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RESEARCH ARTICLE

SURGICAL MANAGEMENT AND ROLE OF IMATINIB THERAPY IN GIANT GIST: A SINGLE-BASED CANCER CENTER SERIES

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ABSTRACT

Introduction: Gastrointestinal stromal tumors (GIST) represent 3% of all GIT tumors (Lech, Korcz et al., 2015) and 85% of all mesenchymal tumors of the gastrointestinal tract (GIT), their biological behavior ranges from borderline to malignant depending on the size and the mitotic activity, tumor site, tumor vascularization and infiltration (Lech, Korcz et al. 2015). **Patients and methods:** This is a retrospective observational study comprising 90 cases of Giant GIST in the National Cancer Institute during the period from 2010 to 2020. **Results:** All the giant GIST patients underwent surgical resection, including 77 cases (91.7%) of R0 resection, 5 cases (5.9%) of R1 resection and 2 cases (2.4%) of R2 resection, besides, 16 cases (19.2%) underwent multiorgan resection and 24 cases (28.6) underwent lymphadenectomy. **Discussion:** To our knowledge this is one of the largest series of published Giant GIST. Many case reports of giant rare subtypes of GISTS were published. The incidence of the large size of the tumors in this study is 40.4% which is high compared to the published data estimating that only 20% of GIST tumors present as giant GIST., this is because most of the GIST are diagnosed after reaching very large sizes causing symptoms(Kimura, Togawa et al. 2020). **Conclusion:** Complete surgical excision combined with targeted therapy imatinib can improve the prognosis significantly whether used in the neoadjuvant setting to downsize the tumor or in the adjuvant setting to decrease recurrences. Overall survival and DFS in this study are excellent and comparable to the literature

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) represent 3% of all GIT tumors (Lech, Korcz *et al*., 2015) and 85% of all mesenchymal tumors of the gastrointestinal tract (GIT), their biological behavior ranges from borderline to malignant depending on the size and the mitotic activity, tumor site, tumor vascularization and infiltration (Lech, Korcz *et al*. 2015). It was thought that they arise from the interstitial cell of Cajal but recently it was proved that they arise from multipotent mesenchymal cells and express CD 117 in 95% of cases unlike leiomyomas and leiomyosarcomas which are CD117 negative (Miettinen, Makhlouf H Fau - Sobin *et al*., 2008). Giant GIST represents a subcategory that it is recognized by its large size defined as > 10 cm , they have an insidious onset and they can grow to very large sizes (Miettinen, Makhlouf H Fau - Sobin *et al*., 2008). Large tumors (> 10 cm) on presentation are diagnosed in only 20% of patients (Joensuu, Vehtari A Fau - Riihimäki *et al*.,). GIST can be found in many sites from the esophagus to the anus but the most common location is the stomach followed by the small bowel but can be found in rarer sites like the peritoneum, omentum, mesentery, rectum, pancreas (Wang, Liu *et al*., 2017).

GISTs typically present in adults over 40 years (median age 55-60 years) and only exceptionally in children (Miettinen and Lasota, 2003). An early diagnosis, while the tumor is still small, all is uncommon and symptoms mostly depend on the site of the tumor, obstruction of the ampulla of Vater or dysphagia, abdominal swelling and even intussusception of the small intestines are the most common symptoms. Diagnosis is usually confirmed by CT of the abdomen and pelvis and upper /lower GI endoscopy with mostly a submucosal tumor with intact mucosa seen, a CT-guided biopsy is always needed prior to the management. Molecular and genetic subtyping of GIST is not done routinely, it had been suggested that the cost effectiveness of molecular subtyping is low as it is more cost effective to do a clinical testing with the C-KiT inhibitor imatinib mesylate to test for the responsiveness of the tumor. In our institution we confirm the diagnosis of GIST using the immunohistochemistry on biopsy or the final resected specimen to test for the immune markers like CD117, CD 34, DOG-1, S100 and PDGFR alpha is done occasionally in a minority of cases. Most of the GISTs are C-KIT positive and less than 3% is PDGFR alpha positive (Oppelt, Hirbe *et al*. 2017). The NIH classification for GIST Risk Stratification Was modified in 2006 by Miettinen *et al*, considering the anatomic site of the primary tumor besides tumor size and mitotic count in 50 high power fields (HPF).

Miettinen and Lasota established five risk groups, with eight subgroups, considering a benign class of tumor (Miettinen and Lasota). Management of Giant GIST represents a challenge in diagnosis and the need for the neoadjuvant Imatinib mesylate, a tyrosine kinase inhibitor (Miettinen and Lasota) to downsize the tumors especially in sites where the surgical resection may have a detrimental effect on the function and quality of life of the patient like in rectal and pancreatic GIST. Surgery is the principal line of treatment to achieve cure with R0 resection. The surgical approach and extent of surgery is determined by the site of the tumor and the approach may differ from open to laparoscopic according to the size.
We hereby report a series of giant GIST diagnosed in tertiary cancer center in Egypt during 10-year period from 2010 to 2020.We describe the clinicopathological characteristics of giant GIST and their surgical management, the need for imatinib therapy either as adjuvant or neoadjuvant in this subcategory of GIST. We also report the overall survival and disease-free survival of these patients.

PATIENTS AND METHODS

This is a retrospective observational study comprising 90 cases of Giant GIST in the National Cancer Institute during the period from 2010 to 2020. Patients' files were reviewed and Clinicopathological parameters collected are namely: age, gender, clinical presentation, comorbidities, true cut biopsy, type of radiological diagnosis, tumor characteristics, pathological markers of diagnosis, tumor size on final pathology and on imaging, risk stratification of the tumors, prognostic classification. The surgical resection type as well as the date of surgery, intra or post operative complications, pathology results were reviewed and recorded. last follow up date and last follow up status, primary/metastatic at initial presentation. Recurrence date, sites and number of recurrences. A descriptive analysis was performed using the SPSS version 20.The outcome was assessed in the form of 1,3,5 and 7 years disease-free survival and overall survival. Neoadjuvant Imatinib was given as 400mg/day/12 months with CT assessment of response. Adjuvant Imatinib was given to high-risk groups according to the NCCN prognostic groups guidelines. The duration and dose of the imatinib therapy is mainly dependent upon the response and the follow up assessment as well as the therapy toxicity. In 2006, Miettinen *et al* modified the NIH classification, considering the anatomic site of the primary tumor besides tumor size and mitotic count in 50 high power fields (HPF). Miettinen and Lasota established five risk groups, with eight subgroups, considering a benign class of tumor. (Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol*. 2006;23:70–83). A new modified high-risk group included all patients designated as high risk by the NIH classification and, in addition, patients with non gastric tumors 2–5 cm and >5 mitoses per 50 HPFs, or 5–10 cm and ≤5 mitoses per 50 HPFs, and all patients with tumor rupture into the abdominal cavity regardless of tumor size or mitotic count. (Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol*. 2008;39:1411–1419).

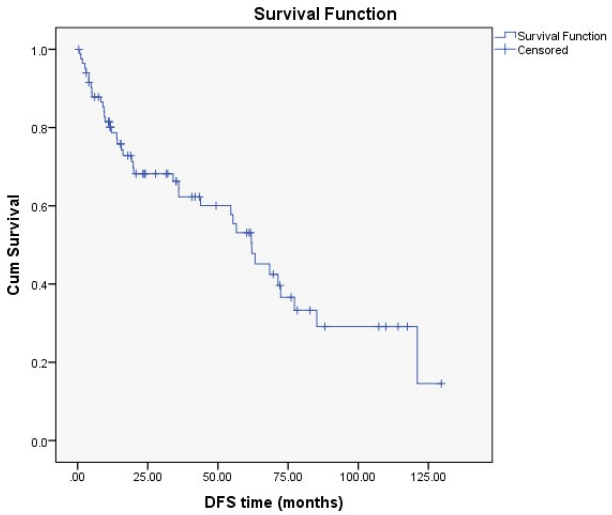
Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1–5.0	≤5	Any
Intermediate risk	2.1–5.0	>5	Gastric
	<5.0	6–10	Any
	5.1–10.0	≤5	Gastric
High risk	Any	Any	Tumor pressure
	>10.0	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1–5.0	>5	Nongastric
	5.1–10.0	≤5	Nongastric

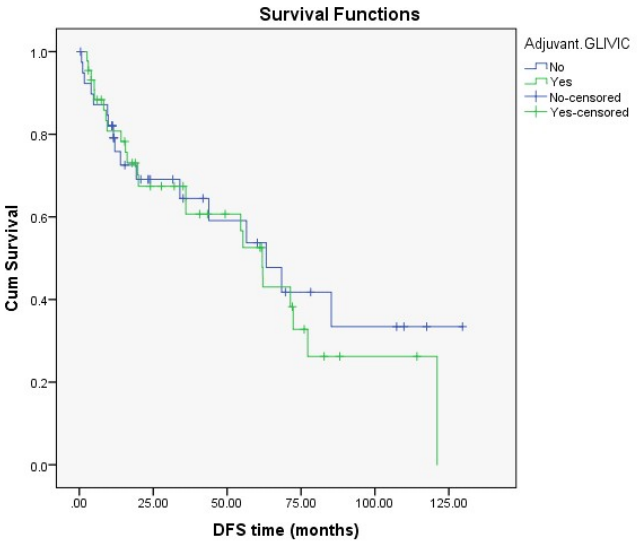
Current guidelines recommend adjuvant therapy with imatinib in high-grade High-risk GISTs are tumors that have a high number of mitoses, increase in size, and do not come from the stomach. Another important prognostic factor is tumor rupture. This is a very heterogeneous class of tumors, and for this reason several authors try to identify new prognostic factors. The biological field seems to be the most widely undertaken path in the literature. Radiological imaging could be another interesting field to analyze. Laparoscopic and open approaches are compared to verify different oncological outcomes. Even between small GISTs (tumors <2 cm in diameter), there are high-risk factors that should be carefully evaluated. During the period from 2010 till 2020, 210 patients presented to the NCI with a diagnosis of GIST, forty percent of cases were giant GIST(n=84/210cases). Seventy-eight (n=78) cases presented as primary tumors (92.9%) and 6 cases (7.1%) were metastatic at initial presentation. There were 39(46.4%) male and 45(53.6%) female patients with a median age of 59(34-86) years. Primary giant GIST of 35 cases(41.7%) were located in the stomach,20 cases(23.8%) in the small intestine,3 cases(3.6%) in the colon and 3 cases(3.6%) in the rectum, and 3 cases(3.6%) in pancreas and duodenum while 30 cases (22.7%) were outside the gastrointestinal tract (mesentery, retroperitoneum, abdominal cavity, omentum, ovary etc.) and pelvic. High risk group represented 79 cases (94.4%)of all giant GIST with 50 cases(58.8%) having a mitosis of >5/50 hpf. The most common presentation was swelling (abdominal, pelviabdominal, hypochondrial) in 58 cases (69%), abdominal pain in 16 cases (19%), less frequent presentations are loss of appetite, loss of weight, hematemesis, intestinal obstruction, urinary symptoms, metastasis in the liver or lung in the rest of the cases (12%). All the giant GIST patients underwent surgical resection, including 77 cases (91.7%) of R0 resection, 5 cases (5.9%) of R1 resection and 2 cases (2.4%) of R2 resection, besides, 16 cases (19.2%) underwent multiorgan resection and 24 cases (28.6) underwent lymphadenectomy. Surgical margin was negative in 77 cases (91.7%), positive in 2 cases (2.4%), close in 5 cases (6%). Postoperative complications occurred in 4 cases (4.8%) and all were treated conservatively, intraoperative complications occurred in 4 cases in the form of excision of external iliac vein and repair with dacryon mesh, ureteric injury and bilateral stenting, splenic injury in 2 cases. Nine cases were admitted to the ICU post-surgery due to associated comorbidities. No intraoperative mortality or postoperative mortality. As for the immune markers, CD117 (C-KIT) was positive in 76 cases (90.5), CD34 positive tumors 64 cases (76.2%), Actin positive in 50% (42 cases). Prognostic group 6 (A and B) were 57 cases (67.9%) , group3 (A and B) were 20 cases(23.8%) ,group 5 was 6 cases (7.2%) and 1 case was group1(1.2%). Eleven giant GIST cases (13.9%) received neoadjuvant imatinib 400 mg/d as targeted therapy before surgery, 10 cases achieved partial regression of the tumor on CT imaging post neoadjuvant imatinib therapy and one case progressed. The median duration for neoadjuvant therapy was 12 months (range 3-60 months). one case (1.2%) received palliative imatinib. Adjuvant imatinib was given to 44 cases (52.4%) of high-risk groups patients. Relapse and metastasis occurred in 25 cases, 22 cases (88%) experienced one recurrence and 3 cases (3.6%) relapsed twice. All recurrent cases were treated by surgical resection and imatinib therapy. Distal recurrences were in the liver in 14 cases, peritoneal metastases in 8 cases and 2 cases relapsed in the lungs. Twenty cases relapsed distally (23.8%),2 cases relapsed locally (2.4%) only, and 3 cases had distal and local recurrences (3.6%). The median time to recurrence/death (date of surgery till date or recurrence/death) was 23.33 months. Disease free survival is 52.4% (44 cases) and 40 cases(47.6%) were having residual/recurrence. The 1-, 3-, 5-year overall survival rates of giant GIST were 92.5%, 72.8.%,68.2% respectively. Sixty-three cases were still alive at the end of the study (75%),21 died (25%). The 1-, 5-, 7-year recurrence-free survival rates of giant GIST were 89.1%, 55.4%, 14.6% respectively and high-risk group were 99.1%, 91.7%, 84.2% respectively.

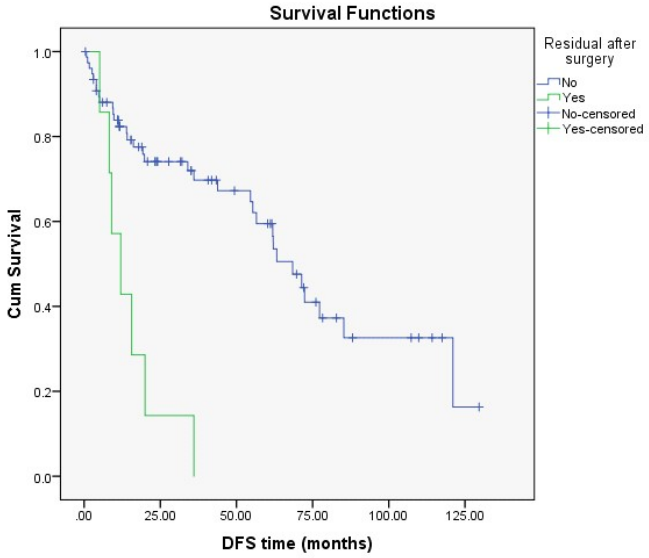
DISCUSSION

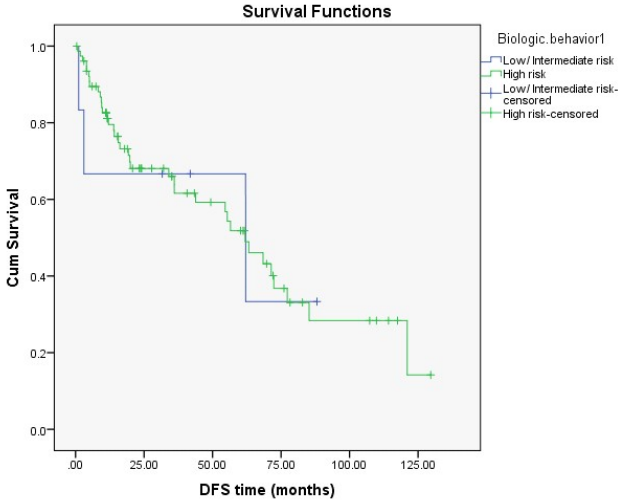
Complete open surgical resection of giant GIST is the cornerstone of curative treatment for localized and locally advanced GIST(Frankel, Chang Ae Fau - Wong *et al*.).

Survival curves

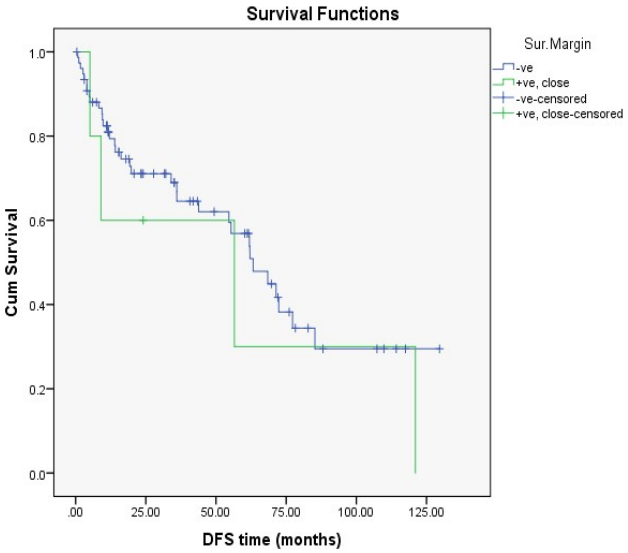


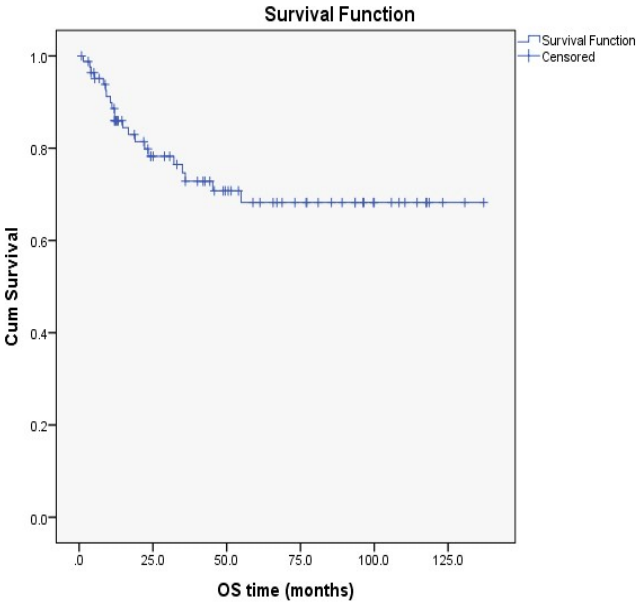


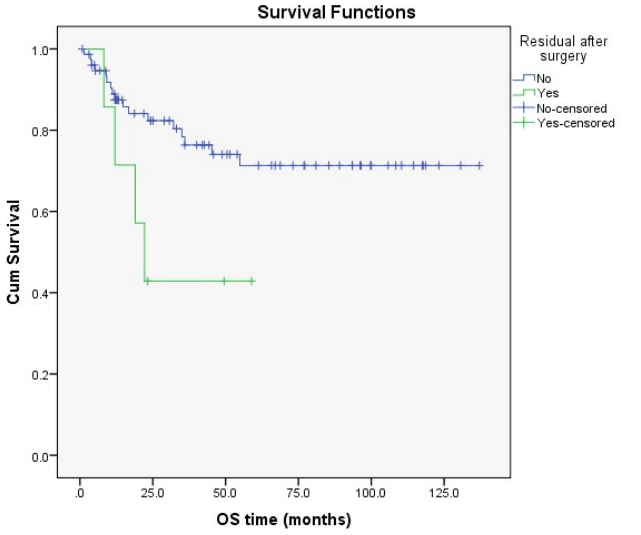


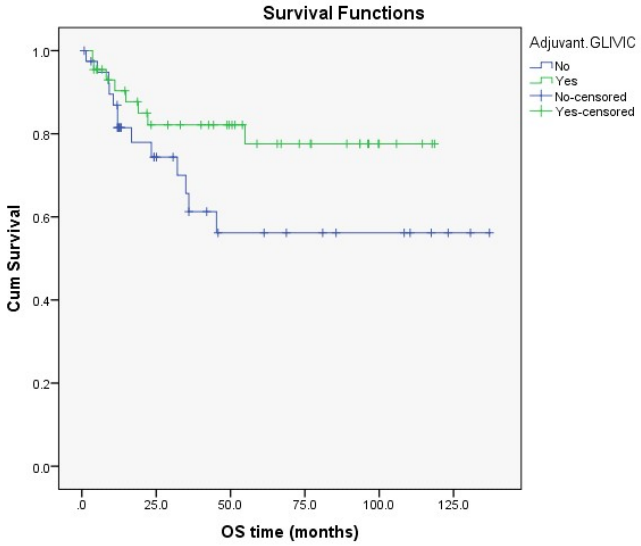


Overall survival curves:









In this study all cases were resected as per the current National Comprehensive Cancer Network (NCCN) guidelines recommendation (Von Mehren, Randall *et al*. 2018). All but one case underwent an open surgical approach which is more oncologically safe. Laparoscopic resection of GIST above 5cm and especially giant >10cm in size is controversial to avoid rupture of the tumor during manipulation and seeding of the peritoneal cavity (Guo, Li *et al*.). No randomized clinical trial had been done to compare the resection of giant GIST by laparoscope versus the open approach. The type of surgery was dependent on the site of the tumor, in many cases, multiple organ resection was essential to achieve R0 resection and negative microscopic margin. The rectal site and the pancreatic sites are worth mentioning as they are peculiar because of the need to perform an extended type of surgery like abdominoperineal resection or Whipple procedure with extra morbidity and mortality. Limited resection in these organs and a negative microscopic margin is all what is needed to achieve a good outcome (Huang, Chen *et al*.)

There were few cases of giant GIST in the rectum or pancreas in our study because the presentation may be early due to the confined space which make giant tumors uncommon in these sites. Local resection of GIST when feasible is acceptable in organs like the rectum, esophagus and pancreas as long as we do a complete resection(R0) regardless of margin width. Preservations of the sphincters and the organs is the rule in GIST surgery. Resection with microscopic residual(R1) is a negative prognostic factor and has a high incidence of recurrence. Macroscopic residual predicts the highest local recurrence and has a negative effect on disease specific survival. The local recurrence rate after R0 resection is reported in other series to be 9%,while R1 resection predicted poor recurrence free survival and disease specific survival in giant GIST(>10cm) and in high risk tumors (high mitotic count >5/50hpf) (Gouveia, Pimenta Ap Fau - Capelinha *et al*). R1 resection (i.e. microscopically positive margin) has in some studies shown similar prognosis as R0 resection, in other studies wider surgical margins improved prognosis when feasible(Åhlén, Karlsson *et al*). Postoperative complications were very few in our cases and managed conservatively, only 9 cases were admitted to the intensive care unit due to associated comorbidities. Intraoperative complications with only one case of vascular injury requiring dacryon mesh repair. There was no postoperative mortality in this study. Gastric GIST represents the major location in our study in concordance with the literature, sleeve and partial gastrectomy was done in most of gastric cases, unlike adenocarcinoma which is reported to have submucosal spread in the GIT and requires more radical resection. Open sleeve or partial gastrectomy with clear surgical margins is considered curative for giant GIST(Thakkar, Wani Sv Fau - Shetty *et al*). GIST are not known to metastasize to the lymph nodes as they do not have a lymphatic permeation. Lymphadenectomy was done as part of the main surgical procedures like in colectomy cases. Pathological assessment revealed negative lymph nodes in all cases. Lymphadenectomy should only be done when suspicious lymph nodes are found(Canda, Ozsoy Y Fau - Nalbant *et al*.). To our knowledge this is one of the largest series of published Giant GIST. Many case reports of giant rare subtypes of GISTS were published. The incidence of the large size of the tumors in this study is 40.4% which is high compared to the published data estimating that only 20% of GIST tumors present as giant GIST., this is because most of the GIST are diagnosed after reaching very large sizes causing symptoms (Kimura, Togawa *et al*. 2020). The most common presentation is abdominal or pelvic swelling and site-specific symptoms. Contrary to other reported series, in which the most common clinical presentation of GIST tumors is gastrointestinal bleeding, additionally, acute abdomen due to tumor rupture, obstruction, abdominal pain, early satiety, bloating, or fatigue related to anemia can occur(Van Den Abbeele 2008). The median age was 59 years old with predominant female gender (53.3%) in concordance with most of the published series. CT is the investigation of choice to diagnose GIST, together with a guided biopsy, a diagnosis can be made accurately. The size and location of the tumor can be determined.

We performed a correlation of the imaging size and the final pathology size of the tumor and there were no difference between them. 18FDG-PET scanning is an important tool as it can determine the anatomical and the metabolic activity of GIST tumors. It is effective in staging and restaging GISTs, and for evaluating therapeutic response to a variety of treatments in the setting of neoadjuvant imatinib and guide further treatment. It is to be noted that the decrease in size of the tumor and the change in metabolic activity is obvious on PET long before it appears on CT (Van Den Abbeele 2008). Very few cases had PET CT because upfront surgery was done for most of the patients in our study. Most of our cases where located in the stomach followed by small bowel in concordance with the literature (McKey, Alskafi *et al*. 2022), Also we have rare locations of the giant GIST in this cohort like the omentum, retroperitoneum and mesentery. Imatinib mesylate, a protein kinase inhibitor that blocks KIT proteins has been introduced as systemic therapy for locally advanced and metastatic GIST (Andtbacka, Ng Cs Fau - Scaife *et al*.). Neoadjuvant imatinib is indicated when GISTS are in the rectum, oesophagus, pancreas and reaching very large sizes that mandates multiorgan resection. The standard protocol is imatinib for 6 months with pretreatment PET CT to assess the response. In this study, all cases regressed partially after neoadjuvant imatinib, and the response was assessed by CT with contrast and only in few cases were PET CT used due to limited resources in our center. Preoperative imatinib can decrease tumor volume and is associated with complete surgical resection in locally advanced primary GISTs. Early surgical intervention should be considered for imatinib-responsive recurrent or metastatic GIST, since complete resection is rarely achieved once tumor progression occurs (Andtbacka, Ng Cs Fau - Scaife *et al*.).The overall pathologic CR rate to medical therapy is less than 5% of patients (Choi and Feig 2007). Downsizing of giant GIST facilitates the use of the Laparoscopic approach and helps achieving a negative

resection margin, also imatinib can consolidate the tumor capsule and decrease the risk of bleeding (Guo, Li *et al*.). In case of progression on therapy, surgery should be done for locally advanced GIST. In this series, only 13 cases(15.5%) received neoadjuvant treatment in the form of imatinib to downsize the tumor prior to surgery or due to irresectability.R0 resection was achieved in 91.7% of cases(n=78) with upfront surgery while R1 resection was done in 7.3% of cases (n=7). Current guidelines recommend adjuvant therapy with imatinib in High-risk GISTs which are tumors that have a high number of mitosis, increase in size, and do not come from the stomach. Another important prognostic factor is tumor rupture. This is a very heterogeneous class of tumors, and for this reason several authors try to identify new prognostic factors. The biological field seems to be the most widely undertaken path in the literature. Adjuvant imatinib was given to 44 cases (52.4%) of high-risk patients in this study. Risk assessment after resection determines the need for adjuvant imatinib treatment. (Canda, Ozsoy Y Fau - Nalbant *et al*.). Ruptured GIST incidence is reported to be approximately 3% (Nishida, Cho *et al*. 2018)and is considered to be associated with a high risk of peritoneal recurrence(Kimura, Togawa *et al*. 2020). Small intestinal GISTs tend to have an even worse out-come than GISTs of the stomach. Extramural growth tumors correlated significantly with small intestinal location and frequency of peritoneal dissemination probably as a consequence of tumor rupture or due to microscopic serosal penetration (Agaimy, Vassos N Fau - Wunsch *et al*.) In this study DFS was 52.4% and overall survival is 75%.Unfortunately, despite a macroscopically complete resection, up to 50% of disease will recur at a median of 24 months. Most recurrences occur along the peritoneal and serosal surfaces or within the liver; lung and other soft tissue metastases only develop late in the course of progressive disease (PD)(Winer and Raut 2011).The three risk factors most predictive of recurrence are primary tumor size, mitotic count(measured per 50 high power fields), and tumor site of origin(Dematteo, Gold *et al*. 2008). It has been shown that recurrence of GIST is more with R1 resection and in high-risk cases with increased mitosis and large size >10cm. In this study recurrence was correlated with R1 resection, size and site of the tumors and with adjuvant imatinib. The most common recurrence site is the liver in our cases, however GIST are known for their metastatic potential to many organs in the abdominal cavity. Peritoneal nodules are common metastasis from GIST (Terzi 2014). We had one and two recurrences in a substantial number of cases that were treated successfully with complete surgical resection. In recurrent tumors, patients can receive imatinib or sunitinib therapy and do cytoreductive operations to achieve a macroscopically complete (R0 or R1) resection when safely possible. Less than 25% of all patients with advanced GIST on TKI therapy will be considered surgical candidates (Winer and Raut 2011). OS rates approaches 100% at 1-year after surgery in patients with recurrences or limited progression, and only 0–60% at 1 year for those patients with generalized progression. Thus, response to TKI therapy at the time of surgery also correlates with both PFS and OS.

Overall survival for GIST is excellent for all stages and sizes reaching 75% at the end of our study reflecting the importance of achieving a complete resection of the tumors. Even after incomplete resection (R1),a good survival could be achieved with adjuvant imatinib. In population-based cohorts of GIST-patients treated with surgery alone, the 15-years recurrence-free survival was estimated to be 60% (Joensuu, Vehtari A Fau - Riihimäki *et al*.)

CONCLUSION

Giant GIST is common in GIST and more likely occurs in rare sites like the omentum, mesentery, retroperitoneum but still the most common site is the stomach followed by the small intestine as for small GIST. The giant GIST by definition retain one of the bad prognostic factor which is the large size >10cm and this stratify most of the giant GIST in the high risk group. Complete surgical excision combined with targeted therapy imatinib can improve the prognosis significantly whether used in the neoadjuvant setting to downsize the tumor or in the adjuvant setting to decrease recurrences.

Overall survival and DFS in this study are excellent and comparable to the literature.

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