Journal of Cancer Therapy, 2016, 7, 319-328
Published Online April 2016 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2016.74034

Gastrointestinal Stromal Tumors (GISTs), Surgical Management and Clinical Outcome

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Received 9 February 2016; accepted 25 April 2016; published 28 April 2016

Abstract

Introduction: This study investigated the incidence, surgical management and outcome of Gastrointestinal Stromal Tumors (GIST) in Upper Egypt. Methods: A retrospective review of all GIST patients admitted a South Egypt Cancer Institute between Jan. 2010 and Dec. 2015 was conducted. Patients' demographics, clinical presentation, tumor characteristics, radiological, pathological and immunohistochemical findings, surgical procedures, recurrence and mortality were recorded. Results: A total of 36 GIST patients were identified, stomach was the most common site (27.8%) followed by the small intestine (19.4%) and the large intestine (16.7%). The mean age at time of diagnosis as 52.8 ± 14.4 (ranged from 17 to 76 years). Of these 36 cases, 20 (55.6%) cases were males and 16 (44.4%) cases were females with a ratio of 1.2:1. About 22 cases (61.1%) presented with primary tumors, eight cases (22.2%) had primary tumors and metastases, three cases (8.35) presented with recurrent mass, whereas one case (2.2%) presented either with recurrent mass and metastases or metastases only. The majority of cases (22) had tumorsize >5 cm. Patients were stratified as high, intermediate, low and very low risk (50.6%, 30.6%, 11.1% and 2.8%, respectively). Almost all the cases were surgically managed and 75% were completely resectable. During follow up (average 26.5 months), 22 patients showed complete recovery, 7 had recurrent or metastatic disease and 2 died due to liver metastasis. Conclusion: The incidence of GIST in Upper Egypt is apparently low. Surgical resection is the preferred choice of treatment. The demographic data of GIST patients in South Egypt Cancer institute were similar to those published in the literature. Other prospective studies are required to assess the prognosis and the effect of treatment.

Keywords

Gastrointestinal Stromal Tumors (GISTs), Demography, Surgery, Clinical Outcome

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How to cite this paper: Salem, A.A.S., Elshoieby, M.H., Maximos, D.W. and El-Saba, T.M. (2016) Gastrointestinal Stromal Tumors (GISTs), Surgical Management and Clinical Outcome. *Journal of Cancer Therapy*, **7**, 319-328.
http://dx.doi.org/10.4236/jct.2016.74034

1. Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms, accounted for 1% - 3% of all gastrointestinal malignancies, which arise anywhere within the gastrointestinal tract [1]. Earlier, GISTs were considered as variants of smooth muscle tumors. With the advancement of moleculartechnology and immunochemistry, GISTs recognized as originating from interstitial cells of Cajal or their stem cell precursors [2]-[4].

GISTs occur throughout the GI tract and are most commonly seen in the stomach (60%), followed by jejunum and ileum (30%), duodenum (5%), colorectum (4%), esophagus, or appendix (1%) [5]-[9].

The term was first coined by Mazur and Clark in 1983 to describe a heterogeneous group of gastrointestinal non-epithelial neoplasms [10]. In 1998, Hirota and co-workers reported that GISTs contained activating c-kit mutations, which played a central role in its pathogenesis [11]. Furthermore, GISTs express CD34 and the KIT on their surface [12]. Finally, GISTs are defined as pleomorphic mesenchymal tumors of the GI tract that express the KIT protein CD117 and often also CD34 on immunohistochemistry [13]. Over 90% of GISTs occur in adults over 40 years of age, with a median age of 63 years. However, GIST cases have been reported in all ages, including children. The incidence does not differ with sex, though a study reported that there is a slight predominance of males [14].

GIST is known for its wide variability in biological behaviors and it is difficult to predict its malignant potential [15] [16]. Tumor size, mitotic rate and tumor site are considered as the most important prognostic parameters for patients after surgery [17]. However, neither small size nor low mitotic rate could exclude malignant potential [18]. On the other hand, some enormous tumor with high mitotic rate could also achieve long-term survival, even without adjuvant therapy [19]. The post-operation outcome of GIST is highly variable, with 5-year survival rate ranging from 48% to 80% [20] [21]. This study will analyze the incidence, surgical management and outcome of Gastrointestinal Stromal Tumors (GIST) in Upper Egypt.

2. Patients and Methods

A retrospective analysis was conducted for all the patients (36 patients) who were admitted to the surgical oncology department at South Egypt Cancer Institute, Assiut University, Egypt between Jan. 2010 and Dec. 2015. Patients with a confirmed diagnosis of GIST were included in the study. The collected data included patients' gender, age, clinical presentations, radiological investigations, laboratory findings, tumor characteristics, pathological findings, surgical procedures, intra and post-operative complications. Investigations included X-ray, ultrasonography, CT scan, barium study, MRI and endoscopy. Immunohistochemical analysis was performed using markers such as CD117, Mitotic rate was measured using high power fields (HPF). Post-operative complications, recurrence and mortality data were recorded during the follow up period. This study was approved by the ethical committee at South Egypt Cancer Institute.

3. Statistical Analysis

Data were processed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL). Numerical variables were expressed as the mean ± SD unless otherwise stated. Discrete variables were analyzed using the chi-square test or Fisher's exact test. The P values were considered to be statistically significant at the 5% level. The relations of patient, tumor and treatment characteristics to outcome (DFS, OS and recurrence) were tested by univariate analysis using the Log rank test. A $P < 0.05$ was considered significant.

4. Results

This study included 36 cases of GIST patients. The mean age at time of diagnosis was 52.8 ± 14.4 (ranged from 17 to 76 years). Of these 36 cases, 20 (55.6%) cases were males and 16 (44.4%) cases were females with a ratio of 1.2:1. About 22 cases (61.1%) presented with primary tumors, eight cases (22.2%) had primary tumors and metastases, three cases (8.35) presented with recurrent mass, whereas one case (2.2%) presented either with recurrent mass and metastases or metastases only.

Regarding site of involvement, stomach was the most common site (27.8%) followed by the small intestine (19.4%) and the large intestine (16.7%). Concerning histopathologic type, the most common was the spindle cell type (63.9%). The tumor size ranged from 2 cm to 40 cm with a mean of 13.4 ± 8.7. With respect to the immu-

nologic features of the tumor, c-kit positive GIST (58.3%) was the most immunophenotyping pattern. **Table 1** summarizes the clinicopathological features of GIST patients.

Using NIH consensus approach for defining risk of aggressive behavior, most of the cases (50.6%) found to be of high risk of aggressive behavior. **Table 2** summarizes risk categories.

4.1. Surgical Treatment

All patients underwent surgical exploration. Complete resection was accomplished in 27 patients (75%); 22 patients (61.1%) with primary disease, five patients (22.2%) with metastatic disease. The details of the extent of surgical resection are shown in **Table 3** and **Figures 1-3**.

4.2. Postoperative Complications

There were no postoperative mortalities. Postoperative morbidity was reported in six patients (16.7%). Reoperation was resorted to in one patient (2.8%). This patient had had been explored to relieve postoperative adhesive

Table 1. Demographic and clinicopathological features of GIST patients (n = 36).

Variables	Total No. (%)
Age (mean ± SD)	52.8 ± 14.4
Gender	
Male	20 (55.6%)
Female	16 (44.4%)
Mode of presentation	
Primary	22 (61.1%)
Primary + metastases	8 (22.2%)
Recurrence	3 (8.3%)
Recurrence + metastases	1 (2.8%)
Metastases	1 (2.8%)
N/A	1 (2.8%)
Site of involvement	
Stomach	10 (27.8%)
Small intestine	7 (19.4%)
Colorectal	6 (16.7%)
Omentum	4 (11.1%)
Retroperitoneal	3 (8.3%)
Hepatic	1 (2.8%)
Pelviabdominal	4 (11.1%)
N/A	1 (2.8%)
Histopathology	
Spindle cells	23 (63.9%)
Epithelioid cells	7 (19.4%)
Mixed	5 (13.9%)
N/A	1 (2.8%)
Tumour size	
≤2	1 (2.8%)
>2 - 5	4 (11.15%)
>5 - 10	11 (30.6%)
>10	20 (55.6%)
Mitotic count per 50 HPF	
≤ 5	11 (30.6%)
5 - 10	14 (38.9%)
>10	3 (5.6%)
N/A	9 (25%)
c-kit immunoreactivity	
Negative	8 (22.2%)
Positive	21 (58.3%)
N/A	7 (19.4%)

Table 2. Risk stratification of GIST patients using NIH consensus guidelines for defining risk of aggressive behavior (Fletcher 2002).

Risk Category	No. of patients (%)
Very low	1 (2.8%)
Low	4 (11.1%)
Intermediate	11 (30.6%)
High	20 (50.6%)

Table 3. Management and outcome of GIST cases.

Management	
Completely resectable	
Partial gastrectomy	8
Gastrectomy + splenectomy	2
Gastrectomy + colectomy + splenectomy	1
Gastrectomy + distal pancreatectomy + splenectomy	1
Whipple s Operation	1
Resection of small intestinal loops	2
Colectomy	3
Transverse colectomy + small intestinal loops	1
Low anterior resection	1
Abdomeno-perineal resection	1
Omentectomy	3
Excision of retroperitoneal tumors	1
Hepatic resection Blood transfusion units (within 24 h post-operation) (1 - 6)	2
Hemoglobin (before operation)	4
Hospital length of stay (days) (1 - 35)	
Follow up period (months) (1 - 72)	9.7 ± 2
Complications	8.5
Bleeding	26.5
Infection	3 (8.3%)
Deep vein thrombosis	2 (4.4%)
Outcome	0
Alive without recurrence/metastasis	26 (72.2%)
Alive with recurrent/metastatic disease	7 (19.4%)
Died	2 (4.4%)
Lost to follow up after surgery	1 (2.2%)

intestinal obstruction after failure of conservative treatment. Four patients had wound infection and three patients had wound dehiscence, but all were managed conservatively.

4.3. Survival

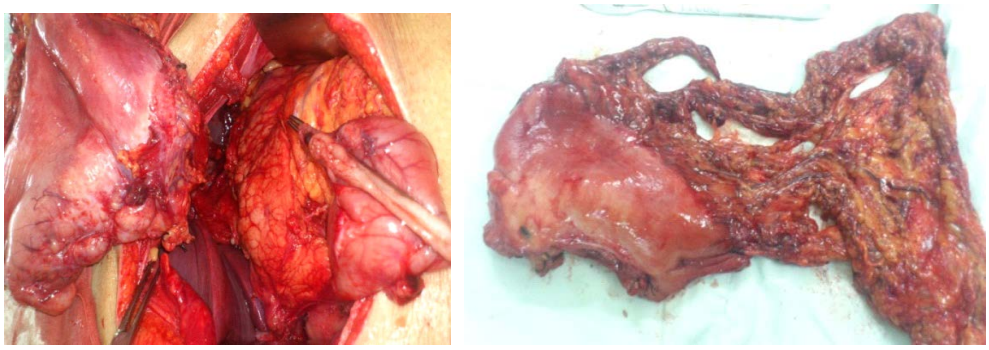
Patients who had complete resection (n = 27) had survival chance. Those with inoperable lesions survived few weeks after presentation. For the 27 patients who underwent curative surgery, the median follow-up period was 12 months (Range 2 - 72 months). At 5 years, the overall survival was 51%. On univariate analysis of the clinicopathological risk factors (**Table 4**), age, sex, tumor size, mitotic index, c Kit immunoreactivity and histopathologic type did not influence the survival outcome **Figure 4**.

5. Discussion

Over 90% of GISTs occur in adults over 40 years of age, with a median age of 63 years. However, GIST cases have been reported in all ages, including children. The incidence does not differ with sex, though a study reported

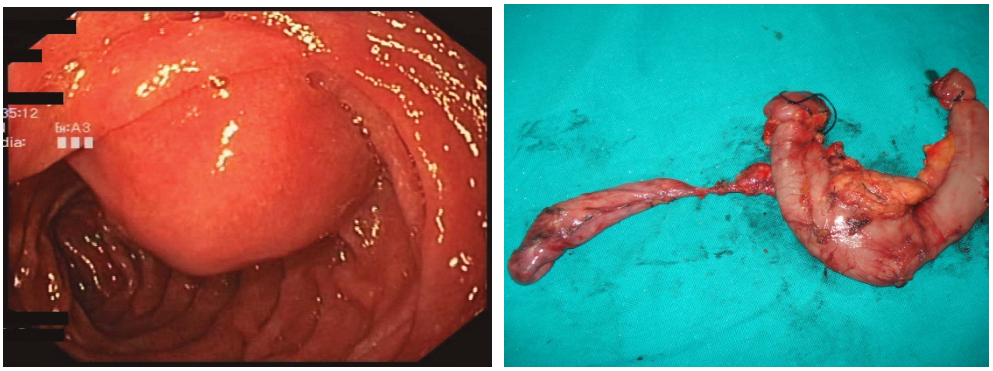
Table 4. Univariate analysis of OS for GIST patients.

Clinicopathologic variables	No.	Mean survival	P value
Age			
<40	6	60	P = 0.4
≥40	30	43	
Gender			
Male	20	42	P = 0.3
Female	16	51	
Mitotic count per 50 HPF			
≤5	11	50	P = 0.4
5 -10	14	36	
>10	3	48	
Tumour size			
≤2	1	53	
>2 - 5	4	48	P = 0.4
>5 - 10	11	34	
>10	20	42	
c-kit immunoreactivity			
Negative	8	48	P = 0.4
Positive	21	42	
Histopathology			
Spindle cells	23	46	
Epithelioid cells	7	54	P = 0.5
Mixed	5	21	



(a) (b)

Figure 1. Showed gastric GIST with (a) Operative and (b) Postoperative images.



(a) (b)

Figure 2. Showed Endoscopic image of duodenal GIST (a) with postoperative specimen after Whipple s operation (b).

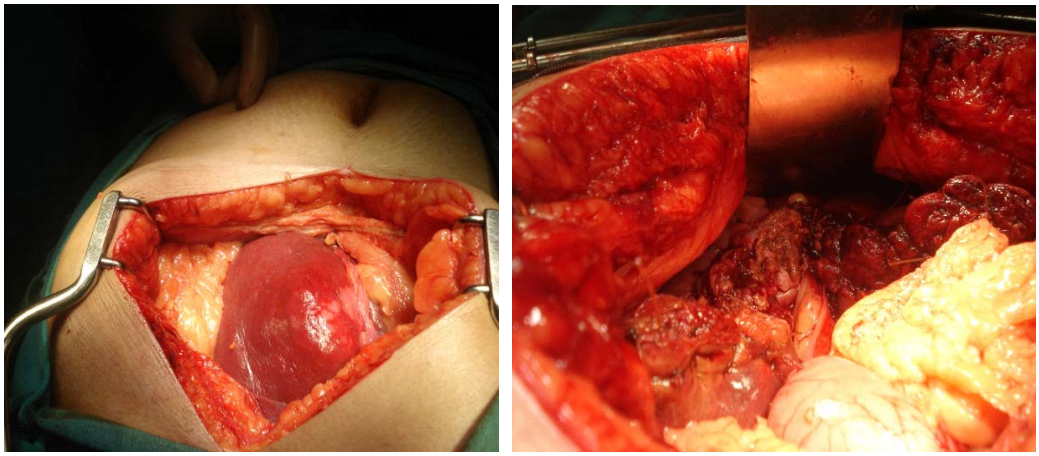


Figure 3. Showed small intestinal GIST metatastasis to liver underwent resection anastomsis of small intestine and wedege liver resection.

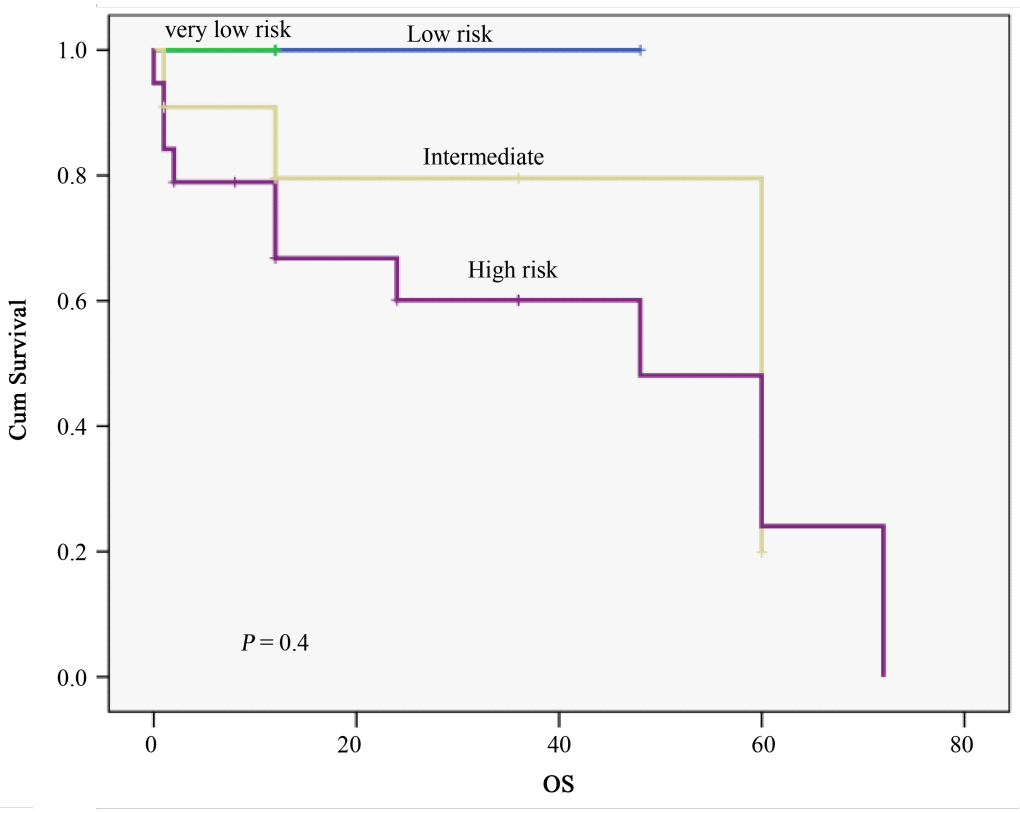


Figure 4. Survival in relation to risk stratification.

that there is a slight predominance of males [14]. In our study, the mean age of GIST patient was similar to other published data [22]. Similarly, a study in Egypt by Al Kalaawy *et al.* [23] reported that the median age was 54 and ranged from 18 - 77 years. Another study in Jordan on 93 cases revealed that the average age of GIST patients was 53 years [24]. In another study by Al-Thani *et al.* that included 48 cases, the average age at presentation was 48 years [25].

Our study revealed slight male predominance. A slight male predominance in GIST incidence was reported in Taiwanese study but the Chinese survey showed equal rates of incidence similar to the Italian hospital study [26]-[28]. The Taiwanese data demonstrated younger age and female sex as independent predictors of better

survival.

GISTs occur throughout the tubular GI-tract from the lower esophagus to the anus. The most common site is by far stomach (60% - 70%) followed by small intestine, rectum and colon. Only small numbers of cases have been reported in the esophagus and appendix [29] [30]. A number of primary GISTs have been reported outside the GI-tract proper in the abdomen, specifically in the omentum, mesenteries, and retroperitoneum [31] [32].

In the current study, the most common site of GIST was the stomach followed by the small intestine and then the large intestine. These data are in accordance with Barakat *et al*. [24] who reported that the stomach is the most common site followed by the small intestine and the large intestine. Also, another study by Lee *et al.* [33] revealed that primary tumour site of GIST was stomach then the small intestine. Moreover, a review by Miettinen *et al*. reported the same previous site predilection [34]. Our study revealed that the median tumor size was 10 cm and ranged from 2 to 40 cm. Tumour size is important in risk assessment of the disease. An Egyptian study revealed that the median tumour size was 18 cm with a range from 5 - 42 cm [23].

Surgical resection remains the treatment of choice for all resectable tumors since it is the only chance for cure [20] [35]. In this study, patients who underwent complete resection had a 5 year survival of 51% which is comparable with other reports [20] [36] [37].

A 1 - 2 cm margin was advocated to achieve adequate resection [38]. However more recently, Dematteo *et al*. [39] demonstrated that tumor size (and not a wide negative microscopic margin) was more important in determining survival. In our study complete macroscopic resection was undertaken in 27/36 patients (75%). The goal of surgery is complete resection of gross disease avoiding tumor rupture and achieving negative margins. Incomplete resection should be performed only for palliation of emergency symptoms e.g. bleeding, pain or mass effect [40]. Tumor rupture should beavoided as it is associated with intra-abdominal dissemination of tumor cells and subsequent high risk of local tumor recurrence [41]. We agree with De Matteo *et al*. and Blanke that-GISTs rarely go to lymph nodes, solymphadenectomy in the absence of gross involvement is not needed [20] [42].

The histologic features of GIST vary, and to some degree this variation is site-dependent. Most commonly, GISTs have a spindle cell pattern (60% - 70%), whereas epithelioid cytology is seen in 20% - 30% of cases exclusively or focally, and a pleomorphic pattern rarely (<5%). In all GI-sites, GISTs often grow between bundles of smooth muscle fibers often creating a micronodular, plexiform pattern. Most of the small and large intestinal GIST are also spindle cells. These data are in agreement with our data that revealed spindle cell was the most common histologic type.

Upon stratification of cases using NIH criteria, the data showed that 50.6% were at high risk, 30.6% at intermediate risk, 11.1% were at low risk, and 2.8% were at very low risk. These data similar to Al-Thani *et al*. who reported that 33% were at high risk, 31% at intermediate risk, 26% at low risk, and 10% at very low risk However in this study risk stratification into very low, low, intermediate and high risk has no impact on survival rate ($P = 0.4$).

KIT-positivity in GISTs is typically strong and global. Membrane staining is often present, and this pattern is more readily observed in epithelioid GISTs. In this study the number of positive cases was 21 cases (58.3%). These data are lower than the published data in the literature. this difference could be attributed to the fact that there were 7 cases were missed from the archive and we do not know their immunostaining profile which was considered as one of the limitations.

Another limitations of this study is the absence immunostaining for CD34and SMA and the small number of patients. The frequency of CD34-positivity varies by site. GISTs of esophagus and rectum are nearly consistently CD34-positive (95% - 100%). There is no difference in the frequency of CD34-expression between benign and malignant GISTs, and site-specific studies do not show significant survival differences between positive and negative cases [43] [44].

The incidence of GIST in Upper Egypt is apparently low. Surgical resection is the preferred choice of treatment; our data revealed that the dempgraphic data of GIST patients in South Egypt Cancer institute were similar to those published in the literature. Other prospective studies are required to assess the prognosis and the effect of treatment.

Acknowledgements

We thank all members of Surgical Oncology Department of South Egypt Cancer Institute for their kind coopera-

tion. All authors contributed to the creation of and approved the manuscript.

Conflict of Interest

The authors declared no conflict of interest and no financial issues to disclose.

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