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Original Research Article

Outcome and prognostic factors of primary gastrointestinal stromal tumours following complete surgical resection

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ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms. Surgical excision is the definitive treatment for primary localized GISTs. Targeted therapy represented by tyrosine kinase inhibitors has clearly improved the survival rates in patients with GISTs. The aim of this study was to identify prognostic factors influencing tumor recurrence and survival after curative resection of primary GISTs.
Methods: This study was conducted on thirty seven patients with localized primary GIST who were operated on in the Department of General Surgery. Then completed adjuvant therapy in the medical Oncology Department, Faculty of Medicine; Tanta University Hospital, from March 2016 to August 2017. All patients' data, clinical presentations, radiological and endoscopic data, surgical procedures, complications, and survival data were collected, reviewed and analyzed.
Results: The mean age of the studied cases was 53.62 years. 14 patients were males and 23 patients were females. Eleven patients had performance status 2. Abdominal pain was the most common complaint. 4 patients presented with acute intestinal obstruction. Ileum was the most common site (14 cases) followed by stomach (13 cases). We reported four cases of extra-gastrointestinal stromal tumors (EGISTs). According to the mitotic index in studied cases; sixteen patients had mitotic count >5/50 HPF. Surgical excision was done in all cases with histopathologically negative resection margins. Thirty three cases showed good complete response without local recurrence or distant metastasis.
Conclusions: Performance status of patients, tumor size and mitotic index were independent prognostic predictors for tumor recurrence or metastasis.

Keywords: Outcome, Prognostic factors, Gastrointestinal stromal tumours, Resection

INTRODUCTION

Although rare, gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms, accounting for 1-2% of all neoplasms of the digestive tract.[1] They are derived from malignant transformation of the interstitial cells of Cajal, c-KIT-positive cells of neuroendocrine origin that function as the pacemaker in peristalsis.[2]

Only 70% of patients with GISTs are symptomatic. Initial diagnosis may be difficult as symptoms and signs are often nonspecific; such as nausea, vomiting, vague abdominal discomfort, weight loss and early satiety. Bleeding due to erosion into the GI lumen may lead to patients presenting with hematemesis, melena or anemia. Rupture of a GIST can result in acute abdominal pain presenting as a surgical emergency.[3]

Approximately 10-30% of GISTs are regarded as clinically malignant; therefore, all GISTs have malignant potential and no GIST can truly be considered benign.[4,5]

Lymph node metastasis are uncommon in the adult form of GIST, however, metastasis to the liver is frequently seen.[6] Advances in endoscopic techniques and contrast-enhanced computed tomography (CECT) might be useful in diagnosis of GISTs. In addition, CECT scanning plays an important role in the detection and monitoring of post-treatment metastasis regression.[7]

It is a general consensus that surgical excision is the definitive treatment for primary localized GISTs without peritoneal seeding or metastasis.[8,9] The discovery that the mutational activation of KIT and platelet derived growth factor receptor-alpha (PDGFRA) genes stimulated the growth of these cancer cells has revolutionized treatment.[10] Last but not the least; targeted therapy represented by tyrosine kinase inhibitors (TKI as imatinib and sunitinib) has clearly improved the survival rates in patients with primary, metastatic or recurrent GISTs.[11] The aim of this study was to identify prognostic factors influencing tumor recurrence and survival after curative resection of primary GISTs.

METHODS

This prospective study was conducted on Thirty Seven patients with localized primary GIST who were operated on in the Department of General Surgery. Then completed adjuvant therapy in the medical Oncology Department, Faculty of Medicine; Tanta University Hospital, from March 2016 to August 2017.

Patients included in this study had localized resectable non metastatic GIST with complete surgical resection. All patients were subjected to history taking, general examination, local examination of abdomen and preoperative laboratory investigations. Radiological investigations were done for studied cases included contrast enhanced computed tomography (CECT) of abdomen and pelvis. Endoscopic ultrasound (EUS) was useful diagnostic adjunct in some selected cases to assess the depth of invasion as well as allowing for fine needle aspiration (FNA) under EUS guidance.

Performance status of our patients was assessed according to the Eastern Cooperative Oncology Group (ECOG) score also called the WHO or Zubrod score runs from 0 to 5, with 0 denoting perfect health and 5 denoting death.[12] Our surgical approach was based on preoperative investigations, and was determined by tumor size, location and growth character (exophytic or endophytic).

Operations performed for GIST in studied cases

Wedge resection of the stomach, partial gastrectomy and gastrojejunostomy, duodenal resection, segmental resection of the jejunum and ileum.

Table 1: WHO or Zubrod score.

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead.

Postoperative follow-up

Patients were referred to medical oncology department to receive suitable TKI adjuvant targeted therapy. Adjuvant imatinib prescribed for every patient for one year in a dose of 400 mg per day orally. Patients were followed postoperatively at 6 months intervals till the end of study for any complaints, any complications and local recurrence of tumor or distant metastasis. Based on follow-up data, this study determined the prognostic impact of age, gender, tumor size, mitotic count, necrosis, mucosal ulceration, location of tumors and type of operation.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Categorical data were examined using the Chi-square test. Fisher's exact test was applied, as appropriate, to check for differences of the demographic, clinical and clinicopathological parameters between the independent study-cohorts. Estimates for disease-free survival (DFS), disease-specific-survival (DSS) and overall survival (OS) were obtained by the Kaplan-Meier method and differences between Kaplan-Meier curves were investigated by the log-rank test. P value differences <0.05 were considered statistically significant.

RESULTS

Abdominal pain was the most common complaint and was present in 24 patients. In this study, GISTs in the ileum was the most common site (14 cases-37.8%) followed by stomach (13 cases-35.1%). While we reported four cases of extra-gastrointestinal stromal

tumors (EGISTs) (10.8%); 2 cases in the mesentry of ileum and another 2 cases in retroperitoneal space. The largest size was 24×20×17 cm in the stomach while the smallest size was 2×1.5×1.5 cm in the ileum in two cases. All patients who had GIST ≤10 cm had good prognosis with complete response while the patients who developed local recurrence with or without distant metastasis had sizes more than ten centimeters. GISTs invading the mucosa in 14 patients (37.8%). Thirty three patients in this study presented with tumor necrosis. Only one patient presented with histopathological positive lymph nodes of GIST in stomach (Table 2).

Table 2: Demographic data and clinico-pathological data of patients of this study.

	Total (n=37)		Complete response (n=33)		Recurrent /distant metastasis (n=4)		Test of sig.	P value
	No.	%	No.	%	No.	%		
Sex								
Male	14	37.8	10	30.3	4	100.0	χ^2=7.368	^{FE}p=0.015
Female	23	62.2	23	69.7	0	0.0		
Age (years)								
Min.-Max.	23.0-75.0		23.0-75.0		36.0-65.0			
Mean±SD	53.62±12.51		53.82±12.41		52.0±15.21		t=0.271	0.788
Median	55.0		55.0		53.50			
Performance status								
0	11	29.7	11	33.3	0	0.0		
1	15	40.6	15	45.5	0	0.0	χ^2=7.707	^{MC}p=0.010
2	11	29.7	7	21.2	4	100.0		
Complaint								
Abdominal pain	24	64.9	20	60.6	4	100.0	χ^2=2.429	^{FE}p=0.276
Vomiting	12	32.4	11	33.3	1	25.0	χ^2=0.113	^{FE}p=1.000
Dyspepsia	2	5.4	2	6.1	0	0.0	χ^2=0.256	^{FE}p=1.000
Hematemesis	5	13.5	5	15.2	0	0.0	χ^2=0.701	^{FE}p=1.000
Melena	4	10.8	4	12.1	0	0.0	χ^2=0.544	^{FE}p=1.000
Intestinal obstruction	4	10.8	4	12.1	0	0.0	χ^2=0.544	^{FE}p=1.000
Abdominal distension	1	2.7	0	0.0	1	25.0	χ^2=8.479	^{FE}p=0.108
Site of GIST								
Stomach	13	35.1	11	33.3	2	50.0		
Ileum	14	37.8	13	39.4	1	25.0		
Jejunum	5	13.5	5	15.2	0	0.0	χ^2=4.735	^{MC}p=0.516
Duodenum	1	2.7	1	3.0	0	0.0		
Retroperitoneal	2	5.4	1	3.0	1	25.0		
Mesentery	2	5.4	2	6.1	0	0.0		
Size of GIST (cm)								
≤2	2	5.4	2	6.1	0	0.0		
2–5	6	16.2	6	18.2	0	0.0	χ^2=3.958	^{MC}p=0.234
5–10	12	32.4	12	36.4	0	0.0		
>10	17	45.9	13	39.4	4	100.0		
Mucosal ulceration								
Yes	14	37.8	13	39.4	1	25.0	χ^2=0.314	^{FE}p=1.000
No	23	62.2	20	60.6	3	75.0		
Tumor necrosis								
Yes	33	89.2	29	87.9	4	100.0	χ^2=0.544	^{FE}p=1.000
No	4	10.8	4	12.1	0	0.0		
Lymph node infiltration								
Negative	36	97.3	33	100.0	3	75.0	χ^2=8.479	^{FE}p=0.108
Positive	1	2.7	0	0.0	1	25.0		
Mitotic index (…/50HPF)								
≤5	21	56.8	21	63.6	0	0.0	χ^2=5.886	^{FE}p=0.028
>5	16	43.2	12	36.4	4	100.0		

Continued.

	Total (n=37)		Complete response (n=33)		Recurrent /distant metastasis (n=4)		Test of sig.	P value
	No.	%	No.	%	No.	%		
WHO classification (2000)								
Benign	7	18.9	7	21.2	0	0.0	χ^2=1.791	^{MC}p=0.503
Borderline	14	37.8	14	42.4	0	0.0		
Malignant	16	43.2	12	36.4	4	100.0		
Risk of aggressive behaviour (NIH classification) (2002)								
Very low	2	5.4	2	6.1	0	0.0	χ^2=3.141	^{MC}p=0.396
Low	5	13.5	5	15.2	0	0.0		
Intermediate	11	29.7	11	33.3	0	0.0		
High	19	51.4	15	45.5	4	100.0		

Table 3: Demographic data and clinico-pathological data of patients of recurrence.

	Case 1 local recurrence	Case 2 local recurrence	Case 3 local recurrence and distant metastasis to liver and bone	Case 4 local recurrence and distant metastasis to liver and lung
Age (years)	42	65	65	36
Sex	Male	Male	Male	Male
Performance status	2	2	2	2
Complaint	Abdominal pain	Abdominal pain and distension	Abdominal pain and vomiting	Abdominal pain
Duration of complaint	6 months	3 months	3 months	1 year
Site of GIST	Ileum	Stomach	Stomach	Retroperitoneal space
Size of GIST	13×9 cm	24×20×17 cm	25×20 cm	16×12×10 cm
Mucosal ulceration	No	No	Yes	No
TNM staging	T4N0M0	T4N0M0	T4N1M0	T4N0M0
Tumor necrosis	Yes	Yes	Yes	Yes
Resection margins	Negative	Negative	Negative	Negative
Mitotic index (…/50 HPF)	> 5	> 5	> 5	> 5
NIH classification	High	High	High	High
WHO classification	Malignant	Malignant	Malignant	Malignant
c-kit marker	Positive	Positive	Positive	Positive
Type of operation	Segmental resection and anastomosis	Partial gastrectomy and gastrojejunostomy	Partial gastrectomy and gastrojejunostomy	Surgical excision
Postoperative complications	No complication	Wound infection	Wound infection	No complication
Follow up period	24	18	24	26
Disease free survival	18	15	20	24

According to the mitotic index in studied cases; twenty one patients were had mitotic count ≤5/50 HPF, while sixteen patients had mitotic count >5/50 HPF. The four patients who developed local recurrence with or without distant metastasis had mitotic count more than 5/50 HPF. According to World Health Organization (WHO) classification of GISTs (2000), the four patients who developed local recurrence with or without distant metastasis were malignant GISTs. According to classification of The National Institute of Health (NIH) of the United States 2002 (Risk of aggressive behavior of GIST); the four patients who developed local recurrence with or without distant metastasis had GISTs with high risk of aggressive behavior (Table 2).

The patients were followed up routinely after surgery every 6 months. Disease-free survival (DFS) was defined as the time from surgery to the first event of recurrent disease, distant metastasis or death. Follow up period of our patients ranged from nine months to twenty six months with a mean of 16.59 months. Thirty three cases showed good complete response without local recurrence or distant metastasis (89.2%). Cases of local recurrence without distant metastasis; recurrent GIST in ileum was localized and treated with furthermore segmental

resection and anastomosis followed by Imatinib mesylate as adjuvant therapy for three years, the other recurrent GIST was locally advanced in stomach and received Imatinib mesylate. The cases of local recurrence with distant metastasis started Imatinib mesylate which scheduled for three years (Table 3).

Survival analysis

Survival analysis is the analysis of time-to-event data. Time to event means the time from entry into a study until a particular event, for example onset of illness. Such data describe the length of time from the origin to an endpoint of interest. Survival analysis methods are usually used to analyze data collected prospectively in time. Kaplan-Meier is a statistical method used in the analysis of time to event data. This method is very useful in survival analysis as it is used by the researchers to determine and/or analyze the patients who lost to follow up or dropped out of the study, those who developed the disease of interest or survived it.

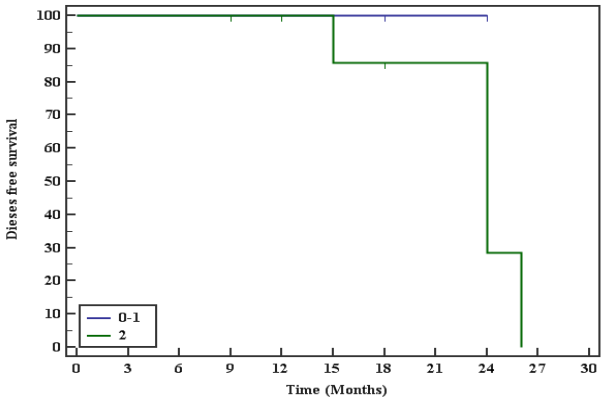

Figure 1: Kaplan-Meier survival curve for disease free survival with performance status of patients.

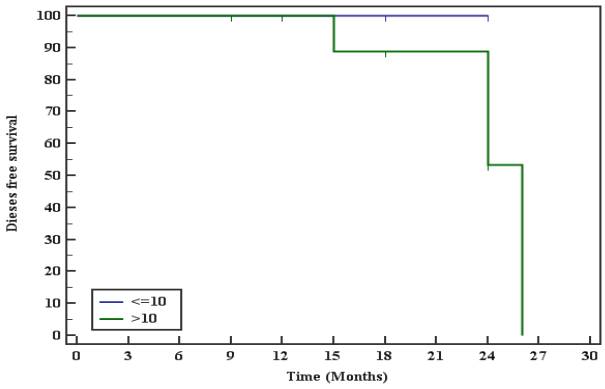

Figure 2: Kaplan-Meier survival curve for disease free survival with size (cm).

All patients in our study with primary resectable GISTs were followed up and evaluated in the survival analysis. A survival analysis regarding DFS suggested that 1) performance status of patients (p=0.005), 2) tumor size (p=0.036) and 3) mitotic rate (p=0.028); were all associated with DFS. So, performance status of patients, tumor size and mitotic index were independent prognostic predictors for tumor recurrence or metastasis. Another possible objective of the analysis of survival data may be to compare the survival times of two or more groups. A simple test of statistical significance is the log-rank. It can be used to test whether the survival of individuals in two or more groups is significantly different. Use of the log-rank test showed that the DFS of patients with tumor size ≤10 cm, lower mitotic rate (≤5/50 HPF) and performance status 0 or 1 were at lower risk for GIST recurrence (Figure 1-3).

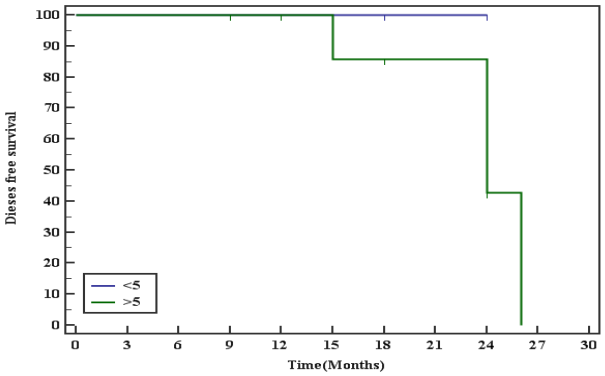

Figure 3: Kaplan-Meier survival curve for disease free survival with mitotic index.

DISCUSSION

Complete surgical resection avoiding tumor rupture or injury to the pseudocapsule is the initial treatment for primary and localized GISTs. The introduction of imatinib, a tyrosine kinase inhibitor, has dramatically improved treatment outcomes. To improve the prognosis of patients with a substantial risk of recurrence, all the guidelines recommend adjuvant therapy with imatinib, which improves not only recurrence free survival but also the overall survival of high-risk patients.[13,14]

All patients who developed tumor recurrence in our study were males and their ages ranged from 36 years to 65 years with a mean age of 52 years (SD=15.21). These findings agree with that of Kramer et al, who reported tumor recurrence more in males.[15] Prasertcharoensuk et al, showed that recurrence was more in males (52.9%).[16]

It was observed that our patients who have a worse performance status and limited functional capacity tend to have more difficulty in tolerating targeted treatments. These patients have less favorable outcomes than more fit patients with better PS, regardless of the treatments given. Patient PS can and usually does change over time. Patients can experience a gradual worsening of their PS as their tumor progresses, both from the tumor itself and from the cumulative adverse effects of treatments. On the

other hand, effective treatment can lead to an improvement in PS if a patient is limited by tumor-related symptoms (as opposed to other chronic medical conditions unrelated to tumor) that improve as the tumor responds to treatment.

In our study; abdominal pain was the most common complaint (64.9% of patients), while thirteen patients (35.1%) presented with emergency complications of GISTs (5 patients with hematemesis (13.5%), 4 patients (10.8%) with melena. 4 patients (10.8%) with acute intestinal obstruction). These findings are comparable with that of Sorour et al, who recorded 45 patients (46%) presented with GIT bleeding and 26 patients (28.3%) presented with acute intestinal obstruction from total 92 patients presented with emergency complications of GISTs.[17] Morrison and Hodgdon, recorded two patients of GISTs presented with acute intestinal obstruction.[18] We reported ileo-ceacal intussusception in two patients (5.4%) with ileal GISTs. Pirşcoveanu et al, reported ileo-ceacal intussusception as a case report.[19] While ileo-ileal intussusception due to GIST was recorded by Fersahoglu et al, whereas Giestas et al, recorded jejuno-jejunal intussusception.[20,21] Jameel et al and Zhou et al, recorded Gastro-duodenal Intussusception caused by gastric GISTs.[22,23]

In this study; the small bowel was the most common site of GISTs (20 patients followed by the stomach (13 patients). These are consistent with the study of Yin et al, who showed slight predominance of small bowel GISTs (48.5%) over gastric GISTs (45.4%).[24] Contrast to other studies which confirmed that the stomach is the most common site of GIST followed by the small bowel.[15,16] We reported four patients of extra gastrointestinal stromal tumors (EGISTs) (10.8%); these results were similar to that of Du et al who reported the incidence of EGISTs in 15 out of 141 patients (10.6%).[25] Cho et al described similar incidences of the disease (10.1%).[26]

Recurrence of GISTs in the present study occurred in patients had GISTs in stomach, ileum and retroperitoneal space. So no specific site of GIST considered a risk factor for recurrence. These results are consistent with that of other studies as Yin et al, Prasertcharoensuk et al, 2017.[16,24] Contrast to Corless et al, who demonstrated the importance of location of GIST in the risk of disease recurrence.[27] Whereas Mandrioli et al, demonstrated that GISTs that arise from the small intestine have less favorable prognosis than gastric GISTs.[28]

All the patients in our study who had GIST ≤10 cm (20 cases - 54.1%) had good prognosis with complete response while the patients who developed local recurrence with or without distant metastasis (4 cases - 10.8%) had sizes more than ten centimeters. These results are supported by other studies that confirmed that large size is very important prognostic factor of GIST as it is associated with higher rate of recurrence.[16,24,29,30]

We reported recurrence in four cases only one of them had mucosal invasion. Mucosal invasion may cause GIT bleeding resulting in early diagnosis, consequently less recurrence and better prognosis. This finding is supported by Yin et al.[24] This observation was opposed by Bai et al, as they observed that mucosal invasion is associated with an aggressive clinical course.[31]

Tumor necrosis of GISTs is present in all patients with recurrence. So, tumor necrosis associated with poor prognosis. This is confirmed by Bai et al, and Hou et al.[31,32] Liu et al, said that presence of tumor necrosis is significantly associated with larger tumor size, higher mitotic index, tumor rupture and presence of nuclear atypia.[30]

The four patients who developed local recurrence with or without distant metastasis had mitotic count more than 5/50 HPF. These results are consistent with that of Mandrioli et al, and Park et al, who confirmed the importance of mitotic index in treatment, prognosis and outcome of GISTs; mitotic count >5/50 HPF associated with poor prognosis and high rate of recurrence.[28,33]

All the patients in our study were followed up and evaluated in the survival analysis. During the follow-up period, 10.8% of patients experienced tumor recurrence or metastasis. Time to recurrence ranged from 15 months to 24 months. It is observed that survival analysis regarding disease free survival (DFS) suggested that 1) performance status of patients, 2) tumor size and 3) mitotic index were all associated with DFS. So, performance status of patients, tumor size and mitotic index were independent prognostic predictors for tumor recurrence or metastasis.

CONCLUSION

The recurrence rate related to the unpredictable behavior of gastrointestinal stromal tumors (GISTs) continues to be a major topic of investigation since no actual risk evaluation scales have proven to be exceedingly effective in predicting prognosis. We therefore focused in this study on evaluating the prognostic factors influencing tumor recurrence and survival after curative resection of primary gastrointestinal stromal tumors. In our study; age of patients, gender, tumor necrosis, mucosal ulceration and type of operation are not related to outcome of GISTs. Also, we did not find the site of the GISTs to be significantly related to prognosis of GISTs. We found that the tumor size, the mitotic index of tumor and performance status of patients were the strongest predictive factors.

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