

Gastrointestinal Stromal Tumors: Prevalence, Clinical Presentation, Management and their Outcome

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Abstract

Gastrointestinal stromal tumours (GIST) are the most common non-epithelial tumours of the gastrointestinal tract. Prediction of clinical behaviour based on morphologic features has been particularly difficult. Definitive surgery remains the treatment of choice for patients with localized GIST. The current study aims to analyze the prevalence, clinical presentation of GIST in a defined population, their management and outcome. The present prospective and retrospective observational study was conducted during the period of May 2013 to May 2015 in the Department of Surgery of NIMS Medical College & Hospital, Jaipur, India. A total of 30 confirmed patients of Gastrointestinal stromal tumors (Histopathology and CD117+) admitted under department of surgery were taken prospectively from June 2013 to June 2015 (2 years) and retrospectively from June 2010 to May 2013 (3 years). Data were recorded in Microsoft Excel sheet and then transferred and analyzed by SPSS 16.0 software using appropriate tests. The differences were considered to be significant at p-value < 0.05. Most common clinical presentation was abdominal pain (86.7%) followed by blood in stools, vomiting (56.7% and 53.3% respectively) and Hematemesis (26.7%). The prevalence of GIST, out of total GI malignancy was found to be 2.8% in present study. Most common clinical presentation was abdominal pain (86.7%) followed by blood in stools, vomiting (56.7% and 53.3% respectively) and Hematemesis (26.7%). As per the NIH criteria, 43.3% GIST were classified as high risk while 20% and 36.7% were of intermediate and low risk. Laparotomic surgical Resection along with chemotherapy was the most common management strategy employed for patients of GIST. Laparoscopic Resection was employed in 2 cases. Recurrence was observed in 1 case. Out of the 30 cases of GIST, 27 patients were alive till the follow up period, 2 cases were lost to follow up and a single mortality was observed. While GISTs continue to present a diagnostic and therapeutic challenge, our experience demonstrates the excellent oncologic outcomes and favourable safety profile that may be obtained, with increasing use of surgical resections and adjuvant chemotherapy (TKI).

Keywords: Clinical Presentation, Gastrointestinal Stromal Tumors, Management Outcome, Prevalence

Introduction

Gastrointestinal stromal tumours (GIST) are the most common non-epithelial tumours of the gastrointestinal tract. These tumours have been associated with conceptual as well as practical problems for several decades. Earlier lack of rigorous diagnostic criteria for GIST has been due to incomplete understanding of its origin and differentiation and has led to a highly variable nomenclature over the years. Prediction of clinical behaviour based on morphologic features has been particularly difficult. [1] Surgery alone or in combination with traditional chemotherapy or radiation therapy largely has been ineffective in treating the majority of patients with malignant GIST. [2] Recent breakthroughs regarding the pathobiology and treatment of GIST include observations that GIST closely simulates the interstitial cells of Cajal (ICC) morphologically and

immunophenotypically; detection of the tyrosine kinase receptor, KIT, in both ICC and GIST [3, 4]; and gain-of-function mutations in the *KIT* gene that play an early and important role in the development of GIST.[4–7]

GISTs account for approximately 1% to 3% of all malignant GI tumours [8]. The clinical features can vary depending on the anatomic location, size and aggressiveness of the tumour. Most symptomatic patients have tumours larger than 5 cm in maximal dimension. In a series of cases with leiomyomas and leiomyosarcoma (without separation of the GISTs), there were three major presentations, GI bleeding (40%), abdominal mass (40%) and abdominal pain (20%). Two-thirds of patients had GI bleeding while 25 to 40% presented with an intestinal obstruction. Intestinal perforation can also occur uncommonly. [9].

Different types of treatments are available for patients with gastrointestinal stromal tumors based on the stage of tumor. Definitive surgery remains the treatment of choice for patients with localized GIST. Complete surgical resection is recommended for small gastric GISTs <2 cm at high risk of recurrence based upon EUS appearance (irregular borders, cystic spaces, ulceration, echogenic foci, or heterogeneity in appearance). For tumors that lack these features, endoscopic surveillance is an option [10]. Targeted Intervention is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells [11]. The current study aims to analyze the prevalence, clinical presentation of GIST in a defined population, their management and outcome.

Materials and Methods

Study Design and Duration: The present prospective and retrospective observational study was conducted during the period of June 2014 to May 2015 (1 year) in the Department of Surgery of NIMS Medical College & Hospital, Jaipur, India.

Sample Size: A total of 30 confirmed patients of Gastrointestinal stromal tumors (Histopathology and CD117+) admitted under department of surgery were taken prospectively from June 2014 to May 2015 (1 year) and retrospectively from June 2011 to May 2014 (4 years).

Inclusion Criteria

1. Tumour site in or adjacent to the gastrointestinal tract, mesentery, omentum, or retroperitoneum
2. Spindled and/or epithelioid histologic appearance compatible with GIST; and
3. Unequivocal immunoreactivity for CD117.

Exclusion Criteria

1. Terminally ill Patients
2. Patients with chronic diseases
3. Patient age less than 18 years.

The study was approved by the Institutional ethical committee of the college. A detailed history of all the patients was taken along with thorough clinical and general examination. Complete blood count (CBC) and measurement of CD 117 was done. Standard treatment guidelines were followed for each patient based on the clinical symptoms and stage of the disease. Data of the retrospective sample was obtained from medical records.

Blood Sample Collection: About 5-6 ml of venous blood was collected, 3 ml blood was taken in EDTA vials and remaining 3 ml was centrifuged to separate serum from the cells as soon as the clot was formed.

Measurement of Haematological Parameters: The 3 ml peripheral venous blood was taken in sterilized EDTA vials. Blood samples were processed manually for various haematological indices mainly hemoglobin (Hb), total leukocyte count (TLC), mean corpuscular value (MCV), mean corpuscular hemoglobin (MCH) and mean

corpuscular haemoglobin concentration (MCHC). The CBC and haemogram were assayed in Sysmex haemocytometer analyzer. The Erythrocyte sedimentation rate (ESR) was determined by Wintrobe's method.

Diagnosis of Cases: All cases were diagnosed based on histological confirmation from a surgical specimen. Diagnostic criteria of GIST were: (i) histological findings showing spindle cells or epithelioid cells in surgical specimens; and (ii) on immunohistochemistry (IHC), neoplastic cells were positive for c-Kit (CD117) with or without positive CD34. Positive IHC staining was defined as staining of >50% of tumor cells. Negative IHC staining was defined as either scattered positivity or staining of <50% of the tumor cells.

Statistical Analysis: Data were recorded in Microsoft Excel sheet and then transferred and analyzed by SPSS 16.0 software using appropriate tests. The differences were considered to be significant at p-value < 0.05.

Results

The prevalence of GIST, out of total GI malignancy was found to be 2.8% in present study (Table 1). Mean age of the patients was 58.2 years with one third of them were over 60 years of age. Male predominance was observed in study subjects with male to female ratio of 1.3:1. Most common clinical presentation was abdominal pain (86.7%) followed by blood in stools, vomiting (56.7% and 53.3% respectively) and Hematemesis (26.7%). Other presentations were extreme fatigue, bowel obstruction and urinary retention. A total of 13.3% patients were asymptomatic (Table 2). Oesophageal Adenocarcinoma was the most common malignancy found in patients with GIST (2/4). One patient each had Gastric Adenocarcinoma and Colorectal cancer. Most of the cases were diagnosed by either USG or CT scan while endoscopy was required in 70% patients (Table 3). Most common site for GIST was stomach (63.3%) followed by small bowel (23.3%), duodenum (6.7%), colon (3.3%) and rectum (3.3%) (Table 4). Spindle cell type was the most common type of GIST (66.7%) observed in present study followed by epithelioid (13.3%) and mixed (6.7%) type. Out of total 30 cases of GIST, 76.7% were localized to tumor site, 16.7% were locally advanced while metastasis to live was observed in 2 (6.7%) cases. As per the NIH criteria, 43.3% GIST were classified as high risk while 20% and 36.7% were of intermediate and low risk (Table 5). Laparotomic surgical Resection along with chemotherapy was the most common management strategy employed for patients of GIST. Laparoscopic Resection was employed in 2 cases (Table 6). Bleeding (3 cases), Infection (2 cases), DVT and Obstruction (1 case each) were the most common complications observed. Recurrence was observed in 1 case. Out of the 30 cases of GIST, 27 patients were alive till the follow up period, 2 cases were lost to follow up and a single mortality was observed (Table 7).

Discussion

We reported 30 cases of GIST over a duration of 5 years. The prevalence of GIST, out of total GI malignancy was found to be 2.8% in present study. GISTs account for approximately 1% to 3% of all malignant GI tumours [8]. Various epidemiological studies showed the incidence of GIST as 5-20 per million of the population [12-14]. The Taiwanese cancer registry-based study reported more than 5% increase in incidence of GIST in ten years [12]. This increase in incidence can be attributed to recent advances in diagnosis using histological and immunohistochemical markers as well as advances in radiographic imaging and endoscopy of the small bowel. A 30-year study in Japan also showed similar trend of significant increase in the GIST incidence during the last decade [15]. However, it is difficult to compare the incidence rates in different countries due to the differences in study time periods and the lack of application of KIT immunohistochemical confirmation in some studies. GIST associated symptoms varies with the site and size of the lesion. The common site for GIST reported in almost all studies is stomach, accounted nearly 41% in a Jordanian study population [16], and more than half of GIST cases in Saudi Arabian and Egyptian studies [17,18]. Moreover, one in five

GIST patients in Saudi Arabian study had tumors in the small bowel [18]. Nearly half of the cases in the Egyptian study presented with gastrointestinal bleeding; followed by symptoms such as intestinal obstruction in nearly 30%, intraperitoneal hemorrhage in 15%, and rupture and peritonitis in 8% [17]. In a study by Hassan et al., 56% of patients had tumors in stomach followed by 27% of small bowel origin. Abdominal pain was present in most of the patients (85%). Blood in stool and vomiting was reported in more than half of the patients. However, bowel obstruction was seen in less than 10% of patients [19]. The National Institutes of Health (NIH) consensus criteria, also known as Fletcher's criteria, were the first risk stratification system developed for GIST [92]. In present study, as per the NIH criteria, 43.3% GIST were classified as high risk while 20% and 36.7% were of intermediate and low risk. Eight prognostic categories based on tumor size and mitotic activity with four subdivisions of risk groups was used to assess the malignant potential. The 5 cm size was the cut-off value to define low and non-low risk tumors [21]. Notably, 62% of the patients in a study by Hassan et al. fall into the non-low risk category. Following the Fletcher et al. criteria; 33% are at high risk, 31% at intermediate risk, 26% at low risk and 10% at very low risk categories [22]. In Saudi Arabian GIST study, nearly 41% were at high risk, 35% at intermediate, 8% at low risk, and one case was very low risk for metastasis [18]. The Jordan based study revealed, out of 27 GIST cases; 64.3% were high risks, 9.5% intermediate risk, 14.3% low risk, and 4.8% as very low risk [16]. Hassan et al. showed 43.8% were at high risk followed by 18.8% intermediate and 37.5% low risk [22]. Non-gastric tumors account for 37.6% i.e 11 cases in present study, out of which 2 were showing metastasis (100%). Non-gastric tumors accounted for nearly 90% of the tumors metastasized in a study by Tryggvason et al. [14]. More than half (6/11 cases) of the non-gastric tumors are at high risk according to Fletcher's criteria. Notably, 81.8% (8/11 cases) of non-gastric GISTs fall in high or intermediate risk which is consistent with previous studies showing high risk of progression for non-gastric tumors [14,18].

Spindle cell type was the most common type of GIST (66.7%) observed in present study followed by epithelioid (13.3%) and mixed (6.7%) type. Spindle cell GIST were the most common, comprising 64.5% of tumors as is reported in other studies [23-27]. Almost 70% of the epithelioid tumors originated in the stomach. In a study by Hassan et al. [22], most common histological type of GIST was Spindle cell type 31 (67.4%) followed by epithelioid type (15.2%). In another study by Mongan AM et al. the most common histological subtype was spindle cell carcinoma (65%), followed by mixed epithelioid/ spindle cell (15%) and epithelioid cell (13%) [28]. Surgical Resection along with chemotherapy was the most common management strategy employed for patients of GIST in our study. Laparoscopic Resection was employed in 2 (6.7%) cases. Surgical resection is the effective and established mode of treatment for GISTs. Neoplastic mass and gastric wall excision with sufficient surgical margins can be achieved with different surgical techniques which depend on the tumor dimension and localization [29]. Out of total 30 cases of GIST, 76.7% were localized to tumor site, 16.7% were locally advanced while metastasis was observed in 2 (6.7%) cases. In a study by Hassan et al. 65% of the GISTs were localized to the primary organ site and 15% were locally advanced. Small GISTs are usually dealt with wedge resection, whereas gastric resection and total gastrectomy is often conducted in cases of large GISTs localized near the cardia [22].

The National Comprehensive Cancer Network (NCCN) [30] suggested laparoscopic techniques should be used only in tumors less than 2 cm in size. However, there are some reports indicating laparoscopy was effective and safe in removing larger GISTs but inadequate resection margins or tumor spillage leading to disease progression, recurrence and poor survival remain as main issues [31].

Presence of residual tumor is associated with early recurrence and short survival. Sorour et al. [17] reported 3 and 5 years disease free survival for all GIST patients as 73.2% and 64.5% respectively. Tumor sizes have a

significant impact on overall survival. Surgery among low and intermediate-risk patients generally produces good outcomes, whereas high-risk tumors often recur after resection. In a study by Hassan et al. more than three quarter of patients were alive without any disease during the follow up period. Two out of 42 patients died and 7 patients were alive with recurrent or metastatic disease [22].

No recurrence was observed in present study till the duration of follow up while only single mortality was observed. One of our expired patients presented with liver metastasis. The maximum tumor size in this patient was 17 cm and was at high risk according to all risk stratification systems discussed here.

Our study is in line with the previous studies that pointed out liver as the common site for metastasis. The retrospective analysis of 200 GIST patients underwent surgery, revealed that 47% was already metastatic at diagnosis, and the most frequent sites were the liver (50%) and peritoneum (20%) [32]. Sorour et al. [17] found, one patient had liver metastasis and 5 had peritoneal metastasis, in their series of 92 patients. Unresectable patients normally have short survival and frequent recurrence. Studies have shown that median survival among unresectable GIST patients was around 12 months (ranges from 2 to 20 months).

Conclusion

GISTs represent an unusual but increasingly encountered neoplasm. Synchronous tumours appear to occur with more frequency than in the general population and this potentially non-random association requires further investigation. While GISTs continue to present a diagnostic and therapeutic challenge, our experience demonstrates the excellent oncologic outcomes and favourable safety profile that may be obtained, with increasing use of surgical resections and adjuvant chemotherapy (TKI).

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TABLES

Table 1. Prevalence of GIST among GI Malignancies

Variable	N
Total GI Malignancies	1071
GIST	30
Prevalence	2.80%

Table 2. Distribution of subjects based on Clinical Presentation

Clinical Presentation	N	%
Abdominal pain	26	86.7%
Vomiting	16	53.3%
Hematemesis	8	26.7%
Blood in Stools	17	56.7%
Fatigue	7	23.3%
Bowel Obstruction	2	6.7%
Urinary Retention	1	3.3%
Asymptomatic	4	13.3%

Table 3. Distribution of subjects based on Investigation performed

Investigations	Performed	Significant	%
X-ray	30	2	6.7%
USG	30	22	73.3%
CT	30	29	96.7%
Barium	4	4	13.3%
MRI	2	2	6.7%
Endoscopy	21	17	70.0%

Table 4. Distribution of subjects based on site of GIST

Site	N	%
Stomach	19	63.3%
Small Bowel	7	23.3%
Duodenum	2	6.7%
Colon	1	3.3%
Rectum	1	3.3%
Total	30	100.0%

Table 5. Distribution of subjects based on Risk Stratification of GIST

Risk Stratification (NIH)	N	%
High	13	43.3%
Intermediate	6	20.0%
Low	11	36.7%
Total	30	100.0%

Table 6. Distribution of subjects based on Type of Management

Management	N	%
Laparotomy surgical Resection	24	80.0%
Laparoscopic Resection	2	6.7%
Chemotherapy (TKI)	26	86.7%
Radiotherapy	0	0%

Table 7. Distribution of subjects based on Outcome

Outcome	N	%
Alive	27	90.0%
Lost to Follow up	2	6.7%
Death	1	3.3%
Total	30	100.0%