Original Research Article

Gastrointestinal Stromal Tumors (GIST): Is the Incidence rising in India? —A Hospital Based Analysis

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Abstract

Context: Gastrointestinal stromal Tumors (GISTs) are rare Tumors of the gastrointestinal (GI) tract; vbut they are the most common amongst the mesenchymal Tumors. However, there are very few published articles on patients with the diagnoses of GISTs from the Indian subcontinent and particularly from the eastern part of India. Also we noted an increased number of patients with the diagnosis of GISTs in our clinical practice compared to the past decade and have observed an increased incidence of Tumors arising from the small bowel and large bowel compared to the stomach. **Aims:** To study the incidence of symptomatic GISTs, the demographic details, clinical presentations, the histopathological and immunohistochemical features and survival of the patients and response of these Tumors to imatinib therapy. **Settings and Design:** A retrospective study based on hospital registry conducted in the Departments of Radiotherapy and General Surgery, IPGME&R- SSKM Hospital, Kolkata and NRSMCH, Kolkata. **Subjects and Methods:** Cross sectional imaging and endoscopic evaluations were used to diagnose the Tumors. Tumor categorization required microscopic and immunohistochemistry studies for c-Kit, DOG-1 and other tumor markers. High risk group Tumors were treated with imatinib 400 mg/day for 3 years duration. **Statistical Analyses:**Incidence of GISTs was analysed using Pearson Chi-square test and survival was analysed using Kaplan-Meier survival curve and Pearson Chi-square test. **Results:** Incidence of GISTs in 2010-2011 was 0.37% among all GI malignancies, whereas, in 2018-2019 it was 2.48% suggesting 85% increased observation with p value of <0.001. The commonest tumor location was in the small bowel (40.7%), followed by stomach (25.4%) and colo-rectum (10.2%). Mean duration of imatinib therapy was 19.33 months with 84% overall survival. Estimated three-year OS (overall survival) was 73.6%. Estimated mean OS was 66±5.39 months with 95% CI 55.6-76.7. Mean survival of patients with metastatic disease on imatinib therapy was 16.88 months with p=0.000. Primary response to imatinib therapy was observed in 93.87% (43/46) patients. Patients developing disease progression on imatinib were treated with Sunitinib and they demonstrated partial response. **Conclusion:** We have documented an increased incidence of gastrointestinal stromal Tumors and there is increased proportion of small bowel and colorectal Tumors compared to gastric Tumors.

Keywords: Gastrointestinal Stromal Tumors, Incidence, cKIT, DOG-1, Imatinib.

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Introduction

Among all Gastrointestinal tract (GI) Tumors, stromal Tumors are rare, but they are the commonest of the mesenchymal Tumors. The incidence of Gastrointestinal stromal Tumors (GISTs) was reported to be 10-15/million population in different studies [1-3]. It is also known that GISTs comprise less than 1% of all primary GI malignancies [4]. However, any concrete data on the incidence of GISTs in India is lacking. It is also known that 30-40% of GISTs are malignant and 60% of them arise in the stomach[5]. But our clinical experience suggested a greater proportion of these Tumors were arising from the distal bowel. So, we wished to study the incidence of symptomatic GISTs, the demographic details and the clinical-pathological features of these Tumors.

Subjects and Methods

The study was conducted in the Departments of Radiotherapy and General Surgery, IPGME&R-SSKM Hospital, and NRSMCH, Kolkata. Our data source was prospectively maintained departmental cancer registries. For quantification of the incidences of GISTs we retrieved data of all patients diagnosed with GI malignancies from 2010-2011 and 2018-2019. Patients received Imatinib from our Institute since 2016 when it was distributed by the State Government. So, we included data of patients with GISTs and the treatment they received from our cancer registries from 2016-2019.

The Tumors were categorised according to modified NIH risk stratification criteria and the survival data were analysed. We also studied the tumor-response to Imatinib therapy.

Sixty one patients were included in this study from 2016-2019. The diagnostic armamentaria included ultrasound abdomen, CECT abdomen, MRI studies, Endoscopic Ultrasound evaluation, upper GI and lower GI endoscopy including guided biopsy when feasible and indicated, capsule enteroscopy, image guided FNAC and/or biopsy, and PET/CT. Histological diagnosis of GIST was made as per light microscopy features. An Immuno-histochemistry study for c-KIT was carried out initially to confirm the histological suspicion. c-KIT negative Tumors were further subjected to IHC studies for DOG 1 and CD 34 to reach to a definitive diagnosis. IHC studies for SMA, S-100 and desmin were used as per the pathologists' discretion to differentiate c-KIT negative Tumors from other soft tissue sarcomas as described in the literature [6].

Demography and clinical presentation:

Among the sixty one patients in this study thirty five patients were male and twenty six were female and the median age of presentation was 52 years (18-80 years) [clinical data included in Table-1]. The common presentations were abdominal lump (25.9%), GI bleeding (24.1%) and pain abdomen (20.7%). Fourteen patients (24.1%) presented with a combination of these symptoms. Presentations with acute or chronic small bowel or large bowel obstructions were not uncommon. Cases with acute abdomen also included a ruptured ileal GIST. Commonest tumor location was small bowel (40.7%), followed by stomach (25.4%) and colo-rectum (10.2%). Most Tumors required wedge resection only; mostly using open methods and few with laparoscopic assisted techniques. Some cases required multivisceral resection in the form of distal gastrectomy or total gastrectomy with or with-out splenectomy or segmental resection of small bowel and colon, or abdomino-perineal excision of rectum (APR). One jejunal tumor required excision along with non-anatomical resection of liver metastasis.

We have also encountered three rare extra-gastrointestinal GISTs [detailed data included in Table-2]; one arising from the retro-peritoneal tissue in the primary lesser sac location, one arising from the dome of the urinary bladder and the other arising from the uterine adnexa. Primary lesser sac tumor was excised completely (R0 resection)**.** The tumor arising from the anterolateral wall of the urinary bladder required wide local excision of the tumor along with retro-peritoneal lymphadenectomy. The uterine GIST presented as an adnexal soft tissue mass along with a tumor nodule in the broad ligament and complete excision of the tumor was achieved through a total abdominal hysterectomy and bilateral salpingo-oophorectomy along with excision of the broad ligament nodule. This patient had previously undergone excision of a pelvic hemangiopericytoma six years back.

Nine patients presented with disseminated metastatic disease involving liver or peritoneum; among them, four patients had the primary lesion in the stomach, and, two in the small bowel. However, the primary lesions were not detected in the other three patients. Among these three patients one patient had multiple small liver and peritoneal nodules, one patient had multiple variegated liver lesions associated with a large ill-defined intra-abdominal lump in the perigastric location and the third patient had diffuse peritoneal disease without any demonstrable liver lesion.

Average tumor size was 9.4 cm (range 2.5-22cm), tumor necrosis was noted in 65% of the cases and tumor rupture was noted in a single case. 13% Tumors were of epithelioid type, 1.63% was of mixed cell type,

and, the rest were of spindle cell type. Lymph node infiltration was noted in two patients, one with ileal tumor in a young adult female patient and the other in a sixty-year-old male with primary lesion arising from the urinary bladder.

On immunohistochemistry examination, 88.6% (n=44) of the Tumors were positive for CD 117, 76.7% (n=30) were positive for CD 34, and 100% (n=25) were positive for DOG1. Modified NIH classification (2008) was used for prognostication. Majority (78.7%) had high risk lesions followed by intermediate risk (11.5%), low risk (4.9%), and very low risk (3.3%) lesions. Moderate risk and high risk cases including patients having undergone incomplete resection and patients with metastases were treated with imatinib as the first line therapy. Five patients received imatinib in neoadjuvant setting for locally advanced non-resectable disease. Sunitinib was given to patients who were intolerant or resistant to imatinib treatment.

Results:

Incidence of GISTs was analysed using Pearson Chi-square test and survival was analysed using Kaplan-Meier survival curve and Pearson Chi-square test.

Incidence of GISTs: In 2010-2011 the incidence was 0.37% among all GI malignancies reported to our centers, whereas, in 2018-2019 the incidence was 2.48% with a p value of <0.001.

Mean duration of imatinib therapy in our patients for all indications was 19.33 months with overall survival (OS) at this time was 84%.

Estimated three-year OS for all patients was 73.6%

Estimated mean OS for all patients was 66 ± 5.39 months with 95% CI 55.6-76.7 [Fig-1].

Mean survival in patients with metastatic disease on imatinib therapy was 16.88 months with p=0.000 [Fig-2].

Primary response to imatinib therapy was observed in 93.87% (no =46) patients. Patients developing recurrence on imatinib therapy were treated with Sunitinib and they demonstrated partial response to this second line drug.

Common adverse effects noted in our patients treated with tyrosine kinase inhibitors were gastrointestinal symptoms and bone marrow suppression.

Table 1: Demographic and clinicopathological features of patients with GISTs in our series

Age		
	18 -30	03
	31-40	11
	41-50	16
	51-60	22
	61-70	07
	71-80	02
Gender	M	35
	F	26
Symptoms	Incidental diagnosis	02
	Pain	12
	Bleeding	14
	Mass	15
	Combination of symptoms	14
	Bowel obstruction	03
	Tumor rupture	01
Tumor Location	Stomach	19
	Duodenum	04
	Jejunum	15

	Ileum	08
	Colon	05
	Rectum	03
	Extra-intestinal	03
	Primary lesion not identified	03
	Data NA	01
	Total	61
Metastatic at presentation		09
	Stomach +Mets	04
	Jejunum+Mets	02
	Unknown primary	03
Procedure done		
	Wide local excision	25
	Multivisceral resection	11
	Tumor excision	01
	Incomplete resection	01
	Biospy taken	23
Tumor Size	2-≤5 cm	09
	>5-≤10	21
	>10	27
Macroscopic type	Spindle cell	52
	Epithelioid	08
	Mixed cell	01
Mitotic Rate	≤5/50 HPF	25
	≥5/50 HPF	30
	Data N.A.	06
cKIT	Positive	39
	Negative	05
	Data N.A.	17
DOG-1	Positive	25
	Negative	00
	Data N.A.	36
CD34	Positive	23
	Negative	7
	Data N.A.	31
SMA	Positive	6
	Negative	17

	Data N.A.	38
S-100	Positive	01
	Negative	24
	Data N.A.	36
Desmin	Positive	01
	Negative	14
	Data N.A.	46
Modified NIH Risk Group	Very low	02
	Low	03
	Intermediate	07
	High	48
	Data N.A	01
Imatinib		
Adjuvant	Total treated	40
	Response	38
	Primary resistance	03
	Death	07
Neo-Adjuvant	Total treated	09
	Response	08

Table 2: Clinical data

S. N.	Age/ Gender	Site	Presentation Metastatic (M)/ Nonmetastatic (NM)	Lymph node invasion/Serosal deposit	Size cm	Mitoses	Risk group	CD 117	Rx	Type of resection	Follow up (months from diagnosis)	OS (months from diagnosis)
1	56/M	Lesser Sac	NM	LDI	15	5/50	H	P	Sx	R0	Rec 48mo	Alive 60
2	30/F	Uterine adnexa	NM	SeD	16	>5/50	H	P	Sx	R2	SD	Alive 24
3	59/M	UB	NM	LDI	8.5	5/50	H	P	Sx	R0	Rec 18	Dead 22

Table 3: Selection of TKI based on Gene Mutations

Selection of TKI based on Gene Mutations		
Gene	Mutation	TKI.Dose
KIT	Exon 11	Imatinib-Mesylate 400 mg/day
	Exon 13	
	Exon 17	
	Exon 9	Imatinib-Mesylate 800 mg/day
PDGFRA	Exon 18 D842V	Sunitib 50mg/day
		Regorafenib 160mg/day
	Exon 12	Imatinib-Mesylate 400 mg/day
	Exon 14	
	Exon 18 non 18 D842V	
Wild Type		Sunitib 50mg/day
		Regorafenib 160mg/day

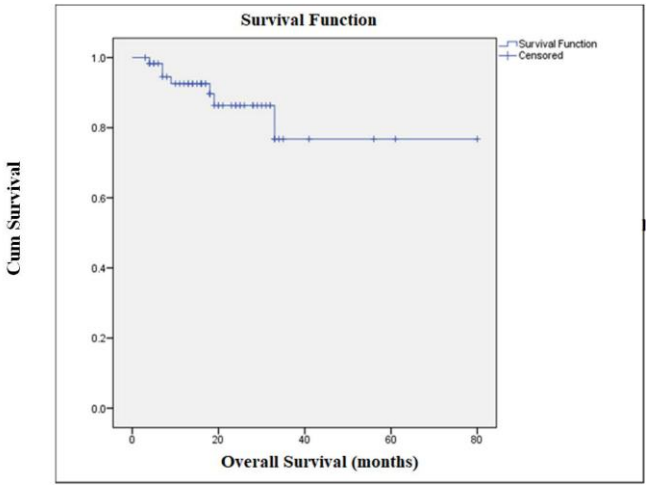

Fig1: K-M curve showing overall Survival of all patients at the median follow up

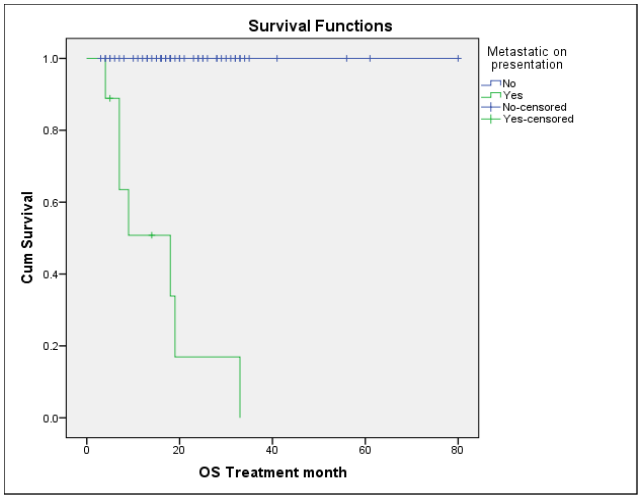

Fig 2: K-M curve showing overall Survival for patients with metastatic lesions at presentation

Discussion

GISTs are quite rare Tumors, the incidence being 10 to 15 cases per million as per world literature [7-8]. Recently more symptomatic Tumors are being identified. In Netherlands it was reported to be 12.7/million population in 2003, however, a rising trend was noted and the incidence was 17.7/ million population in 2012 [2]. Studies from Shanghai, China have also documented a significant rise in the incidence of GISTs in the recent years [3]. This may be attributed to the increased use of sophisticated imaging modalities and improved histopathogy and immunohistochemistry techniques [5-9]. However, the possibility of true increase in the incidence of GISTs may not be ruled out. The present study documents an 85% ($p<0.001$) increased incidence of GISTs among all GI malignancies reported to the study centers in West Bengal, India, over a period of eight years.

Median age at diagnosis of patients with GISTs is 60 years with almost equal gender distribution [5-7]. This was a decade earlier in our series, compared to western studies, but, earlier disease onset has been reported by other authors from India as well [10]. GISTs can originate anywhere in the GI tract, the most common site being stomach (40–60%) and small intestine (30–40%). Other sites are colon, rectum and esophagus. Rarely GISTs are found primarily in extra-intestinal locations such as in the mesentery or retro-peritoneum

[11]. We experienced highest frequency of GISTs in small bowel (40.7%) followed by stomach (25.4%) and colo-rectum (10.2%). Some studies from India also documented an increased proportion of small bowel (35%-43%) and large bowel (20%) Tumors compared to gastric Tumors [12]. Identification of more frequent advanced Tumors in the small intestine may reflect an early diagnosis of proximal Tumors since we have a low threshold for the diagnostic use of esophagogastroduodenoscopy and cross sectional imaging modalities to investigate patients presenting with upper abdominal symptoms in the tertiary care centers in India. Nevertheless, the possibility of a "distal shift" cannot be ruled out and needs to be studied with increased power.

GISTs mostly present with vague abdominal symptoms, awareness of an abdominal mass, gastrointestinal bleeding and rarely with acute abdomen because of small or large bowel obstruction or tumor rupture. Other rare presentations include iron deficiency anemia, obstructive jaundice from pressure symptoms or symptoms from metastatic disease [7]. While mesenteric, omental, peritoneal, and liver metastases are common, lymph node and extra-abdominal metastases, such as, lung, bone or cerebral metastases are very rare [13-17]. The common presentations of GISTs in our study were abdominal lump (25.9%), GI bleeding (24.1%) and pain abdomen (20.7%). We have also noted jejunal intussusception and tumor rupture presenting as acute abdomen. Although most gastrointestinal stromal Tumors are sporadic, familial and syndromic forms are also known to occur [18-20]. An associations with other synchronous or metachronous gastrointestinal malignancies have also been reported [21]. We found a metachronous uterine adnexal GIST following six years of excision of a pelvic hemangiopericytoma. Hemangiopericytoma-like histological pattern has been reported on histopathological examination of GIST previously [22].

On histopatholgy, morphological findings of GISTs include spindle cell (70%), epithelioid (20%) or mixed cell type (10%) Tumors. However, most of the Tumors in our study were spindle cell type and only 13% were epithelioid and 1.63% was mixed cell type. Lower incidence of epithelioid type Tumors were also reported from Indian studies earlier[12]. Immunohistochemistry studies for confirmation of the diagnosis include KIT, CD-34, and DOG-1 studies. About 85% - 95% Tumors are KIT positive [23]. KIT negative Tumors with histological suspicion of GISTs need further evaluation with DOG-1 and CD 34 to confirm the diagnosis. DOG-1 is expressed in 88%-100% GISTs [24-25]. Almost 90% of gastric GISTs and 50% of non-gastric GISTs express CD34 [26]. Moreover, to differentiate GISTs from other soft tissue sarcomas immunostaining for Vimentin, SMA, Desmin, S-100 etc. are utilized [26]. In our studies 88.6% (44) of the Tumors were positive for CD 117, 76.7% (23) were positive for CD 34, and 100% (25) were positive for DOG1. These findings are corroborative with previously published literature [23-25].

Risk Assessment**:** Fletcher et al. first described the risk categorization of GISTs based on tumor size and mitotic rate [27]. In 2006 Miettinen and Lasota added tumor site as a third independent factor [28]. This classification system led to the Armed Forces Institute of Pathology (AFIP) criteria and the modified National Institute of Health criteria [29]. We have used the modified NIH criteria by Joensuu, which includes tumor rupture as another independent risk factor and reliably predicts risk of progression in GISTs.

Survival of high risk GISTs are significantly altered through tyrosine kinase inhibitors, the prototype of which is Imatinib mesylate. Imatinib inhibits c-kit activation and causes tumor cell apoptosis. Intermediate risk and high risk group patients are treated with minimum three years of imatinib therapy. Metastatic Tumors are treated for long duration with Imatinib. However, on long term therapy secondary mutations appear which mostly involve the tyrosine kinase ATP binding pockets. Sunitinib and other kinase inhibitors, such as, nilotinib, dasatinib, regorafenib are used as second or third line therapy or in an event of development of toxicities on imatinib therapy [30].

The mean OS (66 ±5.39 months with 95% CI 55.6-76.7), estimated 3-yr OS (73.6%) and OS of patients with metastatic disease (16.88 months; p=0.000) in our series are lower compared to world literature [31]. Wang et al. demonstrated 92.6% 3-yr OS for all GISTs and 3-yr OS of 97.8% for intermediate group and 80.0% for high risk group Tumors [3]. Poorer outcome in our study may be explained by late presentation, poor nutritional and socio-economic status and access to healthcare facilities.

We observed primary resistance to Imatinib in three cases. Mutation studies are particularly helpful in these situations. The most common mutations present in GISTs include gain-in function of c-kit or Platelet derived growth factor receptor A (PFGFRA) genes or silencing of Succinate dehydrogenase (SDH) gene. However, in view of non availability of mutation studies, the patients were empirically switched to second line agent, Sunitinib. Knowledge of gene mutation is important in selection of TKI for

individualized treatment in an event of primary or secondary resistance to Imatinib [32] [Table 3].

Not only for adjuvant therapy, tyrosine kinase inhibitors are also used in the neoadjuvant setting for locally advanced primary Tumors to reduce the vascularity and increase operability of the Tumors. Genetic testing is strongly suggested before starting neoadjuvant therapy as well and a minimum three to six months duration of imatinib therapy is suggested to achieve optimum results before surgical intervention, but not beyond 2 years' time to avoid the emergence of secondary imatinib resistance [33-34]. In our series, we have put five patients with locally advanced primary tumors on neoadjuvant therapy and they are presently in the preoperative phase.

To summarise, the principal features of our study includes an increased incidence of GISTs, early disease onset, and a possible 'distal-shift' with increased proportion of small bowel and large bowel Tumors compared to gastric Tumors. Moreover, the survival of the patients was lower compared to the world literature.

Conclusion

There is a need for large scale multicentric studies to ascertain the incidence and demographic criteria of GISTs in Indian population and to identify the differences with other Asian or Western population if any. Close follow up of all patients diagnosed with intermediate and high risk group gastrointestinal stromal Tumors is mandated to assess the treatment outcome in our population. No significant outcome difference between intermediate risk and high risk group patients could be estimated because of very limited number of patients in the intermediate risk group. Availability of genetic testing is also required to choose the appropriate adjuvant therapy for giving improved survival chances to these patients. Newer approaches such as immunomodulation therapy may bring new horizon in the treatment of patients with high risk disease in future.

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