http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v11i3.15

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Research Article

GIST (Gastrointestinal Stromal Tumours): A Clinical Study of 32 Cases

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Abstract
Background: *GIST (Gastrointestinal stromal tumours) are rare mesenchymal tumours of the Gastrointestinal tract accounting for 3% of Gastrointestinal malignancies and overexpress C-kit proteins CD117, CD34 and PGDFRA.*
Methods: *This clinical study was done on 32 patients of GIST in our institution over a period of 7 years with a minimum follow up of 5 years to study the demographics, presentation, management and prognostic criteria of GISTs.*
Results: *The majority of the tumours originated from stomach and small bowel, a few from Esophagus, Rectum and mesentery. GIST predominantly affected the elderly. CT scan and endoscopy were the main diagnostic modalities with final confirmation by Histopathology and immunohistochemistry. Most of the patients underwent surgical resection followed by oral imatinib.*
Conclusion: *GIST have unpredictable behavior. The malignant potential of the disease depends on the site, size and mitotic index of the tumour. Surgery with imatinib is the main treatment option in absence of response of GIST to Radio or chemotherapy.*
Keywords: *Gastrointestinal stromal tumours, Imatinibmesylate, enbloc resection.*

Introduction

GIST also known as Gastrointestinal Stromal tumours are rare soft tissue tumours arising from mesenchymal tissue of gastrointestinal tract accounting for less than 1% of gastrointestinal tumours. Incidence of GIST as reported is 12.7 and 6.8 per million population in Netherlands and USA respectively[1]. These tumours were historically categorized as leiomyomas or leiomyosarcomas until 1983, when Mazur and Clark coined this term GIST for tumours arising from interstitial cells of Cajal[2]. Further in 1998, with the advent of immunohistochemistry, Hirota et al discovered that these tumours harbor mutation in receptor tyrosine kinase gene KIT and overexpress protein CD117, CD34 and rarely PDGFRA (Platelet derived growth factor receptor alpha). Surgical R0 resection is the mainstay in the treatment in the absence of non response of GIST to radiotherapy and Chemotherapy.

Introduction of tyrosine kinase inhibitor drugs mainly Oral Imatinib mesylate has brought a revolution in its overall management.

Materials & Methods

This study was conducted in a tertiary care Medical College hospital on 32 patients of GIST confirmed on immunohistochemistry over a period of 7 years from 2011 to 2017 with a minimum follow up of 5 years. Aim was to study the demographics, clinical features and management with prognostic criteria. Management included role of Imaging studies and endoscopy, role of Surgery and Imatinib in neoadjuvant, adjuvant and palliative settings.

After detailed clinical examination the patients were further investigated using Ultrasonography, CT scan, Endoscopy (Upper and lower Gastrointestinal). All the patients underwent biopsy either ultrasound, endoscopic or laparoscopic guided. Diagnosis was confirmed by Immunohistochemistry after histopathology.

Results

32 patients were studied between September 2011 to September 2017 over a period of 7 years at our institution. All the patients were in 4^{th} to 7^{th} decades with maximum cases being (n=11,34.37%) in the 5^{th}decade. Youngest patient was 41 years whereas the oldest being 89 years old.

Table 1: Incidence of GIST in Age Group. More common in 5^{th} decade

Age Group	No. of Patients	Percentage %
41-50	8	25%
51-60	11	34.37%
61-70	9	28.12%
71-80	4	12.5%
TOTAL	32	100%

Males (75%) outnumbered females (25%).Sites involved were Stomach (n=15,46.87%),Small bowel (n=10,31.25%),Mesentery and Esophagus (n=3,9.3%) each followed by 1 case of Rectum.

Table 2: Tables showing Site of GIST. Most common Stomach, followed by Small bowel

Site	No. of Patient	Percentage %
ESOPHAGUS	03	9.3%
STOMACH	15	46.87%
SMALL BOWEL	10	31.25%
RECTUM	01	3.12%
MESENTERY	O3	9.3%
TOTAL	32	100%

The common presentation was abdominal Pain in 25% and Upper GI bleed in 21% of the cases.3 patients were asymptomatic detected incidentally on routine upper GI endoscopy.4 patients each presented with dysphagia and intestinal obstruction. Only 3(9.3%) cases had lump in the abdomen. Abdominal Ultrasound was done in all cases, CT scan in 31 patients and 20 patients underwent Upper GI scopy whereas Colonoscopy was done in only 1 patient of Rectal GIST who presented with Rectal bleeding. Liver metastasis was detected in 2 cases while 1 had peritoneal deposits at admission.26 patients underwent primary operation. Gastric wedge resection was done in 9 cases, Proximal, Distal and Total Gastrectomy in 1 case each.3 patients of Esophageal GIST underwent local excision with Intrathoracic anastomosis. Small bowel GIST had bowel resection done in 7 cases while 1 patient underwent debulking. Low Anterior Resection was done in Rectal GIST.15 tumours were between 5-10 cms, 9 were between 2-5 cms and 8 were more than 10 cms. High Mitotic Index (>5 Mitosis/50 HPF) was observed in 17 cases while the remaining 15 had Low Mitotic Index (<5 Mitosis/50 HPF). 31 (96.87%) cases were spindle cell type whereas only 1 case was Mixed type. On Immunohistochemistry CD 117 was positive in 31, CD34 in 17 and PDGFR and DOGI in 1 case each. Thus CD117 was positive in 96% cases and CD34 in 53.12% cases.

30 patients were started on Oral Imatinib except two cases as they died in immediate postoperative period. Duration of Imatinib treatment varied from 1 to 6 years. Overall 5 year survival was 53% (17 cases), out of these disease free survival was seen in 4 patients (23%) while 13 patients survived 5

years or more with the disease while on Imatinib. 2 patients survived 6 years with multiple liver metastasis wherein the primary in small bowel was excised. Out of the remaining 13 patients, 8 were lost to follow up and 5 patients expired within 3 years. Out of these, 4 patients expired within 2 years follow up due to recurrences and liver or peritoneal metastasis. All these patients were high Risk GIST with size >5cms and High Mitotic Index. Three of these cases were Mesenteric GIST.

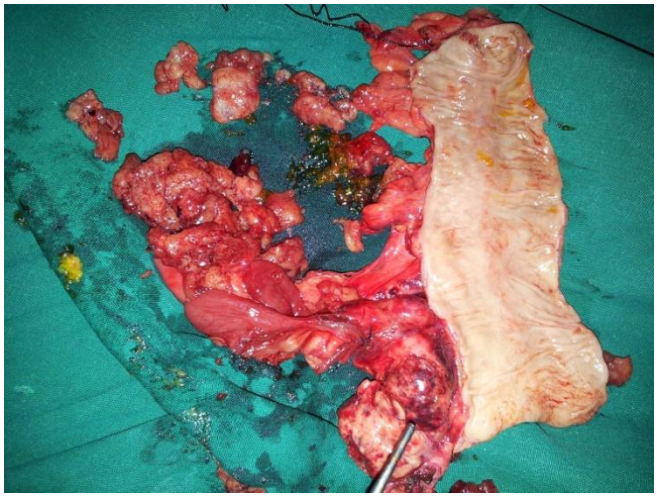

Fig 1. Rectal GIST Anterior Resection done

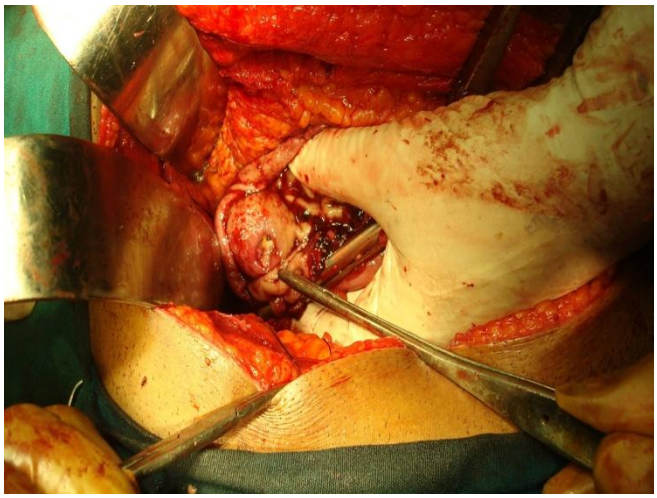

Fig 2. Gastric GIST in fundus of stomach

Discussion

GIST are known to have a unpredictable behavior due to its variable malignant potential. Thus they are better classified as High Risk and Low Risk rather than Benign or Malignant. Our study being conducted over a period of 7 yrs, We could assess 5 year survival in most of the cases and their response to Imatinib. It was found that the disease was mainly prevalent in the elderly in the 5th and 6thdecade.We had no paediatric case .Our mean age was 58.5 years and median was 56.5 years. Mean Age is 53 years and 5% of GIST occur under 30 years of age as reported by Machad[1]. Antonescu at al[3] reported age incidence between 12-87 years with mean age at 57.4 years. Similarly Ueyama et al[4] had in their series incidence from 17-79 years with mean of 55 years. Male preponderance in a ratio of 3:1 was noted by us. Studies conducted by De matto et al[5] and Gier et[6] al also reported slight male preponderance with ratio of M:F= 1.3:1, While Nivedita Singh et al[7] showed Higher male incidence in a ratio of 3.5:1.Our study having a small sample size, no definite opinion could be arrived regarding Male to Female ratio.

In our series, the common site involved was Stomach (n=15,46%) followed by small bowel (n=10,25%).3 cases were found in esophagus and mesentery each and 1 in rectum. This observation is similar to observations reported by Mukul Vij[8] as Stomach (55%), small bowel (29%) and rectum (4%). Study done by Yu Na Kang[9] had 66% cases in stomach and 28% in small bowel. Many studies have reported incidence in Stomach (40%-60%), small intestine (30-40%), 5% each in Colorectum and Esophagus[10,11,12,13]. Site is clearly an important factor in predicting malignant potential as observed by us. Gastric GIST have better prognosis compared to small bowel. Small bowel GISTs have more incidence of metastasis to liver and peritoneum thus affecting prognosis which is observed in most of the studies. EGIST (Extra Gastric GIST) are aggressive and more prone for metastatic disease, recurrences and early death[8]. Also Gier T[6] reported that 7 out of 8 metastatic GIST were non Gastric. Abdominal pain (25%) and upper Gastrointestinal bleed (22%) were common presentation in our series followed by Dysphagia and intestinal obstruction in 3 patients. Surprisingly Only 3 patients had clinical abdominal lump palpable Similar results were

reported by Nivedita Singh[7] with pain in 35% followed by upper gastrointestinal bleeding (16%) cases whereas Pascal Bucher et al[2] had reported upper GI bleed as a common feature in 50% cases followed by abdominal pain in 20% cases. Rare symptoms like constipation, rectal bleeding, nausea, weight loss are also seen in a few patients. Duodenal GIST a rare site can present with Bleeding, Jaundice, pain depending on its location[1].

Imaging modalities lke abdominal Ultrasonography, CT scan and endoscopy have a major role to play in the diagnosis. CT and MRI are the best Imaging modalities[1]. Endoscopic Ultrasound is better in cases of small tumours with very minimal outward umbilication[14,15]. PET scan is mainly indicated for follow up to detect recurrences and metastatic disease.

Histopathology followed by Immunohistochemistry for detection of CD117 protein is the Gold Standard for diagnosis of GIST[1].

Surgery in form of complete enbloc R0surgical resection of tumour with surrounding tissue is the best modality of treatment when feasible. In 50-90% of the cases R0 resection is possible with relapse rate of 5% .Thus R0 resection gives the best survival and only solace as these tumours are unresponsive to Radio or Chemotherapy..Also resection of Liver Metastasis can be done wherever possible. Debulking procedure is the option when R0 resection is not possible. The rate of resectibility varies from 50 to 90%.Our rate of resectibility was 81% which is similar to most of the studies. Dematto et al[4] and Pascal Bucher[2] reported resectibilty of 86% and 90% respectively.26 of our patients underwent Surgical Resection. Wide resection margins are not associated with better prognosis as the tumours do not exhibit intramural spread hence only tumour free margin is sufficient.In our study out of 26,24 cases underwent curative R0 resection. Among 12 cases of Gastric GIST, 9 had wedge resection,1 each had proximal and distal Gastrectomy. Remaining one case underwent Total Gastrectomy who had a large GIST (12x15cms) in the GE junction. None required lymph node clearance. Small bowel GIST underwent resection of the small intestine.1 case of small bowel GIST with multiple liver metastasis underwent only bowel resection .3 cases of Esophageal GIST underwent local excision with intrathoracic esophageal anastomosis. Anterior resection was done in Rectal GIST with good results. In 2 patients with mesenteric GIST local excision with resection anastomosis of small bowel was done whereas on case with a large GIST (18x15 cms) in ileal mesentery, debulking of tumour was done as a small part (2x1 cms) part could not be excised as it was encasing the superior mesenteric vessels.

Since 2002, Imatinib a Tyrosine kinase Inhibitor drug has been the standard of care for Patients with GIST as these patients have no response to Radio and Chemotherapy. Imatinib is a targeted therapy which acts at molecular level has resulted in improved survival rates. It is the first line therapy in High Risk, Recurrent and metastatic GIST. We have used Imatinib in all our patients. The standard dose being 400mg/day while some may start initially with a high dose of 800mg/day. In Neoadjuvant settings, Imatinib has given complete response (1-6%), partial (45-67%) and stable disease in (10-33%) cases[1]. The response rate to Imatinib in recurrent and metastatic disease is around 60-70%[2]. Duration of treatment with Imatinib has been a matter of debate[2]. Current recommendation being to continue it indefinitely. All our patients received Imatinib indefinitely .13 cases received Imatinib for less than 5 years whereas 17 patients received for more than 5 years. Before Imatinib era the median survival was 19 months and 5 year survival was 25%[16]. Apart from these, the response to Imatinib varies from case to case. Some patients have innate resistance to Imatinb, while some develop resistance after initial Response due to emergence of resistant clones[17]. If there progression of the disease while on Imatinib due to resistance, one can increase the dose to 800mg/day. The other option is to start 2nd line tyrosine kinase inhibitor

drugs like Sunitinib, Sorafenib or Regorafenib. Sunitinib the most common 2nd line drug has antiangiogenic and antitumour effects. However no randomized trials have been conducted so far to compare the use of Imatinib with Sunitinib, thus no definite conclusion can be drawn.Some have reported use of Sorafenib when there is resistance to Imatinib and Sunitinib[17].However combination of these drugs has been strongly discouraged[17]. Thus further research is needed. We have observed Resistance to Imatinibin 2 patients, however our experience in using 2nd line drugs is limited due to financial constraints.

In our study the overall 5 year survival was 53%, out of these Disease free survival was in 23% of the cases. In low risk GIST post resection 5 year survival is 95% whereas in High risk cases it is 30% as per Silva etal [17].Overall 5 year survival as reported by Silva et al is 50-55%[18].Machado[1] in his study reported 5 year survival vary from 30-80%.Relapse rate was 5% after complete resection whereas 95% recurred following incomplete resection. Gastric GIST had the best survival, while EGIST had a bad prognosis in form of early recurrence and metastatic disease.

The main prognostic criteria for GIST in terms of Recurrence and disease free survival depend on tumour size (>5 cms) and Mitotic count (>5/50 HPF), Location, prevalence of p16 loss and levels of K1-67L1[1].

Conclusion

GIST are rare mesenchymal tumours of Gastrointestinal tract with unpredictable behavior varying from benign to highly malignant nature having C kit protein positive. The tumour virulence however depends on the site,size and mitotic index of the tumour. Commonly seen in stomach and small intestine but can also occur in Esophagus, Colorectum, mesentery, omentum and retroperitoneum. These tumours are soft, fragile and vascular with high chances of rupture during surgery, have pseudocapsule and without lymph node metastasis. En bloc R0 surgical resection is the mainstay treatment in absence of its response to Radio or Chemotherapy. Targeted therapy in the form of Oral Imatinib a tyrosine kinase inhibitor drug is a novel invention since 2002 which is known to improve survival and delay or prevent recurrences and can be used in Neoadjuvant, adjuvant and palliative settings.

Financial Support and Sponsorship: Nil

Conflicts of Interest: There are no conflicts of interest.

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