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Original Research Article

A clinical study on presentation, age distribution, various diagnostic methods adopted, treatment modalities being used and outcome of gastrointestinal stromal tumors

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ABSTRACT

Background: Gastro intestinal stromal tumors (GIST) are primary distinctive mesenchymal tumors of the gastro intestinal tract. Early diagnosis is important for better clinical outcome. The objective was to study presentation, age distribution, various diagnostic methods adopted, treatment modalities being used and outcome of gastrointestinal stromal tumors.
Methods: Prospective and retrospective, descriptive study was carried out. After admission of the patient, a detailed clinical history was taken. Physical examination was carried out in detail as per the study proforma and findings were noted. All cases provisionally diagnosed as GISTS were further investigated.
Results: Males and females were equally present i.e. 50% each. Pain in the abdomen was the most common clinical presentation in 66.7% of the cases. 12 cases (66.7%) of GISTs present in the stomach and 6 cases (33.3%) of GISTs present in the duodenum in various locations. Diagnostic confirmation was done for all the 18 cases by histopathology. Out of these 18 cases, 10 cases are benign GISTS (55.6%), whereas 8 cases were of malignant GISTS (44.4%). In total, among all the cases, 10 cases are spindle cell type (55.6%), 6 cases of epithelioid type (33.3%) and 2 cases of mixed cell type tumors (11.1%) are seen.
Conclusions: GIST is more a disease of elder age group. CECT abdomen is a good diagnostic modality in detection of GIST. Wide excision with negative margins (2cm from tumor margin) is adequate and treatment of choice for benign tumors.

Keywords: Age distribution, Diagnostic methods, Outcome, Presentation

INTRODUCTION

Gastro intestinal stromal tumors (GIST) are primary distinctive mesenchymal tumors of the gastro intestinal tract, accounting for <1% of all GI malignancies. GIST is non-epithelial in origin. IHC marker CD117 is used for the diagnosis of GIST. The occurrence of GIST is sporadic.[1] Stomach is the most common site of occurrence of GIST in about 70% of the cases followed by small intestine in 20% of the cases. Benign tumors are small in size usually less than 5cm this may be due to slow cell division rates. Patient complains of difficulty while swallowing food or water, there is increased bleeding from GI tract but intestinal obstruction is not so common in GIST. If the tumor increases in size, the patient complains of pain in the abdomen and discomfort. Biopsy gives the confirmatory diagnosis of GIST.[2]

GIST is usually benign and this can vary from 70-80%. Remaining 20-30% can be malignant. The malignant tumors speared to liver and other organs. But in few cases, the malignant tumors can spread to other parts of body like bone etc. lymph nodes are rarely involved in cases of malignant GIST.[3]

Complete surgical resection has been the treatment of choice for localized resectable GISTs. In locally advanced and metastatic GISTs neoadjuvant Imatinib followed by surgery and adjuvant Imatinib is showing successful disease-free survival benefits. Laparoscopic surgery is gaining popularity in the surgical management of GISTS.[4]

It was thought at one time that GIST may not respond to chemotherapy and that time it was told that you may get less than 5% success rate if you use chemotherapy but new chemotherapy with newer drugs has proved that the patient cannot be operated and disease is malignant, then the response rate can be 40-70%.[5]

Present study was carried out to understand more about the disease, from a single centre in Hyderabad. Present study focuses on the clinical presentation, age distribution, various diagnostic methods adopted, treatment modalities being used and outcome and follow-up for the study period.

METHODS

This was prospective, retrospective and descriptive study conducted from April 2010 to April 2014 (4 years), April 2010 to March 2012 (retrospectively) and April 2012 to April 2014 (prospectively).

Patients for the study were selected from in-patients of General Surgery and Surgical gastroenterology units of Mediciti Hospital, Secretariat road, Hyderabad.

Patients with cases of GISTs from the stomach and duodenum, stomach and duodenum with multifocal involvement, who underwent surgical management and who's histopathological reports positive for GIST were included in the study.

Patients with primary GISTs in GIT other than stomach and duodenum and other GI malignancies excluded by final HPE and IHC reports.

Procedure

After obtaining clearance from the institutional ethical committee and the informed consent from the study subjects in the regional language, the data was collected from selected cases in a pre-designed and pre-tested semi-structured proforma. The investigations held were:

- Hematological such as complete blood count, bleeding time and clotting time, liver function tests, kidney function tests, viral screening, blood grouping typing and blood sugars
- Complete urine examination
- Radiological
  - Ultra sound abdomen
  - Chest X-ray
  - CECT abdomen
- Endoscopy
- Endoscopic ultrasound and EUS guided FNAC in few selected cases of duodenal growths.

After admission of the patient, a detailed clinical history was taken. Physical examination was carried out in detail as per the study proforma and findings were noted. All cases provisionally diagnosed as GISTS were further investigated.

Ultrasound abdomen was done as a routine investigation in all cases to rule out other abdominal pathology and the findings noted. Upper GI endoscopy was done and findings noted for the diagnosis.

Contrast enhanced CT abdomen and lower chest was done in all cases to know the site and extent of primary tumor, metastasis and involvement of other organs.

All the other routine investigations prior to surgery were done as per the study proforma and any deviation from the normal range and co morbidities was attended to. All patients were optimized for surgery to reduce the risk and for better outcome during the perioperative period.

Pre-operative correction of anemia was done in patients wherever indicated (Hb% less than 8 gm%).

Dehydration and electrolyte imbalance were corrected by intravenous fluids and supplements.

Antibiotics (Injection Ceftriaxone 2gm, I.V., BID, Injection Metronidazole 500mg I.V., TID) were given 1 day prior to the operation and continued for a period of 3 days post operatively or till the patient were able to take oral/jejunostomy feeds and converted to oral forms till patient was discharged from.

Patient was kept on only liquids on the previous day and nil by mouth from the night before surgery. Cases which presented with obstruction were managed with Ryle's tube placement, resuscitation with IV fluids prior to surgery. One case of acute GI bleed which was not amenable by endoscopic intervention managed with blood transfusions, Ryle's tube placement and normal saline wash and was taken for emergency laparotomy. All the surgeries were carried out under general anesthesia.

Surgery

Neo-adjuvant Imatinib not given to any patient. For stomach GISTs, wide excision of tumor (6 cases), partial

gastrectomy (2 cases), radical gastrectomy (4 cases), duodenal GISTs, wide excision of tumor (2 cases), en masse resection (2 cases) and Whipple's pancreatico-duodenectomy (2 cases).

All the patients were managed by intravenous antibiotics, I.V. fluids. Patients were kept nil orally with continuous Ryle's tube aspiration for first 2 post-operative days. They were allowed sips of liquids/jejunostomy trail feeds from 3rd post-operative day and progressed to soft diet gradually over 3 days once they started tolerating liquids and started to pass flatus and motions. Early ambulation was encouraged. Chest physiotherapy was given for all post-operative patients. First dressing done on the 2nd POD and every alternate day from then forth, observations for surgery site wound infection, seroma formation were done during dressings. Daily drain output and its nature recorded. Abdominal drains removed on the 5th POD and feeding jejunostomy/tube duodenostomy removed after 6 weeks post operatively.

All the specimens were sent to pathology lab for histopathological examination and confirmation of the diagnosis, type of tumor (benign or malignant), histological variant i.e., spindle cell, epithelioid or mixed type.

All the specimen samples were subjected to immune histochemistry to study reactivity to CD 117 biological marker. CD 34 and other immuno histochemical markers not done during this study period.

During the follow up period patients underwent complete blood picture, liver and renal function tests at 3 months interval. UGI Endoscopy with biopsy, CECT abdomen done at 6 months interval in the first year and annually after that. Any recurrences, distant metastasis was recorded. High risk patients for recurrence and patients with distant metastasis were started on adjuvant Imatinib mesylate 400mg/day which were continued as per tumor response and patient tolerance. Patients were given telephonic intimations for follow up and some of the patient's well beings were enquired including tolerance of adjuvant Imatinib. Data regarding cause of death in case of 3 patients during the follow up collected.

All the details were recorded in the standard proforma and according to the findings in proforma, analysis of data was done and came to a conclusion at the end. The data was analyzed using proportions.

RESULTS

Males and females were equally present i.e. 50% each. Most common age group involved was 51-60 years overall. There were 33.3% of the cases in this age group. There were no cases in 0-20 years of age and only one case in 21-30 years of age. This showed that younger age group was not affected by GIST (Table 1).

Table 1: Age and sex distribution of patients with gist.

Age (years)	Male	Female	Total
0-20	0	0	0
21-30	1 (5.6%)	0	1 (5.6%)
31-40	2 (11.1%)	2 (11.1%)	4 (22.2%)
41-50	1 (5.6%)	3 (16.6%)	4 (22.2%)
51-60	2 (11.1%)	4 (22.2%)	6 (33.3%)
6+	3 (16.7%)	0	3 (16.7%)
Total	09 (50%)	09 (50%)	18 (100%)

Pain in the abdomen was the most common clinical presentation in 66.7% of the cases followed by lump in abdomen in 27.8% of the cases. Three patients presented with hematemesis. While eight patients presented with melena. Two cases presented with luminal obstruction and three with incidental presentation (Table 2).

Table 2: Distribution of cases as per clinical presentation.

Clinical features	Incidence
Pain abdomen	12 (66.7%)
Lump abdomen	5 (27.8%)
Hematemesis	3 (16.7%)
Melena	8 (44.4%)
Luminal obstruction	2 (11.1%)
Incidental	3 (16.7%)

Twelve cases (66.7%) of GISTs present in the stomach and 6 cases (33.3%) of GISTs present in the duodenum, in various locations. In the stomach, fundus was the most common site in 22.2% of the cases. In duodenum, second part was the most common site in 16.7% of the cases (Table 3).

Table 3: Distribution of cases as per site of the GIST in GIT.

Site	Number (%)
Stomach	12 (66.7%)
GE junction	1 (5.6%)
Fundus	4 (22.2%)
Body	2 (11.1%)
Antrum	3 (16.7%)
Lesser curvature	1 (5.6%)
Pylorus	1 (5.5%)
Duodenum	6 (33.3%)
First part	1 (5.5%)
Second part	3 (16.7%)
Third part	2 (11.1%)

Diagnostic confirmation was done for all the 18 cases by histopathology. Out of these 18 cases, 10 cases are benign GISTS (55.6%), whereas 8 cases were of malignant GISTS (44.4%). Among the 10 benign cases, 6 cases were spindle cell type GISTS (60%) and rest of the 4 cases were epithelioid cell type (40%). 8 malignant

cases consist 4 cases of spindle cell variety (50%), 2 cases of mixed type (25%) and 2 cases of epithelioid cell tumor (25%) (Table 4).

Table 4: Distribution of cases as per tumor size and malignant status.

Tumor size	Incidence	Benign	Malignant
<2cm	0	0	0
>2≤5cm	10 (55.6%)	9	1
>5≤10cm	7 (33.3%)	1	6
>10cm	1 (5.5%)	0	1
Total	18	10 (55.6%)	8 (44.4%)

In total, among all the cases, 10 cases are spindle cell type (55.6%), 6 cases of epithelioid type (33.3%) and 2 cases of mixed cell type tumors (11.1%) are seen (Table 5).

Table 5: Distribution of cases as per cell type in benign and malignant lesions.

Cell type	Malignant	Benign	Total
Spindle cell type	4 (22.2%)	6 (33.4%)	10 (55.6%)
Epithelioid cell type	2 (11.1%)	4 (22.2%)	6 (33.3%)
Mixed cell type	2 (11.1%)	0	2 (11.1%)
Total	8 (44.4%)	10 (55.6%)	

Follow up was done at 1-week post-operative, 3 months, 6 months and annually once during the study period. 16 out of 18 patients were followed up during the period with minimum duration of follow up being 1 month and maximum duration 3 years.

High risk and intermediate risk patients (remaining 7 of 9 patients, 2 patients died during the peri-operative period) were started on Adjuvant Imatinib mesylate (400mg/day in divided doses).

In one patient, who underwent Whipple's pancreatico-duodenectomy for D2 lesion, with liver metastasis, there was down staging of tumor with regression in size in liver metastasis. Three patients who had discontinued Imatinib during the follow up period, died due to recurrence during the follow up period.

Patient, who presented with hematemesis and underwent emergency surgery, also had history of peripheral vascular disease, he was started on oral Imatinib. There was progression of disease in this patient. He expired after 18 months of follow up secondary to MI.

Second patient who had liver metastasis noticed during the operation also developed lung metastasis and expired after 6 months. Third patient who also had a polyvisceral resection for fundal growth involving spleen and distal pancreas, did not tolerated adjuvant Imatinib expired after 1 year.

DISCUSSION

The incidence of GISTs is common in the elderly age group with mean age at presentation in this study being 48.8 years, which is in lieu with data collected world over showing higher incidence of GIST in elder age group.[6-9]

The incidence of GIST among male and female in the present study was 8:10. There was a slightly higher incidence in the female population and the mean of presentation in the female population was 45.4 years, compared to male patients who presented at much elder age (mean 53.1 years). Few studies show predominance in male populations, few showed female predominant disease and few showed no significant difference. GIST was considered to have similar incidence in both the sexes.[6-8]

This incidence cannot be extrapolated as incidence from general population as the data was a representation of only the inpatients admitted in a single center. The incidence in general population varies with geographical location with US 8 showing higher detection rates/incidence compared to European and Asian countries.[6]

Pain abdomen (66.7%) was the most common presenting complaint followed by gastro intestinal bleeding (both hematemesis, melena) (55.6%). The incidence of GI bleed was higher due to bigger tumor size with overlying mucosal necrosis.[8] A palpable lump abdomen was seen in 5 patients (38.9%). The presentation of GIST is quiet variable and there is substantial delay in the diagnosis of disease by which the size of tumor was quite big. The incidence of luminal obstruction (11.1%), despite large tumor size was less, compared to other malignancies, this may be due to exophytic and cavitary nature of the tumor may delay luminal constriction.[10] The most common symptom on presentation was abdominal pain in 18 (40.9%) patients. Nine (20.5%) patients had GI bleeding, 3 (6.8%) of whom required endoscopic hemostasis and 6 (13.7%) blood transfusions. Four (9.1%) patients had only non-specific dyspeptic symptoms and thirteen (29.5%) patients had lesions discovered during preventive diagnostic studies.

Ultrasound abdomen was able to detect a mass lesion in 13 cases (72.2%). UGI Endoscopy done in all cases. In a case of GI bleed, there was erosion into gastro duodenal artery and bleeding could not be controlled endoscopically and patient was taken up for emergency laparotomy.

CECT of abdomen is an excellent diagnostic tool in diagnosis the primary tumor was able to detect metastasis in 2 patients though it showed evidence of SOLs in liver.[11] GIST could be identified as heterogeneously enhancing exophytic mass in 8 cases (44.4%). Presence of hemorrhage, mucosal ulceration and necrotic areas is features of malignant GISTS in CT.[12]

GIST in the region of stomach was more common that GIST (66.7%) in the duodenum (33.3%) in the present study. Studies published in various international journals show stomach to be the commonest site for GIST (50-70%) followed by small bowel (20%) followed by colorectal area (<10%) and esophagus and extra intestinal sites.[6-8,13] This was a study conducted on GISTs of the gastro-duodenal area and it showed a higher incidence of GISTs in the gastric area, compared to duodenal area. The percentage of GISTs in the duodenal area was 33.3% but is not significant as the incidence in other studies also compared the incidence in the full length of GI tract.

All the surgeries were open laparotomies in this present study. The main indication being patients belonging to lower- and middle-class families, large tumor size with polyvisceral involvement (3 patients) and location of tumor requiring Whipple's pancreatico-duodenectomy (2 patients), one emergency laparotomy for bleeding GIST. Due to tumor size extensive resection may be required.[14] The main factors affecting the choice of open operation are tumor location, tumor size and local attachment to adjacent organs, preoperative tumor perforation and intraperitoneal adhesions.[7,15]

The mean duration of surgery was 210 minutes, range 110-300 minutes. The long duration of surgery can be explained by the need for wide resections being performed, the advanced stage of tumor with involvement of adjacent organs, major surgeries like Whipple's pancreatico-duodenectomy.

The emergence of minimal invasive procedures including laparoscopic, endoscopic and lap assisted endoscopic, robotic surgeries has shortened the duration of hospital stay, post-operative complications. The main drawbacks in these procedures being long learning curve, the tumor size (large sized tumors need open conversion or location of tumor.[14,7]

The mean size of tumor in the present study was 6.53cms, which was in concurrence with tumor size at the time of presentation of disease, as it carries an indolent course before manifestation of symptoms and most are detected at a late stage either because of neglect, illiteracy from patients perspective or delay in diagnosis with normal USG abdomen scans picking the tumor at later stages.[6]

Screening methods need to be implemented and a yearly health checkup need to be performed to catch the disease at an early stage but the feasibility and cost effectiveness needs further evaluation considering the incidence of disease in small percentage of general population.

In the present study, 10 cases were benign and 8 cases were malignant GISTs. The incidence of malignant transformation increased with increase in size of the tumor and non-gastric GISTs, which are according to the findings of various other studies.[6]

The spindle cell variant was the commonest histological variety in both benign and malignant GISTs in the present study. The mixed cell histological pattern was common in malignant GIST. Further genetic studies to find the pattern of KIT and PDGFRA were not performed in the present study and the significance of the mutations in the population cannot be commented up to be compared with other studies.[16]

The percentage of nil risk, very low and low risk patients was higher in the Poskus E et al, can be explained by detection of early stages of disease and the number of asymptomatic patients (10/44 cases) which were detected during a routine health checkup.[7] In this study, the time duration from the development of symptoms and diagnosis is long due to multiple patient related factors like poverty, lack of intellect, poor follow up at OPD departments prior to detection of disease, negligence of symptoms till late stages of disease when the tumor has increased to considerable size or showing features of conversion to malignancy. Compared to AFIP classification, the NIH classification shows over staging or under staging of tumor.[17] The malignant potential in the high-risk group and the poor prognosis in this group of patients are comparable.

CONCLUSION

GIST is more a disease of elder age group. CECT abdomen is a good diagnostic modality in detection of GIST with an acceptable risk of missing small lesions (<1cm) which usually carries minimal risk of metastasis. Also carries risk of down staging with small sized peritoneal deposits being missed and being diagnosed intraoperatively. Wide excision with negative margins (2cm from tumor margin) is adequate and treatment of choice for benign tumors.

Size of tumor is important prognostic indicator with benign lesions in smaller lesions and increasing incidence of malignancy increasing with size of tumor.

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