on two indicators –maximum tumor size, and mitotic figure count – and is used to predict the biological behavior of GISTs, and puts forward four levels of GIST recurrence risk [11]. Most researchers believe that the mitotic count is most accurately expressed as the number of mitosis per 50 HPF, with a mitotic rate of 5 mitoses per 50 HPF being the commonly used limit for tumors with expected benign behavior [12]. Mandrioli et al. reported a mitotic index of >5 to be a strong prognostic factor for disease recurrence [13], while Park et al. emphasized the prognostic significance of the mitotic index in their study. On this rational basis, we grouped our patients according to a mitotic index of 5 mitoses, and found that a mitotic index of >5 was associated with poor prognostic factors such as tumor size, NIH risk (high), irregular borders, necrosis and an increased KI67 index. Accordingly, patients with a mitotic index of >5 had poor oncological follow-up outcomes, such as reduced time to recurrence, increased metastases and reduced disease-free survival [14].

The management of GISTs has improved significantly over the past decade. Before the 2000s, the only proven effective treatment was surgery, but with the introduction of TKIs, the management of advanced disease has changed radically,

allowing adjuvant or neoadjuvant therapy for locally advanced forms of the disease [15]. That said, surgery still remains the main curative treatment for localized and resectable primary disease. The goal of surgery is to achieve macroscopic resection with a microscopically negative margin (R0) and to avoid tumor rupture (R2). A tumor resection that spares the involved organ (i.e. stomach or intestines) is usually sufficient, although a more extensive resection may sometimes be required for the complete removal of the neoplasm [16]. In the present study, tumor localization served as a guide when determining the type of surgery. An R0 resection was performed in 97% of cases, with anR2 resection performed in the remaining 3% of the patients due to the invasion of various surrounding tissues. The mitotic index was not associated with operative variables. An emergency operation was a prognostic factor for survival, and we believe that morbidity and mortality after emergency operations contribute to this finding.

Ki67, a widely accepted nuclear protein associated with cellular proliferation in malignant tumors, has been reported to be associated with prognosis in GISTs [17]. The study by Zhao et al. of 418 GIST patients established a correlation between an increased Ki67 index and the mitotic index, and the authors further identified Ki67 as an independent prognostic factor for recurrence-free survival [17]. Similarly, our study found the Ki67 index to be associated with the mitotic index and to be an independent risk factor for reduced survival.

Previous studies have concluded that necrosis observed macroscopically in a tumor is associated with overall proliferative activity of the tumor, with necrosis-containing areas being observed macroscopically in the most aggressive GISTs [18,19]. Oliveira et al. [19] in their study of 54 GIST cases published in 2015, reported that the presence of macroscopic necrosis in the tumor was associated with a poor prognosis. Our study established a significant correlation between macroscopically observed tumor necrosis and the mitotic value. Mitosis index was higher in patients with tumor necrosis. A significant relationship was also found between tumor necrosis and survival in the present study. Radiological and macroscopic observations of necrosis are associated with tumors with high mitotic activity and/or large tumors, which may contribute to treatment planning in such patients, considering the preoperative aggressive course.

Miettinen et al. [20,21] reported S100 expression to be a marker of malignancy, and more common in small intestinal GISTs. They went on to suggest that S100 may be a poor prognostic marker for gastric location, but not for small intestinal location, although the study was limited by a small number of cases. Other studies in the literature, on the other hand, reported no relationship between prognosis and S100 positivity [22]. In the present study, S100 positivity was associated with a low mitotic index and with reduced survival.

Our study has several limitations. First, it was a single-center study with a limited number of patients, although the sample contained a large group of patients considered as having common characteristics, and consistent with the literature. Due to the absence of data from the patient files in the medical

Table 2. Pathological characteristics and Immunohistochemical results

	Group 1	Group 2	p*		Group 1	Group 2	p*
	n (%)	n (%)			n (%)	n (%)	
Surgical margins				Cd117			
R0	59 (96.7)	44 (97.8)	0.746	Negative	4 (6.6)	2 (4.4)	0.642
R2	2 (3.3)	1 (2.2)		Positive	57 (93.4)	43 (95.6)	
Tumor size	5 (1.5-19.0)	8 (3-24)	<0.001	Cd34			
Pattern				Negative	11 (18.0)	9 (20.0)	0.798
Exophytic	45 (73.8)	27 (60.0)	0.133	Positive	50 (82.0)	36 (80.0)	
Intraluminal	16 (26.2)	18 (40.0)		Desmin			
Borders				Negative	57 (93.4)	44 (97.8)	0.298
Irregular	9 (14.8)	16 (35.6)	0.013	Positive	4 (6.6)	1 (2.2)	
Encapsulated	52 (85.2)	29 (64.4)		S100			
Cell type				Negative	30 (49.2)	31 (68.9)	0.042
Epithelioid	8 (13.1)	2 (4.4)		Positive	31 (50.8)	14 (31.1)	
Mixed	8 (13.1)	10 (22.2)	0.189	SMA			
Spindle	45 (73.8)	33 (73.3)		Negative	20 (32.8)	22 (48.9)	0.094
NIH risk				Positive	41 (67.2)	23 (51.1)	
Low	30 (49.2)	0 (0)		Dog1			
Intermediate	16 (26.2)	5 (11.1)	<0.001	Negative	15 (24.6)	14 (31.1)	0.457
High	15 (24.6)	40 (88.9)		Positive	46 (75.4)	31 (68.9)	
Necrosis	11 (18.0)	21 (46.7)	0.002				
Invasion	11 (18.0)	23 (51.1)	<0.001				
Mitotic index	2 (1-40)	8 (0-50)	<0.001				
Ki67 index	3 (1-40)	10 (1-60)	<0.001				
Ulcer							
Negative	60 (98.4)	41 (91.1)	0.082				
Positive	1 (1.6)	4 (8.9)					

NIH-National Institutes of Health, SMA -Smooth Muscle Actin, DOG1-Discovered on GIST1

Table 3. Univariate and multivariate analyses of factors associated with overall survival

Parameters		Univariate	Multivariate	
		P	HR (95% - CI)	p
Age groups	< 65	0.172	1.000	0.174
	> 65		1.996 (0.737-5.407)	
Gender	Female	0.589	1.000	0.586
	Male		1.314 (0.492-3.509)	
Group location	Gastric	0.145	1.000	0.147
	Non-gastric		2.083 (0.773-5.617)	
Emergency	No	0.027	1.000	0.033
	Yes		3.321 (1.102-10.004)	
NIH risk	Low	0.423	1.000	0.235
	Intermediate		0.200 (0.022-1.802)	0.151
	High		1.238 (0.416-3.681)	0.701
Mitotic count	<5	0.800	1.000	0.798
	>5		1.136 (0.427-3.027)	
Ki67	<5	0.039	1.000	0.043
	>5		2.800 (1.032-7.600)	
Tumor size	<2	0.290	1.000	0.279
	2.1-5		0.621 (0.055-7.035)	0.700
	5.1-10		0.450 (0.040-5.063)	0.518
	>10		1.500 (0.131-17.180)	0.744
Pattern	Exophytic	0.827	1.000	0.825
	Intraluminal		0.888 (0.308-2.556)	
Borders	Irregular	0.056	1.000	0.061
	Encapsulated		2.706 (0.956-7.657)	
Cell type	Epithelioid	0.533	1.000	0.662
	Mixed		0.500 (0.059-4.232)	0.525
	Spindle		1.032 (0.199-5.343)	0.970
Necrosis	Present	0.007	3.783 (1.379-10.376)	0.010
Invasion	Present	0.827	0.888 (0.308-2.556)	0.825
Cd117	Negative	0.356	1.000	0.363
	Positive		0.439 (0.075-2.584)	
Cd34	Negative	0.627	1.000	0.625
	Positive		1.396 (0.367-5.317)	
Desmin	Negative	0.274	1.000	0.289
	Positive		1.025 (1.001-1.057)	
S100	Negative	0.023	1.000	0.028
	Positive		3.134 (1.133-8.670)	
SMA	Negative	0.970	1.000	0.969
	Positive		0.981 (0.363-2.649)	
Dog1	Negative	0.771	1.000	0.769
	Positive		0.852 (0.293-2.481)	
Ulcer	Negative	0.274	1.000	0.478
	Positive		1.009 (1.002-1.021)	
Neoadjuvant therapy	Negative	0.065	1.000	0.073
	Positive		9.444 (0.812-109.855)	
Metastatic growth		0.085	2.852 (0.838-9.710)	0.094
Surgical margins	R0	0.857	1.000	0.859
	R2		1.025 (1.001-1.069)	
Recurrence	Absent	<0.001	1.000	<0.001
	Present		22.636 (5.309-96.512)	
Imatinib therapy		0.992	0.995 (0.359-2.760)	0.992
Postop. ChemoTheraypy		0.019	5.125 (1.160-22.645)	0.031

NIH-National Institutes of Health, SMA -Smooth Muscle Actin, DOG1-Discovered on GIST1

records, the use of imatinib could not be analyzed in our patient group.

Conclusion

GISTs are the most common mesenchymal tumors of the gastrointestinal tract, and most commonly arise in the stomach. While surgical resection is the recommended treatment in localized cases, it alone cannot always provide a cure. Recurrence can occur even in cases with complete resection of the primary tumor. Histopathological examinations are of great importance in identifying high-risk patients who will benefit from adjuvant therapy. Preoperative estimation of prognosis in gastrointestinal stromal tumors will give us an idea of postoperative survival, and is important in determining adjuvant therapy. Detecting, reporting and assessing outcomes of rare cancers such as GISTs can be difficult, and the data may be insufficient for population-wide recommendations and interventions. We believe, however, that the data presented here clarify some important points and may help determine future trends.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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