British Journal of Medicine & Medical Research
5(10): 1280-1286, 2015, Article no.BJMMR.2015.145
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Gastrointestinal Stromal Tumors: Experience from a Single Surgical Unit

Satendra Kumar[1], Satyanam Kumar Bhartiya[1], Somprakas Basu[1], Mohan Kumar[2] and Vijay Kumar Shukla[1*]

[1]Departments of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi- 221005, India.
[2]Departments of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi- 221005, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author SK performed the study design, data collection, review of literature and writing manuscript. Author SKB performed the data collection and review of literature. Author SB performed the data analysis, review of literature and final revision. Author MK performed the data collection and histopathological examination of GIST specimen. Author VKS performed the surgery, study design and final revision. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/13856
Editor(s):
(1) E. Umit Bagriacik, Immunology Research Center, Department of Immunology, Gazi University, Turkey.
Reviewers:
(1) Ahmed Abu-Zaid, College of Medicine, Alfaisal University, Saudi Arabia.
(2) Anonymous, Tunisia.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=717&id=12&aid=6792

Original Research Article

Received 6th September 2014
Accepted 27th September 2014
Published 5th November 2014

ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) are rare tumors, but comprise the most common mesenchymal neoplasms of the gastrointestinal (GI) tract. We report a clinical series of abdominal GIST and discuss the diagnosis and management in Indian patients.
Case Series: The data on demographic profile, clinical presentation and management of 12 cases of GIST from a single surgical unit in the last seven years were studied retrospectively. Preoperatively, ultrasonographic and computerized tomographic scans of the abdomen were the main investigations used for evaluation; the others being upper gastrointestinal endoscopy and X-ray of the chest. Histopathological examination and immunohistochemical evaluation were used to confirm the diagnosis.
Results: The mean age at presentation was 47.9 years (range 35 – 70 years). Mean duration of

**Corresponding author: Email: vkshuklabhu@gmail.com;*

symptoms was of 5 months (range 10 days–2 years). While all 12 patients presented with abdominal pain, 10 complained of abdominal lump. Two patients complained of vomiting and 1 of upper GI bleed. All patients were operated. In 7 cases, the GIST was arising from the ileum, 3 from the stomach and 2 from the mesentery. Nine cases had low grade benign tumors and 3 had malignancy.

Conclusion: Abdominal pain and lump are the most common clinical symptoms of abdominal GIST. Vomiting, upper GI bleeding and weight loss are among the other important symptoms. Most of the tumors are benign and surgical resection remains the mainstay of treatment.

Keywords: Gastrointestinal stromal tumors; imatinib; CD 117; interstitial cells of cajal.

ABBREVIATIONS

Gastrointestinal Stromal Tumors (GISTs), Gastrointestinal (GI), Gastrointestinal Tract (GIT), Interstitial Cell of Cajal (ICC).

1. INTRODUCTION

Although gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract (GIT), overall they are rare neoplasms ranking a distant third in prevalence behind adenocarcinomas and lymphomas [1]. They may also originate from the mesentery and the omentum. In the past, these tumors were a poorly defined pathological entity with uncertainty regarding the origin and terminology often being confused with leiomyomas and leiomyosarcomas. Kindblom in 1998 first hypothesized the origin of these tumors from pluripotential mesenchymal stem cells of the gastrointestinal tract which are programmed to differentiate into the interstitial cell of Cajal (ICC) [2]. These tumors have microscopic features in common with the myenteric plexus subtype of ICC that are found in stomach and intestines, including frequent expression of CD34, embryonic smooth muscle myosin heavy chain, and the intermediate filament nestin. The observation that ICC cells can be immunohistochemically highlighted with an antibody to KIT (CD 117) led to the discovery that KIT is also strongly expressed in most GISTs [3,4]. These not only substantiated the hypothesis that GISTs arise from or share a common stem cell with the ICC, but it also provided a new, more sensitive and specific marker for its diagnosis. Gain-of-function mutations in exon 11 of the c-kit proto-oncogene are associated with most GISTs [5].

Since these tumors are rare, the experience of management is not very common. The presentation may vary and may mimic other gastrointestinal pathology. Although there are some large series in the world literature, those from India are few. We present our experience of management of patients with GIST from a single surgical unit and compare with other series already reported.

2. PATIENTS AND METHODS

From 2004 to 2010, 12 cases of GIST were admitted and managed in a single surgical unit of our university teaching hospital. The data were retrieved from the hospital records retrospectively and the patients were followed up prospectively for a minimum period of five years. Demographic profile of the patients, their clinical presentation and management were noted. Preoperatively, X-ray of the chest, abdominal ultrasonographic examination and contrast-enhanced CT scan of the abdomen were the main investigations for evaluation. Results of other supporting investigations like the esophagogastroscopy, blood biochemistry and hematology were recorded. Histopathological examination with immunohistochemistry was used to confirm the diagnosis.

3. RESULTS

The mean age at presentation was 47.9 years and the mean duration of symptoms was 5 months. All patients complained of recurrent abdominal pain on presentation while abdominal lump was complained of by 10 patients. The demographic profile and presenting symptoms are summarized in Table 1. The tumor could be diagnosed by an ultrasonographic examination in all the ten cases who presented with abdominal lump. However in the two patients in whom abdominal pain was the presenting symptom,

sonographic examination failed to pick up the GIST. Contrast CT scan was diagnostic of GIST in all 12 patients. The mean size of the tumor was 12.6 cm (4.2 cm - 21 cm). Three patients with gastric GIST required additional upper GI endoscopic examination for biopsy and confirmation. Important findings in the CT scan included heterogeneous/ homogeneous/minimally enhancing mass lesion, central necrosis, calcifications, focal thickening of pylorus and intraluminal polypoidal mass in stomach with perigastric fat stranding and enlarged lymph nodes (Fig. 1).

Table 1. Clinical presentation

Mean age	**47.9 years (range 35 - 70 years)**
Male : Female	1.75 : 1
Mean duration	5 months (10 days–24 months)
Abdominal pain	12
Abdominal lump	10
Past history of laparotomy	04
Vomiting	03
Anorexia and weight loss	03
Subacute intestinal obstruction	02
Gastric outlet obstruction	01
Eosinophilia	01
Upper GIT bleed	01

Surgery was performed in all cases. In 7 (58.3%) cases, GIST was arising from ileum whereas 3 (25%) had gastric and 2 (16.6%) had mesenteric origin. The surgical management is summarized in Table 2. Nine cases were low grade benign tumors while 3 were malignant (25%) (Fig. 2).

In one patient with malignant ileal GIST, the tumor was fixed at the root of the mesentery and was infiltrating the pelvic organs, vessels and right ureter, and also had secondaries in the liver. It was locally inoperable and finally the abdomen had to be closed after taking a biopsy. Cut section of the tumors showed grey-white areas and three out of twelve cases also showed focal areas of haemorrhage and necrosis. Microscopic examination revealed spindle cells with elongated hyperchromatic nucleus and moderate eosinophilic cytoplasm arranged in short fascicles along with areas of tumor cells showing epitheloid appearance. Mitotic counts ranged from 1-3/50 HPF (high power field) in nine out of twelve cases while the remaining three showed a mitotic activity ranging from 7-8/50 HPF. Based on the size and mitotic index 7 patients had low risk tumors, 2 patient had intermediate risk tumors while 3 were in the high risk category. All were positive for CD117 (immunohistochemistry) (Fig. 3). The patients with malignant GISTs were put on imatinib mesylate (400 mg/day) lifelong. Of the 3 patients with malignant GIST, one patient died, one was lost to follow up while the third survivor is still on imatinib mesylate and does not have any recurrence at 37 months. All benign GISTs are surviving and are still on regular follow up.

Table 2. Surgical management

Organ Involved	**Surgery performed**
Ileal (7)	Primary resection and anastomosis (6) Exploratory Laparotomy with Biopsy (1)
Gastric (3)	Billroth 1 Gastrectomy 1/3 Billroth II Gastrectomy 1/3 Wide Local Excision of anterior wall tumor (1)
Mesenteric (2)	Wide local excision (1) Wide local excision with segmental resection and anastomosis of small bowel (1)

4. DISCUSSION

GISTs account for less than 1% of all gastrointestinal neoplasm. Incidence of GIST is approximately 10–20 per million people annually world wide [2] and it has a male preponderance, which is in concordance with our series. Mean age at the time of diagnosis of these tumors is usually around 60 years [6], which was found to be lower in present series (47.9 years). Although the most common site of this tumor is the stomach (60%) followed by small bowel (30%) and esophagus and rectum (10%) [7], in the present series the ileum was most commonly involved (58.3%) followed by stomach (25%) and the mesentery (16.6%). Similar results have been reported by Kumar et al. [8] (Table 3). In our series malignancy was found in 25% of cases which is in concordance with other studies reporting a 20%–30% incidence of malignancy [4].

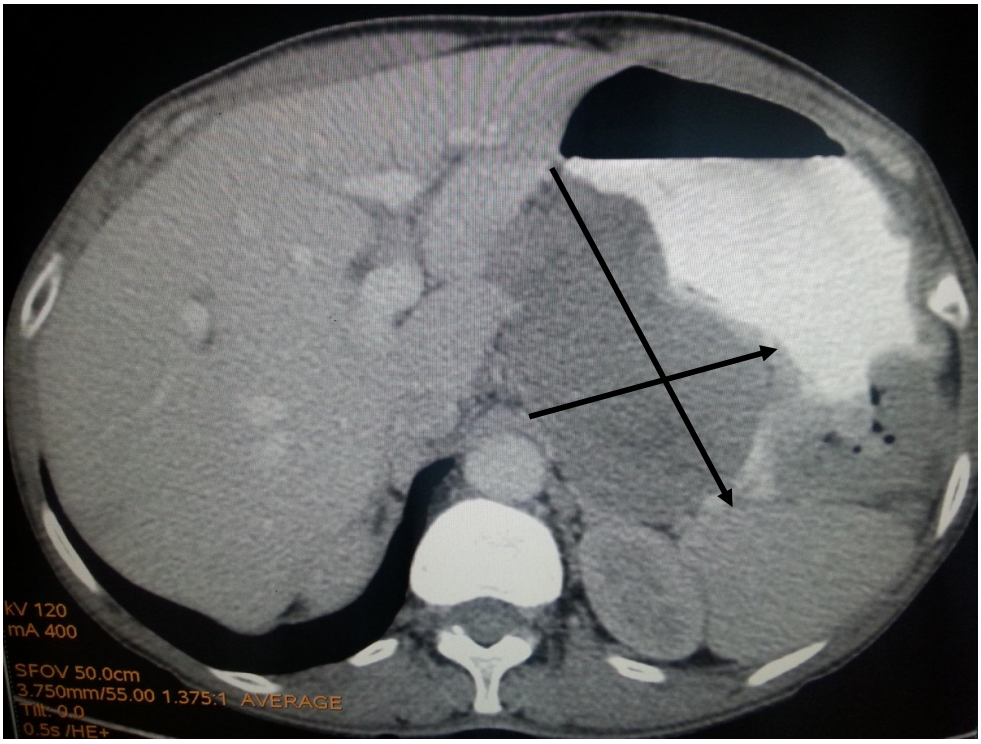

Fig. 1. Axial section CT abdomen showing GIST in the stomach

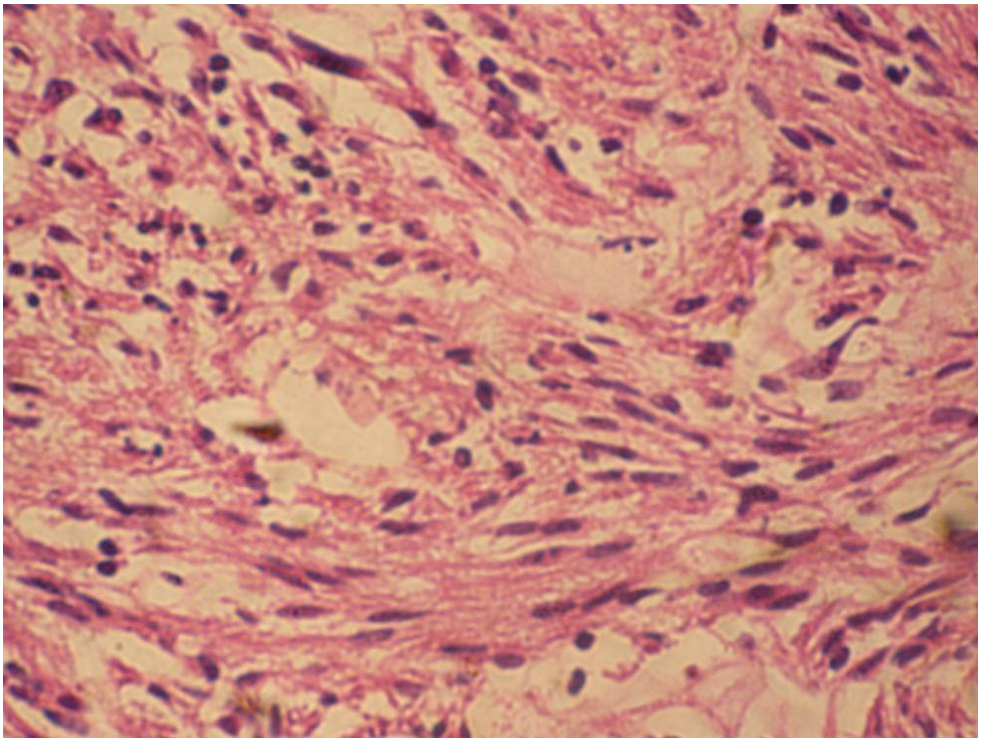

Fig. 2. Microphotograph of spindle cell GIST (H & E stain x 400)

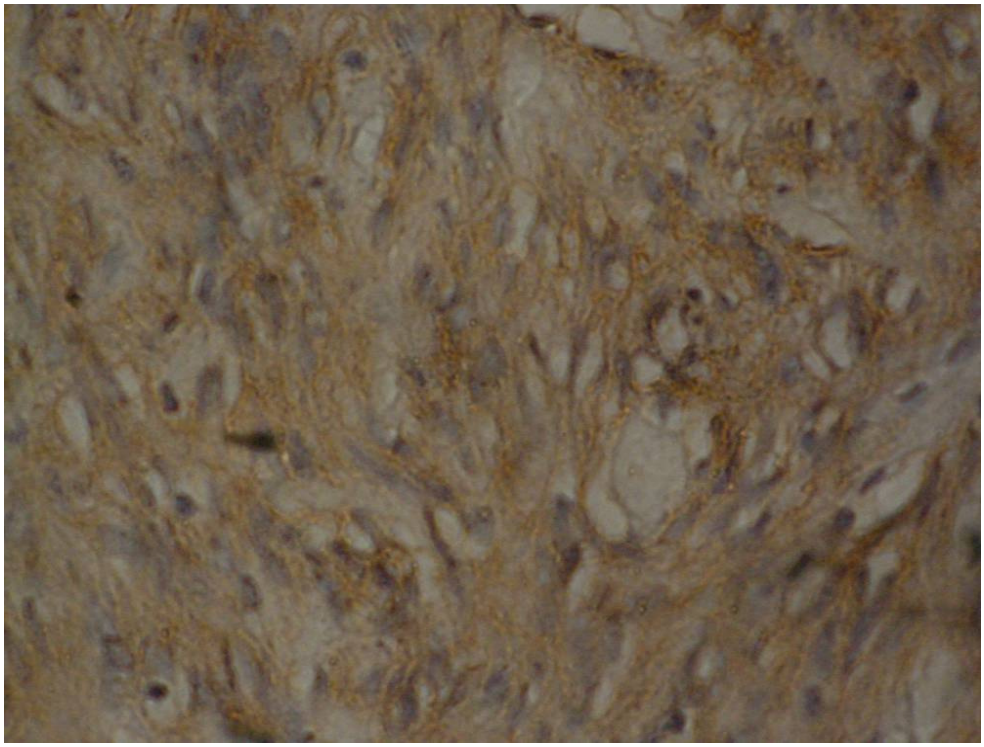

Fig. 3. Immunohistochemistry of CD 117

Table 3. Comparison of previous data of GIST with the present series

	Historical data[7]	Indian data past series[8]	Present series
Mean age of presentation	Middle age (58-60 years)	46.2 years	47.9 years
Gender	No difference	More common in males	More common in males
Presentation	Bleeding (50%) Pain (20%)	Abdominal lump and Pain (69%)	Abdominal lump (83.33%) Pain (100%)
Site	Stomach (60%) Small bowel (30%)	Stomach (31%) Small bowel (54%)	Stomach (25%) Small bowel (ileum) (58.33%)
Location	Subserosal (30%)	Subserosal (69%)	Subserosal (25%)

Clinical presentation of GIST is usually varied. These often present as abdominal lumps with pain and pressure related symptoms, and anemia or GIT bleeding. Smaller GISTs may be asymptomatic and are diagnosed incidentally during endoscopy, radiological imaging or abdominal exploration for other reason [9]. In the present study the most consistent symptom was abdominal pain (100%) and the majority (83.3%) had abdominal lump at initial presentation. This is probably explained by the larger size (mean 12.6 cm) of the tumor in our patients.

The diagnostic work-up is determined by the mode of presentation. Upper gastrointestinal endoscopy is done in patients having anemia, bleeding and radiologically diagnosed lumps of the stomach. Upper GI endoscopic biopsy is usually negative due to submucosal location of the tumor and it increases the risk of hemorrhage. Percutaneous biopsies are acceptable for inoperable tumors [10]. GISTs are immunoreactive for KIT which is a marker of ICC present in the myenteric plexus of stomach and small intestine. KIT is a part of the tyrosine kinase receptor complex containing transmembrane receptor CD117 [11]. CD117 positivity is seen in 90-100% of GIST while positivity for CD 34, the hematopoietic progenitor cell antigen, is reported in 70 – 80% [12]. All the tumors in our series were positive for CD 117. Recently a novel marker, Discovered on GIST 1

(DOG 1) a protein of unknown function has been identified on the surface of GIST which is rarely expressed in other soft tissue tumors. It has been observed that reactivity for DOG 1 may aid in the diagnosis of GIST, including PDGFRA mutants that fail to express KIT antigen [13]. Ki-67 (marker of tissue proliferation) presents a significant prognostic factor for GIST recurrence which could be of great importance in evaluating malignant potential of disease [14].

Recently it has been shown that PET has a valuable potential for diagnostic work-up of GIST [15]. Direct and hematogenous spreads are common. Surgery is the gold standard of curative treatment in which the resected specimen should have negative margins and integrity of the pseudocapsule [16]. Laparoscopic treatment of GIST can be performed taking strict oncological precaution to avoid rupture of the pseudocapsule. However laparoscopic surgery is discouraged in large tumors because of risk of tumor rupture and subsequent high relapse rate. International guidelines recommend laparoscopic surgery only for tumors smaller than 5 cm [16].

Five year overall survival following R0 resection is satisfactory (88%) while it can reach 0% following palliative surgery [17]. The postoperative treatment of palliated patients includes targeted therapy with imatinib mesylate (400 mg per day), which is a tyrosine kinase inhibitor. The current data demonstrate a response in 50% of these cases and a continued response in 75% [11]. Imatinib has also been used to downstage the disease [12]. Recent clinical practice guidelines recommend adjuvant chemotherapy for all patients being categorized as intermediate and high risk groups and in incomplete resections/unresectable tumours and the treatment should continue indefinitely [18]. However mutational analysis is essential before adjuvant therapy is started. It is believed that PDGFRA D842V-mutated GISTs should not be treated with any adjuvant therapy, as this genotype confers resistance to chemotherapy [18]. In metastatic disease adjuvant imatinib therapy is the standard practice, although surgery as a primary mode of therapy is not indicated. There is reliable data to show the effectiveness of a higher dose of imatinib (800 mg per day) in patients with KIT exon 9 mutation [19]. In case of progressive disease with imatinib therapy or in rare cases of imatinib intolerance, sunitinib is the standard second-line therapy [20]. It is difficult to predict the biological behavior of these tumors and the most reliable prognostic factors are the site, size and mitotic index [17]. On the basis of these factors two risk classifications have been proposed [4]. The biological features of these tumors represent important prognostic factors predicting outcome [21].

5. CONCLUSION

GISTs in our series presented at an earlier mean age of 47.9 years (35 – 70 years) with a male preponderance (1.75: 1). Patients had subacute to chronic presentation with mean duration of symptoms of 5 months (10 days – 24 months). Pain and lump in the abdomen were the most common clinical symptoms and was associated with vomiting, upper GI bleed and weight loss. Most of the tumors were benign (75%). Ileum involvement was most common (58.3%). Twenty five percent of these tumors were malignant and mortality rate was 8.3%. Surgical resection remains the mainstay of treatment. Immunohistochemistry (CD117 staining) was positive in all (100%) and thus is an important tool for diagnostic confirmation.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol. 2004;22:3813-25.
2. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol. 1998;152:1259-69.
3. Miettinen M, Lasota J. Gastrointestinal stromal tumors – Definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch. 2001;438:1-12.

4. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33:459-65.
5. Joensuu H. Gastrointestinal stromal tumor (GIST). Ann Oncol. 2006;17:280-6.
6. Pappo AS, Janeway KA. Pediatric gastrointestinal stromal tumors. Hematol Oncol Clin North Am. 2009;23:15–34.
7. Katz SC, DeMatteo RP. Gastrointestinal Stromal Tumours and Leiomyosarcomas. J of Surg Oncol. 2008;97:350–359.
8. Kumar P, Agrawal A, Shah AK, Gambhir RPS, Galagali A, Chaudhry R. Gastrointestinal stromal tumours: Our experience. Indian J Surg. 2010;72:112-16.
9. Everett M, Gutman H. Surgical management of gastrointestinal stromal tumors: Analysis of outcome with respect to surgical margins and technique. J Surg Oncol. 2008;98:588-93.
10. Hashiba T, Oda K, Koda K, Takiguchi N, Seike K, Miyazaki M. A gastrointestinal stromal tumour in the stomach: Usefulness of computerized tomography volumetry. Gastric Cancer. 2004;7:260-5.
11. Rubin BP, Blanke CD, Demetri GD, Dematteo RP, Fletcher CD, Goldblum JR, et al. Protocol for the examination of specimens from patients with gastrointestinal stromal tumor. Arch Pathol Lab Med. 2010;134:165-170.
12. Annaberdyev S, Gibbons J, Hardacre JM. Dramatic response of a gastrointestinal stromal tumor to neoadjuvant imatinib therapy. World J Surg Oncol. 2009;7:30.
13. Robert B West, Christopher L. Corless, Xin Chen, Brain P. Rubin, Subbaya Subramanian, Kelli Montgomery, et al. The novel marker, dog 1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of kit or pdgfra mutation status. Am J Pathol. 2004;165(1):107-113.
14. Belev B, Brcic I, Prejac J, Golubic ZA, Vrbanec D, Bozikov J, et al. Role of Ki-67 as a prognostic factor in gastrointestinal stromal tumors. World J Gastroenterol. 2013;28;19(4):523-527.
15. Kosmadakis N, Visvardis EE, Kartsaklis P, Tsimara M, Chatziantoniou A, Panopoulos I, et al. The role of surgery in the management of gastrointestinal stromal tumours in the era of imatinib mesylate effectiveness. Surg Oncol. 2005;14:75-84.
16. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Casper ES, et al. Gastrointestinal stromal tumors, version 2.2014. J Natl Compr Canc Netw. 2014;12(6):853-62.
17. Chiappa A[1], Zbar AP, Innis M, Garriques S, Bertani E, Biffi R, et al. Prognostic factors affecting survival after surgical resection of gastrointestinal stromal tumours: A two–unit experience over ten years. World J Surg Oncol. 2006;4:73.
18. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: The ESMO/ European Sarcoma Network Working Group. Ann Oncol. 2012;23(Suppl 7):vii49-vii55.
Avaliable:http://annonc.oxfordjournals.org/content/23/suppl_7/vii49.full - corresp-1.
19. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: A meta-analysis of 1,640 patients. J Clin Oncol. 2010;28:1247-53.
20. Demetri GD, Van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumor after failure of imatinib: A randomised controlled trial. Lancet. 2006;368:1329–38.
21. Arolfo S, Teggia PM, Nano M. Gastrointestinal stromal tumors: Thirty years experience of an institution. World J Gastroenterol. 2011;17:1836-9.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=717&id=12&aid=6792