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Large sized gastrointestinal stromal tumors: survival and predictors of recurrence after surgical resection

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Abstract---Background: large gastrointestinal stromal tumors (GISTs) represent a surgical challenge for complete en block resection, which is the mainstay strategy for management. This study was done to determine long term oncological outcomes following resection of GISTs >10 cm. Material and methods: This retrospective study included 52 patients who underwent surgical resection for GIST >10 cm. Our main outcome is to determine the overall survival along with the predictors of post-operative recurrence after large GISTs resection. Results: The stomach was the most commonly affected organ (55.8%). Mass size was larger than 20 cm in 36.5% of our patients and the rest of them ranged between 10 – 20 cm. Anatomical/formal resection was performed in 63.5%of patients, and the remaining ones received a limited resection. After follow-up (median 57 months), disease-free and overall survival had mean values of 80.97 and 100.56 months, respectively. Recurrence was encountered in 36.5%, while the total mortality rate was 26.9%. Multivariate analysis revealed that tumor rupture and CD 34 positive tumors were strong predictors of recurrence. Conclusion: surgical resection of GISTs is the mainstay therapy, but it is associated with relatively high rate of recurrence even with adjuvant tyrosine kinase inhibitor therapy (TKIs).Risk factor

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of recurrence in large tumor included tumor rupture and CD34 positive tumors .So, in the setting of huge GISTs, surgery still the safest and most effective therapy with careful handling of the tumor and en block resection without interruption of psudocapsule , and if rupture occurs , this necessities adjuvant therapy as early as possible with strict follow up plan irrespective of patient risk stratification.

Keywords---GIST, TKIs, recurrence, survival–rupture.

Introduction

Gastrointestinal stromal tumors (GISTs) are clinically infrequent neoplasms of the gastrointestinal tract (1), however GISTs are considered the most common mesenchymal-derived tumor of the GIT (2), they are thought to arise from CD34-postive interstitial Cajal cells in the intestinal wall, involving most commonly the stomach and proximal small intestine, however they may occur in any part of the digestive system, sometimes including the liver, omentum, mesentery and peritoneum (3). GISTs are characterized by considerable clinical diversity, ranging from small, localized, slow-growing lesions to very aggressive tumors of large size that already have massive metastasis upon diagnosis (4). Complete surgical resection remains the most definitive treatment for primary GISTs, although the proven effectiveness of tyrosine kinase inhibitors (TKIs) in increasing relapse-free survival (RFS) has revolutionized the treatment of GISTs (5). Large GISTs carry a technical surgical challenge to achieve complete en block resection in order to obtain the best long term oncological outcomes. Here in we represent our surgical experience regarding the long term results after resection of large GISTs.

Material and Methods

This is a retrospective study that was conducted at Gastrointestinal Surgical Center (GISC), Mansoura University. The study included patients diagnosed with large GIST > 10 cm despite the site of the tumor origin who underwent resection in our center during the period between January 2010 and January 2021. We excluded small tumors < 10 cm, huge locally advanced cases and disseminated tumors which were not amenable for surgical resection. A total of 52 patients were enrolled in the current study. All patients signed informed consent before the surgical procedure after explaining its benefits and risks. Preoperative preparation included proper history taking, clinical examination, as well as routine preoperative laboratory workup, diagnostic imaging studies (computed tomography) and endoscopic GIT procedures.

The patients were kept fasting for at least 6 hours prior to surgery. Chemical and mechanical bowel preparation were done with colorectal tumors. Prophylaxis against venous thromboembolism was done via low molecular weight heparin. All operations were performed under general anesthesia. Laparotomy was the procedure utilized for most cases owing to large size of the lesion. The surgical procedure was dependent on the site of the lesion. Either former/anatomical resection or limited /organ preserving resection were done according to the size, site, relation to surroundings and certainty of the diagnosis, routine

lymphadenectomy was not done if the diagnosis of GIST was sure. Proper handling of the tumor was done during the operation, en block Multivisceral resection was performed when necessary and if rupture occurred, it was recorded.

The excised surgical specimen was sent to the histopathology laboratory in our center for analysis. Specimens were examined for surgical cut margins, mitotic index, and nuclear atypia. Immunohistochemical staining was done, including CD-34, CD-117, DOG-1, SMA, and S-100.GIST risk stratification was done according to NIH classification system. Patients were referred to oncology department to complete adjuvant treatment with imatinib, regular follow up using computed tomography scanning was done, if tumor recurrence occurred, site of recurrence and management were recorded. The main outcome is to estimate the overall survival and disease-free survival in patients who underwent surgical resection of GIST larger than 10 cm and to investigate the predictor factors of tumor recurrence.

Statistical analysis

We used the SPSS software program for windows for data collection, tabulation, and analysis. Categorical data were expressed as numbers and percentages, whereas quantitative data were expressed as either mean (standard deviation) or median (range) if the data were normally or abnormally distributed, respectively. The chi-square test was used to compare categorical variables, whereas the independent sample t-test and Mann-Whitney test were applied for normal and abnormally distributed quantitative variables, respectively. Univariate and multivariate regression analyses were applied to detect the predictors for recurrence after resection. A p-value less than 0.05 was considered statistically significant for all of the previous tests.

Results

The included patients had a mean age of 55.34 years. We included 35men (67.3%) in addition to 17 women (32.7%). Their BMI had a mean value of 28.9 kg/m2. Regarding their clinical presentation, abdominal pain was the most common complaint (69.2%), followed by melena (30.8%) , while palpable abdominal mass was present in 8 patients (15.4%)Previous blood transfusion was reported by 8 patients (15.4%). The previous data are shown in (Table 1).

Table 1
Demographic and clinical characteristic of included patients

Item	data
Age	55.34± 11.66
Sex Male female	 35 (67.3%) 17 (32.7%)
BMI	28.9±5.76
Symptom duration (months)	5.44±7.62

Blood transfusion	
Yes	8 (15.4%)
no	44(84.6%)

The stomach was the most commonly affected organ (55.8%). Extra gastrointestinal stromal tumors (EGISTs) included 7 cases of our patients (2 cases of pancreatic GISTs, 2 cases of retroperitoneal GISTs, 2cases of mesenteric GISTs and one omental GIST). 36.5% of patients had mass size above twenty cm, while 4 cases (7.7%) were above 30 cm. Hepatic focal lesions were detected only in one case of gastric GIST and both 1ry and hepatic metastasis were excised, moreover the liver was infiltrated in one case of duodenal GIST and this case underwent enblock resection. The most common performed surgical procedure was sleeve/ wedge resection of the stomach for gastric GISTs 14 cases, while anatomical gastric resection like total, subtotal, proximal and distal gastrectomy were performed in 30.8% of patients, other procedures performed according to lesion site included Whipple operation, distal pancreatectomy and splenectomy, colectomy, resection anastomosis of small intestine and localized excision of retroperitoneal mass, omental or mesenteric mass. Multivisceral resection was done in 21.2% of cases due to infiltration of the surroundings, enblock resection was the 1st priority to avoid interruption of the psudocapsule, while tumor rupture occurred in 9 cases (17.3%), three of them underwent multivisceral resection.

On analysis of the pathological data, the majority of patients had R0 resection, while only 11.5% of them had R1 resection. Infiltrated lymph nodes were detected in 5.8% of cases. Mitotic index > 5/50 HPF was detected in 63.5% of cases. CD117 was found to be positive in 92.3% of cases. The previous data are shown in table (2). The included patients were followed for an average of 57 months (range, 3 – 134).Post-operative imatinib was commenced for 80.8 % of cases. It was commenced for a median duration of 36 months. Disease-free survival and overall survival had mean values of 80.973 ± 8.49 and 100.562 ± 7.736 months, respectively. Recurrence was encountered in 19 cases (36.5%) in either the local or distant forms (9 cases of gastric GISTs, 6 cases of small intestinal GISTs and 4 cases of EGISTs). The liver was the most common site of recurrence (7 cases), followed by disseminated peritoneal recurrence (5 cases), and combined local and hepatic recurrent disease (4 cases), local recurrences (2 cases) and finally one case of bone metastasis.

The overall mortality rate was 26.9 % (14 cases). Hospital mortality occurred in 2 cases, one case due to pulmonary embolism and the other one due to leakage. At the last follow-up, 34 patients remained committed to the follow-up plan (65.4%), 10 died of the disease itself (19.2%), 4 patients died of a cause unrelated to the tumor, and 4 patients were lost during follow up process (7.7%). Table (3).figure (1), figure (2). There was no significant difference between disease-free survival based on the location of the primary tumor whether gastric or small intestinal ($p = 0.849$). No significant difference was noted between tumors of different locations regarding post-operative overall survival ($p = 0.949$). On analysis of risk factors of recurrence after surgical excision of large GISTs, > 10 cm, tumor rupture and

CD34 positive tumors were found to be significant in both univariate and multivariate analysis. (Table 4) (Table 5).

Table 2
operative and pathological data

item	data
Site	
Stomach	29 (55.8%)
Small intestine	13 (25%)
Colorectal	3 (5.8%)
Others (EGISTs)	7(13.4%)
Size (cm)	25(10-35)
Size 10-19cm	33 (63.5%)
Size 20-29cm	15 (28.8%)
Size >30 cm	4 (7.7%)
Approach	
Open	50(96.2%)
laparoscopic	2(3.8%)
Resection type	
Anatomical/formal resection	33(63.5%)
Limited /organ preserving resection	19(36.5%)
Peritoneal deposits	1 (1.9%)
Omental deposits	3 (5.8%)
Hepatic focal lesions	1 (1.9%)
Multivisceral resection	11 (21.2%)
Tumor rupture	9 (17.3%)
Gross picture of tumor	
Solid	25 (48.1%)
Cystic	1 (1.9%)
Partially solid , partially cystic	26 (50%)
NIH risk stratification	
High	45(86.5%)
intermediate	7 (13.5%)
Mitosis	
>5/50HPF	33 (63.5%)
<5/50HPF	19(36.5%)
Resection status	
RO	46(88.5%)
R1	6(11.5%)
Pathologically positive LN	3(5.8%)
Pathological differentiation	
Spindle	37 (71.2%)
Epitheliod	5(9.6%)
mixed	10 (19.2%)
CD117 (+)	48(92.3%)
DOG-1(+)	34 (65.38%)
CD34(+)	29(55.76%)

Table 3
Overall survival and disease free survival of GISTs >10 cm

Follow up duration (months)	57 (3-134)
recurrence	19 (36.5%)
Disease free survival (months)	80.973 ± 8.49
Overall survival (months)	100.562 ± 7.736
1 year overall survival rate	94.2%
3 years overall survival rate	84.8%
5 years overall survival rate	76.3%
Overall survival with gastric GISTs (months)	95.36 ± 9.57
Overall survival with small intestinal GISTs (months).	111.62 ± 8.77
Final status On follow up Disease related mortality Disease non related mortality Lost follow up/unreachable	 34 (65.4%) 10 (19.2%) 4 (7.7%) 4 (7.7%)

Table 4
Univariate analysis of predictors for GIST recurrence in tumors > 10 cm

	R^2	Univariate analysis	OR	P-value
Age	-	-	-	0.305
Female gender	-	-	-	0.897
BMI	-	-	-	0.449
Duration of symptoms	-	-	-	0.837
Blood transfusion	-	-	-	0.466
Palpable mass	-	-	-	0.466
Size	-	-	-	0.318
Gastric site	-	-	-	0.356
small intestinal site	-	-	-	0.408
Omental deposits	-	-	-	0.999
Limited resection	-	-	-	0.528
Multivisieral resection	-	-	-	0.989
Tumor rupture	30.4%	3.15	7.94	0.005
High risk by NIH	-	-	-	0.217
Partially solid, partially cystic type	-	-	-	0.389
R1 resection	-	-	-	0.124
Pathology positive nodal deposits	-	-	-	0.999
Mitosis >5/50 HPF	-	-	-	0.085
Pathology differentiation, Spindle	-	-	-	0.742
Epithelioid	-	-	-	0.866
Mixed	-	-	-	0.800
Positive CD 117	-	-	-	0.942
Positive CD 34	14.9%	-1.66	4.09	0.043
Postoperative imatinib	-	-	-	0.186

Table 5
Multivariate analysis of predictors of large GIST recurrence

	R^2	Multivariate analysis	OR	P-value
Tumor rupture	41.3%	3.1	6.49	0.011
Positive CD 34		-1.95	4.5	0.034

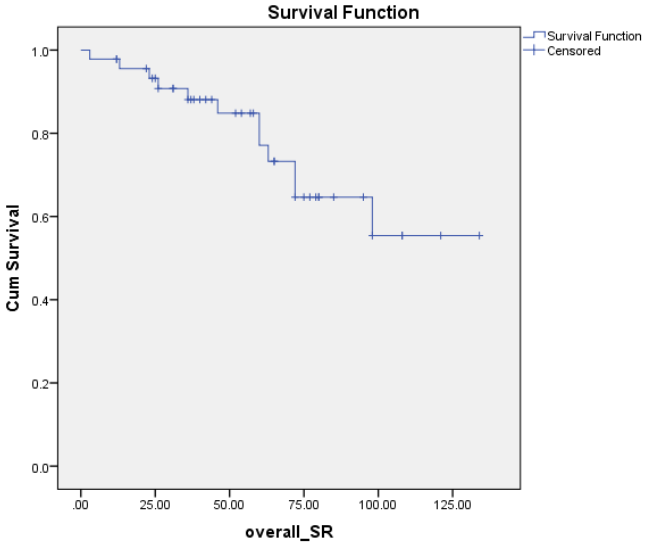

Figure (1)

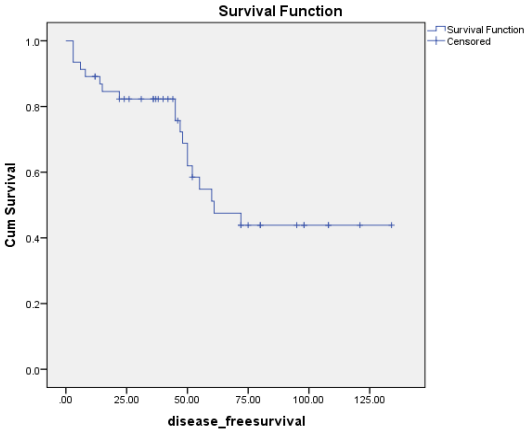

Figure (2)

Discussion

The current investigation was carried out to determine long-term oncological outcomes following surgical management of large GISTs. We included a total of 52 patients who were operated on for GIST. The included patients had a mean age of 55.34 years. This is in accordance with previous studies which reported that

GISTs occur mainly in older adults (6, 7) and it is rarely detected in adults aged less than 40 years (8). In our study, abdominal pain was the most common complaint (69.2%), followed by melena (30.8%) Stanek and his associates reported that pain was the most common manifestation (36.8%), followed by gastrointestinal bleeding (26.5%) (4).

Our findings showed that the stomach was the most commonly affected site (55.8%) followed by the small bowel (25%) Other sites included colorectum and EGISTs. Dematteo and his associates reported that the stomach was the most common affected site by GISTs,(58%) of cases , followed by the small bowel (28%), colon, and rectum (11%), and others (3%) (9). In the current study, there was no significant difference in overall survival regarding tumor site, Sakin et al. reported no significant difference with five-year overall survival rates were 92.9%, 100%, 100%, and 100% for gastric, small bowel, colorectal, and extra GIT neoplasms (3). In the current study, disease-free survival had a mean value of 80.9months, and overall survival had a mean value of 100.56 months with one, three and five year survival rates of 94.2%, 84.8% and 76.3% receptively.

Badic et al. reported that disease-free survival had a mean value of 55.2 months (10). In the study conducted by sakin et al , they reported 5-year disease free survival was 64.7% and 5-years overall survival 90% (3). Bischof and his coworkers. reported that one-, three-and five-year overall survival rates were 98.2%, 93.4%, and 88.65%, respectively (11). In the study conducted by Joensuu, they reported that 5 year survival rates was 71.4% in high risk GISTs patients after 36 months of TKIs. (12) Another study conducted by Demetto et al , reported that After a median follow-up of 7.7 years, the 1-, 3-, and 5-year overall survival rate was 99, 97, and 83%, .The 1-, 3-, and 5-year disease free survival rate was 96, 60, and 40%. (13). On analysis of risk factor of recurrence of large GISTs in our series, it must be noted that factors like high mitotic index and high risk tumors by NIH classification and tumor size should not be significant factors for recurrence as we excluded GISTs smaller than 10 cm from our series and most of our cases are high risk tumors (86.5%) of high mitotic index (63.5%).Our aim to conclude which factors beside the size of the tumor in high risk GISTs could matter in the process of recurrence.

Our study showed that R1 resection doesn't significantly increase risk of recurrence upon multivariate analysis. In the study conducted by Zhu et al, they reported the same finding (14). Also Cananzi et al and McCarter et al, reported no significant difference in DFS in patients with R1 resection when compared to those with RO resection (15, 16). However, Unalp et al and Langer et al reported that R1 resection significantly affects overall survival (17, 18). The reason why the risk of recurrence is not affected by positive resection margins is debatable, but probably due to small sized tumors with low mitotic index in the other studies and commitment of the patients to TKI therapy, also small number of patients with R1 resection. It must be noted that, ESMO has removed positive resection margins as a prognostic factor for tumor recurrence, this in turn should encourage endoscopic and laparoscopic removal of these tumors (14).

Tumor rupture occurred in 9 cases (17.3%) among our series, it is worthy to mention that. tumor rupture was found as a significant risk factor for recurrence

on univariate and multivariate analysis (p=0.005) we also recognized that 8 out of 9 patients with rupture had developed tumor recurrences, so tumor rupture should be considered as a major risk factor for tumor recurrence, and must be avoided during surgery and to be of the same priority when attempting to achieve RO resection. Sakin et al have reported the same findings on their study that was conducted on 74 patients. They recorded two cases of tumor rupture and both had developed recurrences, tumor rupture, according to them, was found significant upon univariate analysis, but lost its significance upon multivariate analysis, probably due small number of cases (3).

Actually we have excluded small lesions and lesions with low mitotic activity from our study, this emphasized the significance of tumor rupture as an independent risk factor for tumor recurrence, which may not be clear in other studies which include larger samples with smaller masses. Tumor rupture is not included in most risk stratification systems of GISTs ,and patient with rupture should be considered at high risk of recurrence irrespective to lesion site , size , or mitotic index , and such operative event should be reported , and the patient should be referred to oncologists for adjuvant TKIs therapy .this conclusion was also reported by Han and his collegues (19). In the present study, positive CD34 marker was found to be significant factor for large GIST recurrence in both univariate and multivariate analysis. In line with our results, Klieser and his associates reported that CD34 positivity was a significant factor for recurrence in both univariate and multivariate analysis.(20) In the study conducted by Demir et al reported that CD34 negative patient had significant better outcome than CD34 positive patients.(21). In the study conducted by Wang and his coworkers they reported that , on univariate analysis, CD34 positive GIST patients had better outcome than CD34 negative patients (5-yaer OS, 87.2% vs. 75.4%, P = 0.006; 5-year RFS, 80.6% vs. 64.3%, P = 0.001), but this parameter lost its significance in multivariate analysis.(22).

Conclusion

Surgical resection of GISTs is the mainstay therapy, but it is associated with relatively high rate of recurrence even with adjuvant tyrosine kinase inhibitor therapy (TKIs).Risk factor of recurrence in large tumor included tumor rupture and CD34 positive tumors .So, in the setting of huge resectable GISTs, surgery still the safest and most effective therapy with careful handling of the tumor and en block resection without interruption of psudocapsule , and if rupture occurs , this necessities adjuvant therapy as early as possible with strict follow up plan irrespective of patient risk stratification.

Compliance with ethical standards

Conflict of interest: All authors declare no conflict of interest.
Ethical approval: For this study was approval from the institutional review board was obtained.
IRB registration code: MD.19.11.258
Informed written consent: was taken from all cases before being enrolled in this w

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