Original Article

Gastrointestinal stromal tumors: A single institute experience from South India

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ABSTRACT

Background: Gastrointestinal stromal tumors (GIST) represent an uncommon form of malignancy and one of best paradigms of molecularly targeted therapy. While the natural history of GIST following treatment with imatinib mesylate is relatively well known from various series in western literature, rarely any series from India has been published in this regard. **Materials and Methods:** Forty-four GISTs cases diagnosed and treated with imatinib between 2005 and 2011 were retrieved from the Department of Medical Oncology database, KMIO, Bangalore. Their clinical, histopathological data, and treatment outcome were analyzed. Kaplan-Meier survival analysis was done. Anatomic site, tumor size, mitotic activity, and extent of resection were correlated with overall survival (OS) using the logrank test. **Results:** Median age was 56 years with a male: female ratio of 2:1. Stomach was the most common site involved. Twenty-nine patients had localized disease of which majority had high risk (65%) features, with a mean tumor size of 10.5 cm (range 4-18 cm) and mitotic rate of 6 (range 4-9)/50 high-power field (HPF). Fourteen patients had metastatic disease at presentation with liver being the most common site. In the adjuvant group, median follow-up was 42 months (m) (range 10-70 m). Estimated recurrence free survival (RFS) and OS at 42 m were 59.9 and 80.6%, respectively. In metastatic group, median follow-up was 28 m (range 2-54 m). The median progression free survival (PFS) and OS were 18 m (95% CI 8.65-27.34 m) and 28 m (95% CI 17.90-38.09 m), respectively. Estimated PFS and OS at 28 m were 38.7 and 46.7%, respectively. **Conclusion:** Patients with GIST still present with larger bulky tumor at diagnosis, this leads to slightly inferior survival in our scenario. Nongastric GISTs; R1 and R2 resection; and mitotic rate >5/50 HPF are the other a factors which have a negative impact on survival.

Key words: Gastrointestinal stromal tumors, imatinib, India

INTRODUCTION

Mesenchymal tumors constitute 1% of primary gastrointestinal (GI) tumor, of which GIST is the most common.[1] Until the discovery of CD117, these were commonly misdiagnosed as smooth muscle tumor of GI tract and were having a dismal prognosis with conventional chemotherapy. Since 2002, with the approval of imatinib mesylate in the treatment of this disease the outcome has drastically improved.[2] While the natural history of GIST following treatment with imatinib mesylate is relatively well-known from various series in western literature, rarely any series from India has been published in this regard.

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MATERIALS AND METHODS

Forty-four GISTs cases diagnosed and treated with imatinib between 2005 and 2011 were retrieved from the Department of Medical Oncology database, KMIO, Bangalore. Their clinical, histopathological data, and treatment outcome were analyzed. The diagnosis was established on the basis of histopathological examination, immunohistochemistry, and genetics. These included CD117 and DOG1 immunostaining, mutation testing for KIT and platelet-derived growth factor receptor-α (PDGFRA was not done. All pathologic material was reviewed by single pathologist. Metastatic workup included computed tomography (CT) scan of abdomen, pelvic, and thorax. Positron emission tomography (PET) scan was not used due to logistic reasons.

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In patients with localized disease after complete surgery, the risk of recurrence was evaluated using the National Institutes of Health (NIH) 2002, "Fletcher's criteria".[3] In patients with high risk patients, adjuvant imatinib (400 mg/day for 1 year) was given since 2009. Patients with metastatic disease at diagnosis were initiated treatment with imatinib 400 mg daily at onset, escalated to 800 mg at progression, or treated with sunitinib when intolerable to imatinib. These patients were followed-up with clinical and radiological examination every 3-6 m.

The recurrence free survival (RFS) and overall survival (OS) was evaluated for all patients using the Kaplan-Meier curve (Statistical Package for Social Sciences (SPSS) 19; SPSS Inc, USA). Anatomic site, tumor size, mitotic activity, and extent of resection were correlated with OS using the logrank test.

RESULTS

Median age was 56 years (range 21-68 years) with a male: female ratio of 2:1. Stomach (52%) was the most commonly involved site followed by small intestine (36%). Twenty-nine cases had disease localized to a single site and 15 cases were metastatic at presentation. Other clinical features are given in Table 1. Mean tumor size was 10.5 cm (range 4-18 cm) and mitotic rate of 6 (range 4-9)/50 high-power field (HPF). All patients had CD 117 positive tumor, DOG1 was positive in 91% (40 cases). CD117 was diffuse strong staining with perinuclear/cyoplasmic pattern in most cases; focal pattern of staining was noted in two cases, these two cases had DOG1 positivity. NIH 2002, "Fletcher's criteria" was applied for nonmetastatic disease, none had very low risk, one case (3%) had low risk, 10 (34%) intermediate, and 18 (65%) belonged to high risk. All cases underwent upfront surgery with R0 resection in 84%, R1 in 13%, and R2 resection in 3% cases followed by imatinib (400 mg/day) for duration of 1 year. Metastatic sites in descending frequency of involvement were liver (85%), peritoneum (13%), omentum (6%), and lungs (1%). None had lymph node or soft tissue involvement. The common toxicities associated with therapy with imatinib are given in Table 1. In the adjuvant group, median follow-up was 42 months (m) (range 10-70 m). Estimated RFS and OS at 42 m were 59.9 and 80.6%, respectively. In metastatic group, median follow-up was 28 m (range 2-54 m). The median progression free survival (PFS) and OS were 18 m (95% CI 8.65-27.34 m) and 28 m (95% CI 17.90-38.09 m), respectively. Estimated PFS and OS at 28 m were 38.7 and 46.7%, respectively [Figure 1]. Nongastric GIST ($P = 0.015$), tumor size (> 10 cm, $P = 0.004$), R2 resection ($P = 0.02$), and mitotic rate >5/50 HPF ($P = 0.023$) were associated with negative impact on survival. Figures 2-5 shows the RFS with each of this risk factor.

Table 1: Clinical profile

Demographic profile	
Symptoms	
Pain (%)	36 (80)
Mass per abdomen (%)	12 (28)
Obstruction/perforation (%)	7 (15)
Weight loss (%)	21 (45)
Intestinal bleed (%)	4 (9)
Median symptom duration	3.5 months
Surgical complication	
Sepsis (%)	1 (3)
Wound infection (%)	2 (6)
Postop adhesion (%)	2 (6)
Adverse events	
All grades	Grade 3-4
Nonhematologic (%)	
Edema-42	8
Diarrhea-22	6
Myalgia-36	
Rashes-40	
Fatigue-20	
Hematologic	
Anemia-9 (%)	2
Decreased WBC count-12	4
Biochemical (%)	
Deranged LFT-25	5

WBC: White blood cell, LFT: Liver function test

DISCUSSION

GIST represents a prototype tumor where insights into the molecular pathogenesis lead to dramatic improvement in clinical outcome. Due to low incidence of disease (0.68 per one lakh),[4] little is known about clinical profile and outcome in Indian scenario. This study highlights on some of these aspects.

Compared to world literature, we have a similar age of presentation, male preponderance, and intra-abdominal location as commonest site of metastasis.[5] On comparing the common site of involvement, stomach was the most common site in our study, which differed from other studies from India but was similar to World Series.[6,7]

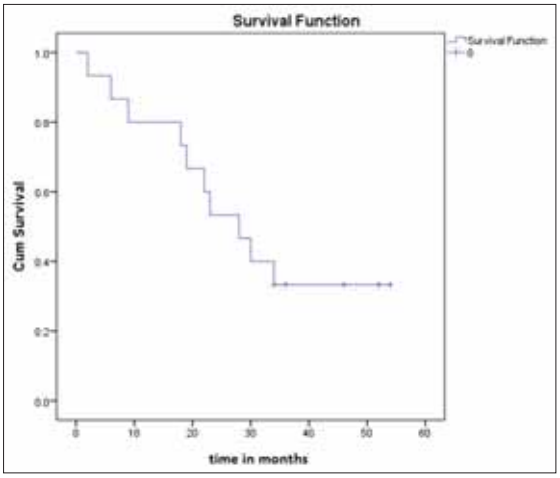

Figure 1: RFS in metastatic setting

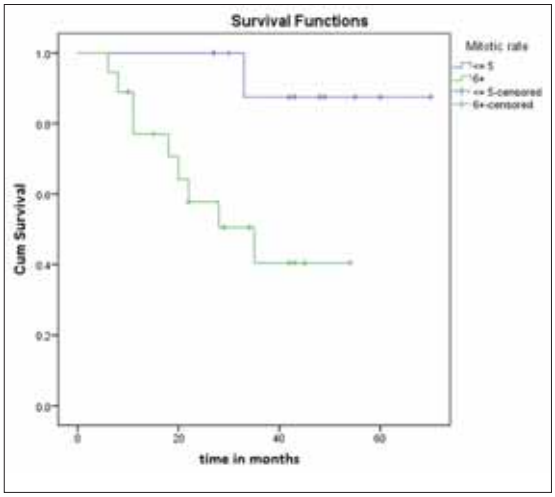

Figure 2: RFS based on mitotic index

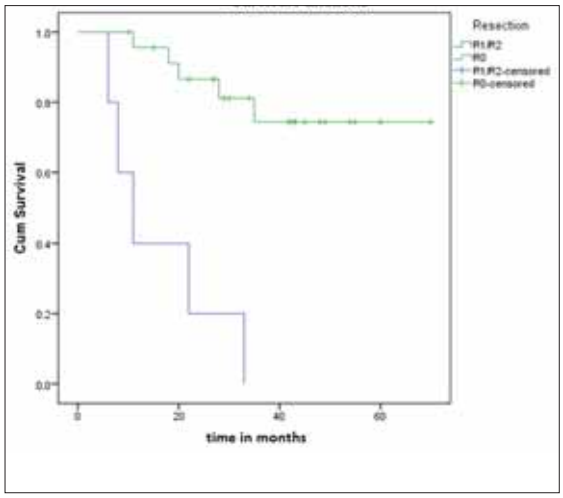

Figure 3: RFS based on resection status

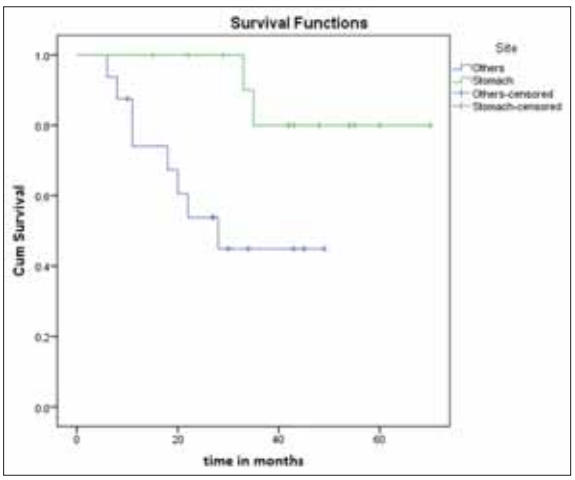

Figure 4: RFS based on site of tumor

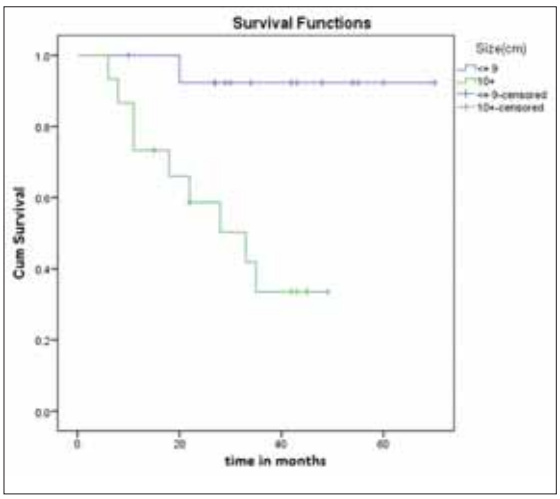

Figure 5: RFS based on tumor size

Many large studies have shown that the factors associated with high risk of recurrence include tumor size, location, mitotic index, type of KIT mutation, completeness of tumor resection, and intraoperative factors like spontaneous or iatrogenic tumor rupture and mucosal invasion.[8,9] Similar outcome has been seen in our study as well. However, molecular studies into the type of KIT mutation and outcome were lacking in our study.

Table 2 shows comparison of OS and RFS in adjuvant setting and metastatic setting at 1, 2, and 3 years of our study with other large studies (which includes the ACOSOG trial: American College of Surgeons Oncology Group, EORTC/ISG/AGITG: European Organisation for Research and Treatment of Cancer/Italian Sarcoma Group/Australasian Gastro-Intestinal Trials Group and US S0033 study).[10-12] We noted a lower survival when compared to World Series probably due to late diagnosis of the tumor and larger bulky tumor presentation in our scenario. In our study size, less than 1 cm constitutes only 3% of cases; whereas in World Series it may represent up to 35% of cases.[13]

Comparing the common toxicities associated with imatinib, we noted a lower incidence of edema (which includes periorbital edema and pedal edema), deranged liver function test, and diarrhea; but a higher incidence of anemia and low white blood cell (WBC) count,[14] indicating imatinib was well-tolerated and frequent monitoring may be only required for cytopenia.

Limitations of our study include the lack of use of functional imaging like PET scan, lack of mutational testing for PDGFRA and KIT, and a small number of patients with a short follow-up.

CONCLUSION

Patients with GIST still present with larger bulky tumor at diagnosis, this leads to slightly inferior survival in our

Table 2: Comparison with other larger studies

	Recurrence free survival (%)			Overall survival (%)		
	1 year	2 year	3 year	1 year	2 year	3 year
Comparison of recurrence free and overall survival at 1, 2, and 3 years on imatinib in adjuvant setting						
ACOSOG (Z9000)[10]	94	73	64	99	97	95
Our study	85.9	74.7	59.9	93.1	89.4	85.7
Comparison of recurrence free and overall survival at 1, 2, and 3 years on imatinib in metastatic setting						
US S0033[11]	71	50	29	86	76	Not available
EORTC/ISG/AGITG[12]	65	50	31	85	69	NA
Our study	69.9	38.7	11	80	53.3	33.3

ACOSOG: American college of surgeons oncology group, EORTC/ISG/AGITG: European organisation for research and treatment of cancer/italian sarcoma group/australasian gastro-intestinal trials group, NA: Not available

scenario. Nongastric GISTs, R1 and R2 resection, and mitotic rate >5/50 HPF are the other a factors which have a negative impact on survival.

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