GASTROINTESTINAL STROMAL TUMORS: A CLINICOPATHOLOGIC AND RISK STRATIFICATION STUDY OF 109 CASES IN SULAYMANIYAH CITY-KURDISTAN REGION OF IRAQ

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ABSTRACT

Background

Gastrointestinal stromal tumors (GISTs) are rare and heterogeneous tumors that occur throughout the GIT most commonly in the stomach or small intestine. They grow from specialized cells in the gastrointestinal tract called interstitial cells of Cajal (ICCs) or precursors to these cells.

Objectives

To describe GISTs cases and perform risk stratification based on both the (AFIP) classification and TNM staging.

Materials and Methods

The data were collected retrospectively from registries and documents in Hiwa Hospital and the histopathology department in Shorsh Teaching Hospital in Sulaimaniyah between 2010 and 2019. The histopathological features extracted from the reports included the site of a tumor, size of tumor, histological type, mitotic count/50 high power fields (HPF), risk behavior assessment, and presence or absence of necrosis, and metastasis. Risk stratification was conducted by assigning the cases to specific risk categories and groups for disease progression based on Armed Forces Institute of Pathology Criteria (AFIPC) and staging according to the TNM system (AJCC 8th edition).

Results

A total of 109 cases of GIST diagnosed between 2010 and 2019 were included. More than half (52.3%) of the cases were female. The age range was 28 to 87 years with a mean age of 58 years. Most (67.9%) of GISTs occurred between 48 and 77 years of age. The mean diameter of tumors was 8.18 cm. Around half (48.6%) of the GISTs were in the stomach, 60.6% of the cases had spindle cell type morphology and 82.6% were CD117 positive. Based on AFIPC risk stratification 34.0 % of the total cases were high risk. As per the Staging criteria of the TNM system (AJCC 8th edition), 37.6% were stage I followed by stage III (28.4%), stage II (17.4%), and stage IV (16.5%).

Conclusion

Most of the patients in the current study had GIST in the stomach and were in a high-risk category. The current epidemiological and morphologic findings were similar to prevailing knowledge. However, only 82.6% were CD 117 Positive.

Keywords: *Gastrointestinal stromal tumor; Extra gastrointestinal tumor; AFIPC risk stratification; TNM staging.*

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are responsible for (1-3 %) of all GI tumors and it is the most common type of mesenchymal tumor in the gastrointestinal (GI) tract [1–4]. The incidence of GISTs ranges from 10 to 20 per million, including incidental small tumors [5]. The median age at diagnosis is 60 years. GISTs have no predilection for either gender but some studies suggest a little male predominance [6-8]. The most common location of GISTs is the stomach (60%), followed by the small intestine (jejunum and ileum) (30%), duodenum (5%), and colorectum (5%) [9-13].

GISTs commonly arise from interstitial cells of Cajal, are generally immunohistochemically positive for KIT (CD117), and contain KIT- or PDGFRA-activating mutations [14-17]. Nevertheless, GISTs also come from the mesentery or omentum, which lacks interstitial cells of Cajal, suggesting an origin from multi-potential mesenchymal stem cells [18]. Most GISTs express the CD117 (72–94%) antigen and the CD-34 antigen (70–78%) [19]. GISTs show CD117 negative especially in GISTs with PDGFRA mutation [13]. Other markers that have been used in the evaluation of GISTs include Desmin, actin, and S100 [20, 19].

GISTs can be divided into three main morphologic types: spindle cell morphology (70%) which shows a variety of histological patterns, epithelioid cell morphology (20%), and mixed spindle and epithelioid cell morphology [21].

Until 2000, the treatment of GISTs was limited to radical surgery, as GISTs are resistant to chemo- and radiotherapy. In 2000, imatinib was first used in GISTs is a tyrosine kinase inhibitor (TKI). This significantly improved median overall survival from < 1 year to > 5 years [22]. However, to identify candidates that will benefit from adjuvant therapy, risk-stratification has to be conducted and prognostic factors should be identified [23,24,3,25,26]. In 2006, Miettinen et al. published a risk classification system termed the Armed Forces Institute of Pathology (AFIP) classification. The main criteria were tumor location, mitotic count, and primary tumor size. Using these three parameters, five risk groups were established (no risk, very low, low, moderate, high risk) of recurrence. In AFIP classification no risk group is considered as benign [24].

The American Joint Committee on Cancer staging system (AJCCS) uses the TNM classification [27]. In 2010 the first TNM classification for GIST was published. This system adopted the classification of Miettinen et al., including the definition of mitotic rate which is counted in an area of 5 square millimeters (5 mm^2), for microscopes with traditional field size, this equals 50 high power fields (50 HPF) at a magnification of 40x (total magnification of 400x). However, the TNM classification is mainly focused on renaming the eight subgroups defined by Miettinen et al. to represent various tumor stages. A minor modification considered metastasis as a stage IV disease similar to other cancer types. The high-risk group introduced by Miettinen and Lasota (2006) corresponds to stage III [28].

To the best of our knowledge, no study has tried to address the clinicopathology and risk stratification of GISTs in Sulaimaniyah, Kurdistan Region of Iraq. Therefore, this study aimed to describe GISTs cases and perform risk stratification based on both the (AFIP) classification and TNM staging (AJCC 8th edition).

MATERIAL AND METHODS

Data of 109 GISTs cases from Hiwa Hospital and histopathology department of Shorsh Teaching Hospital in Sulaimaniyah from 2010 and 2019 were collected retrospectively from registries and documents. The retrieved data included patient demography (age and gender), histopathological and immunohistochemical findings.

The histopathological features extracted from the reports included the site of the tumor, size of tumor, histological type, mitotic count/50 high power fields (HPF), risk behavior assessment, and presence or absence of necrosis, and metastasis. The immunohistochemical profile of tumors was obtained from the documents. Risk stratification was performed according to AFIP by using tumor location, tumor size, and mitotic activity / 50 HPFs, and the cases were assigned to specific risk categories and groups and staging was done by TNM classification (AJCC 8th *edition)*. Statistical analysis was performed using SPSS statistical package version 21.0 (SPSS Inc., Chicago, IL). The results were summarized in tables with frequencies and percentages of the total.

RESULTS

Patient Demography

A total of 109 GISTs cases were included. The age of the patients ranged from 28 to 87 years with a mean age of 58 years. Based on the decade-wise distribution, 67.9 % were between 48 and 77 years of age. Out of 109

cases, 57 (52.3%) patients were males, and the female: male ratio was 1.1:0.9 (Table 1). From the total samples, 102 (93.6%) were resection specimens and 7 (6.4 %) were small core biopsies.

Tumor site and size

The stomach was the site of the majority of tumors (53 of cases, 48.6%) while over 35 cases (32.1%) were located in the small intestine (Table-2). Extra GI GISTs (E-GIST) comprised 6 cases (5.5 %). Tumor sizes ranged from 0.5 to 25cm with a mean size of 8.18 ± 5.45cm. The median size was 8.18cm. Most of the tumors were between 5 and 10cm (48 cases, 44.0 %).

Out of 109 cases, 66 (60.6%) had spindle cell morphology and 39 (35.8%) had necrosis. The mitotic rate was ≤ 5 M/50 HPF for 75(68.8%) cases and 90 (82.6%) cases were CD117 positive. Seventy-seven (70.6%) cases were CD 34 positive and only 11 (10.1%) were Desmin positive Table 3.

Risk stratification

Risk stratification was performed on 91 cases because 18 cases were excluded from risk stratifications as they were having liver, lymph node, or metastasis elsewhere. From 66 tumors with mitotic count ≤5 per 50 HPF, 39 were in the stomach and 28 had a size between 5-10 cm. Of 25 tumors with mitotic count >5 per 50 HPF, 11 were in the stomach and 12 had sizes more than 10 cm. Out of 91 cases, 31 cases (34 %) were high risk. The findings were shown in Tables 4 and 5.

The TNM and AJCC classification of tumors was summarized in Table 6. Of 91 cases, 50 were gastric tumors and 41 were non-gastric. From the 50 gastric cases, 36 were mitosis ≤ 5M/50 HPF from which 16 were T2 with a tumor size between 2 and 5 cm. From 41 non-gastric tumors, 27 were mitosis ≤ 5M/50 HPF from which 13 were T3 with a tumor size between 5 and 10 cm.

Table 7 shows the staging of GISTs based on TNM classifications (AJCC 8th *edition)*. Of 109 cases, 53 (48.6%) were gastric tumors and 41 (37.6%) were stage I. Most of the gastric GISTs (n=33) were stage one whereas most of the non-gastric tumors were stage III (n=20) and IV (n=15).

Characterization of stage IV GISTs

Eighteen (18) cases with liver, lymph nodes, peritoneum, and omentum metastasis were regarded as stage IV regardless of tumor size, location, and mitotic figures according to TNM classification. Twelve of the stage 4 cases were male and 15 of the stage IV tumors were non-gastric. Ten of the cases had a mitotic count of more than 5.

Table 1. Demography of GISTs cases.

Demographic variable		Frequency (%)
Age (years)	28 – 37	9(8.3)
	38 – 47	18(16.5)
	48 – 57	19(17.4)
	58 – 67	33(30.3)
	68 – 77	22(20.2)
	78 – 87	8(7.3)
Sex	Male	52 (47.7)
	Female	57 (52.3)

Table 2. Tumor size and size distribution.

Tumor site and size		Frequency (%)
Site of tumor	Stomach	53(48.6%)
	Duodenum	8(7.3%)
	Small intestine	35(32.1%)
	Colorectum	7(6.4%)
	E-GIST	6(5.5%)
Tumor size	≤2	3 (2.7%)
	>2≤5	27 (24.77%)
	>5≤10	48 (44.0%)
	>10	31 (28.44%)

Table 3. Pathologic and IHC of GISTs.

Pathological type		Frequency (%)
Cell morphology	Spindle	66 (60.6 %)
	Epithelioid	11 (10.1 %)
	Mixed	32 (29.3 %)
Necrosis	Yes	39 (35.8 %)
	No	70 (64.2 %)
Mitotic rate	≤ 5 M / 50 HPF	75 (68.8 %)
	> 5 M / 50 HPF	34 (31.2 %)
CD 117	Positive	90 (82.6 %)
	Negative	19 (17.4%)
CD 34	Positive	77 (70.6%)
	Negative	32 (29.4%)
Desmin	Positive	11 (10.1%)
	Negative	98 (89.9%)

Table 4. Distribution of cases according to AFIP classification.

	Size of tumor in cm	Stomach	Duodenum	Small intestine	Colorectal	E –GIST	Total
Mitotic count ≤5per 50 HPF	≤2	2 no risk	0 no risk	0 no risk	0 no risk	0 no risk	2
	>2≤5	16 very low risk	1 low risk	7 low risk	0 low risk	0 low risk	24
	>5≤10	15 low risk	3 moderate risk	9 moderate risk	0 moderate risk	1 moderate risk	28
	>10	6 moderate risk	1 high risk	4 high risk	1 high risk	0 high risk	12
	Total	39	5	20	1	1	66
Mitotic count >5 per 50 HPF	≤2	0 no risk	0 high risk	1 high risk	0 high risk	0 high risk	1
	>2≤5	0 moderate risk	0 high risk	1 high risk	0 high risk	0 high risk	1
	>5≤10	5 high risk	2 high risk	2 high risk	1 high risk	1 high risk	11
	>10	6 high risk	0 high risk	3 high risk	1 high risk	2 high risk	12
	Total	11	2	7	2	3	25

Table 5. Risk stratification based on AFIP classification.

Site	No risk group (%)	Very low risk group (%)	Low risk group (%)	Moderate risk group (%)	High risk group (%)	Total (%)
Stomach	2 (2.1)	16 (17.5)	15 (16.48)	6 (6.4)	11(12.08)	50 (54.9)
Duodenum	0	0	1 (1.09)	3 (3.2)	3 (3.2)	7 (7.6)
Small intestine	0	0	7 (7.69)	9 (9.89)	11(12.08)	27 (29.6)
Colorectal	0	0	0	0	3 (3.2)	3 (3.2)
E GIST	0	0	0	1 (1.09%)	3 (3.2)	4 (4.3)
Total	2 (2.1%)	16 (17.5%)	23(25.2%)	19 (20.8%)	31 (34 %)	91(100%)

No risk 0%, Very low risk (1.9%), Low risk (3.6%) for stomach, but (4.3%) for non-stomach, Moderate risk (10%-16 %) for stomach but (24%) for non-stomach, High risk (55%-86%) for stomach but (52% -90%) for non-stomach: these % are risk of recurrence according to AFIP classification.

Staging based on TNM classification (AJCC 8th edition).

Table 6. TNM classification of GISTs (AJCC 8th edition).

Tumor size cm	Mitosis /50HPF	T-stage gastric no. (%)	AJCC gastric no. (%)	T-stage non-gastric no. (%)	AJCC non-gastric no. (%)
≤ 2cm	≤ 5	T1 2 (2.1 %)	IA 2 (1.8%)	T1 0 (0%)	I 0(0%)
> 2-5 cm	≤ 5	T2 16 (17.5 %)	IA 16 (14.6%)	T2 8 (8.7%)	I 8 (7.3%)
> 5-10 cm	≤ 5	T3 15 (16.4%)	IB 15 (13.7%)	T3 13(14.2 %)	II 13(11.9%)
> 10 cm	≤ 5	T4 6 (6.5 %)	II 6 (5.5 %)	T4 6 (6.5 %)	IIIA 6 (5.5 %)
≤ 2cm	>5	T1 0 (0%)	II 0 (0%)	T1 1 (1.09%)	IIIA 1 (0.9%)
> 2-5 cm	>5	T2 0 (0%)	II 0 (0%)	T2 1(1.09%)	IIIB 1 (0.9%)
> 5-10 cm	>5	T3 5 (5.4 %)	IIIA 5(4.5 %)	T3 6 (6.5%)	IIIB 6 (5.5%)
> 10 cm	>5	T4 6 (6.5%)	IIIB 6 (5.5%)	T4 6 (6.5%)	IIIB 6 (5.5%)
		50 (54.9%)	50 (45.87%)	41 (45.05%)	41 (37.6%)

Table 7. staging by TNM classification (AJCC 8th edition).

Staging TNM	Gastric (%)	Non-gastric (%)	Total case (%)
STAGE I	33 (30.2%)	8 (7.3%)	41 (37.6%)
STAGE II	6 (5.5%)	13 (11.9%)	19 (17.4%)
STAGE III	11 (10.09%)	20 (18.3%)	31(28.4%)
STAGE IV	3 (2.7%)	15 (13.7%)	18 (16.5%)
Total	53 (48.6%)	56 (51.37%)	109 (100%)

Table 8. Characterization of stage IV GISTs.

Characteristics		Frequency
Gender	Male	12
	Female	6
Cell morphology	Spindle	12
	Epitheloid	2
	Mixed	4
Site	Stomach	3
	Duodenum	1
	Small intestine	8
	Cororectal	4
	E-GIST	2
Mitotic	≤ 5	8
	> 5	10
Site of metastasis	Liver	9
	Lymph node	3
	Peritoneum and omentum	6
Size of tumor T	T2	2
	T3	9
	T4	7

DISCUSSION

As it was mentioned before, the purpose of this study was to describe the epidemiology GISTs and to perform risk stratification. A total of 109 GISTs cases were studied and the mean age of patients was 58 years. Most of the patients were between 48 years and 77 years of age. The age of GISTs cases in this study resembles similar studies [32-34]. A study from Turkey reported a mean age of 62.8 ± 13.3 years [32], similarly, the mean age was 61.18 ±14.13years in Thailand and more than half of the cases occurred after the age of 60 years [33]. Similarly, a study from the south of Iraq showed that the median age at diagnosis was 57 years and the majority (72%) were diagnosed between the ages of 40 to 70 years [34]. Another study from China also reported an average age of 55.77 ± 13.70 years [36].

In the current study, 52 (47.7%) patients were males, and 57 (52.3%) were females. Female: male ratio was 1.1:0.9. Likewise, a study from Iran concluded that females tend to be affected more than males [35]. A study from the southern part of Iraq found no gender predilection (24 male and 23 female cases) [34].

The most frequent sites of GISTs in descending order were stomach, small intestine, duodenum, colorectal region, and E-gist. This pattern is similar to the patterns reported by studies done in the south of Iraq [34], Iran [35], Turkey [32] and Thailand [33], and China [36]. Nevertheless, these findings were in contrast with the outcomes of studies by Antonescu et al. [37] and Bhalgami et al. [38] which found slightly more GISTs in the small intestine than the stomach.

In the current study, tumor size ranged from 0.5 to 25 cm with a mean size of 8.18 ± 5.45 cm. The median size was 8.18 cm. Most of the tumors were 5–10 cm (44 cases 40.36 %). Likewise, a study from Thailand reported a similar tumor size range (0.6 to 25.5 cm), mean tumor size (8.78 ± 5.6 cm). However, the median size of GISTs (6.8 cm) was lower [33]. A study from Pakistan also reported a similar result [40]. A study by Li et al. [39] from China similarly found that most of the tumor's size be between 5 cm and 10 cm (40.8%). Nevertheless, a study from the USA reported larger tumor sizes, most were ≥ 10 cm with a mean size of 7.8 cm [37] and another study in China found a smaller tumor size smaller than 5 cm for most of the patients [36].

The histopathologic findings of the current study showed that tumors were predominantly spindle cell morphology type (60.6 %) followed by mixed type (29.3%) and epitheliod morphologies (10.1%). The predominance of spindle cell morphology was unanimously reported by many studies [32, 33, 40, 43]. Furthermore, studies from Turkey [32] and Thailand [33] similarly found a higher frequency of mixed type morphology than epithelioid type. On the other hand, studies from Pakistan, Korea, and Europe showed a lower mixed type than epithelioid cell type [40-43]. According to published literature, the type of cellular morphology of GISTs is a spindle cell type in most cases, whereas epithelioid cell type comprises approximately 20–25%, and only a small number of cases are expected to have mixed spindled-epithelioid histology [9, 13]. The similarity of the current findings with the study from Turkey [32] may indicate the effect of ethnicity and geographic variations on histologic cell types.

In this study, 39 cases (35.8%) had tumor necrosis. This finding was supported by similar studies from Thailand and Europe [33, 43]. A study by Alqusous et al. [44] reported a higher percentage (40.5%, n=17 cases). On the other hand, three studies reported a lower rate of necrosis [35, 45, 46]. The number of patients involved in the studies that found both a higher and lower rate of necrosis was lower than the current study and studies that support the current finding. Therefore, it will not be wrong to infer more than one-third of GISTs cases develop tumor necrosis.

Most of the cases in the present study (68.8%, n=75) had low mitotic activity (≤ 5 M / 50 HPF) and 34 cases (31.2%) had high mitotic activity. A previous study conducted in the same region also showed low mitotic activity was more common (55.6%) among GISTs cases in the Kurdistan region [47]. A study from China revealed that most of the GISTs cases (67.3%) had low mitotic activity [36]. Nevertheless, a study from Iran showed that half of the cases have low mitotic activity [35].

In terms of immunohistochemical profile, 82.6% of GISTs cases were positive for CD117, 70.6% were positive for CD34 and 10.1% were positive for desmin. Similar studies from Pakistan (95.0%) and China (94.5%) reported a higher positivity for CD117. The CD34 positivity of the current study is similar to the study from Pakistan (70.0%) although it is lower than what was reported from China (86.2%) [40, 48]. A study from Iran reported higher CD117 positive cases (100%) and lower CD34 (47.8%) and desmin positive cases (4.3%) [35]. The percentage of desmin-positive cases in the current study was similar to the findings of Muhammed et al. [49]. According to published literatures, most GISTs express CD117 antigen (72-94%) and CD34 antigen (70-80%) [8, 19 , 20]. Other immunohistochemistry markers include smooth muscle actin (30-40%), S100 (10.0%) and Desmin expressed by fewer than 5% [8, 50].

In the present study, the risk stratification revealed that 16 (17.5%), 23 (25.2%), 19 (20.8%), and 31(34.0%) were very low risk, low risk, moderate risk, and high-risk groups, respectively. These findings were supported by similar risk stratifications done in southern Iraq, Turkey, and Malaysia [32, 34, 49]. Nevertheless, a study done in China showed a higher frequency of very low risk as compared with other risk groups [36]. The TNM staging in this study showed that 41 (37.6%), 31 (28.4%), 19 (17.4%) and 18 (16.5%) cases were stage I, II, III, and IV, respectively. Non-stomach cases were very common in all states except stage I. Other similar studies that they did staging according to the 7th UICC/ AJCC TNM, however, came up with lower advanced stages (stage III and IV) than the present study [51, 52]. This difference might be explained by the ethnic and geographical variations and the health-seeking behavior of the people.

Limitation of the study

This study has extensively addressed the important points of GISTs histopathology features and risk stratifications. However, there are certain limitations like our sample size although could not be considered small compared with similar previous studies, it is still small to draw statistical inferences and another limitation is that the PDGFRA test which is genetic mutation was not done for cases that were negative for CD117 antigen.

In conclusion, our study shows that in Sulaimanyah city GISTs most often affect patients aged between 40 to 70 years, affect both genders equally, and most commonly involve the stomach. When compared to GIST patients from other parts of the world, the disease was more advanced in Iraqi patients and a higher proportion of patients belonged to the high-risk group. Further studies are required to substantiate the findings of our study, and to evaluate the reasons for these differences.

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