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# Gastrointestinal Stromal Tumours - A Case Series - Our Experience over Three Years in a Tertiary Care Centre in India

**Dr. G. Harishwar Goud[1], Dr. N. Shravan Kumar[2]**

[1]Post Graduate student, Department of General Surgery, Kamineni Institute of Medical Sciences, Narketpally, Telangana, India, Email ID: *harishwargandeti[at]gmail.com*

[2]Assistant Professor, Department of General Surgery, Kamineni Institute of Medical Sciences, Narketpally, Telangana, India

*Running Title: Case Series of Retrospective Observational Study*

**Abstract:** ***Background: This study defines a series of 10 cases of Gastro - Intestinal Stromal Tumours managed in a teaching hospital attached to a medical college over 3 years. Methods: Medical records of the 10 cases of Gastro - Intestinal Stromal Tumoursmanaged during January 2016 through December 2018 were reviewed for patient demographics, clinical presentation, investigations, sites, treatment, histology, immunohistochemistry and Imatinib therapy. Follow up for recurrence over the period ranging from 6 months to 4 years was done. Results: Gastro - Intestinal Stromal Tumours was common in men. Age ranged 28 to 75 years. Sites involved were - small bowel in 5, stomach in 2, mesentery in 2 and rectum in 1. Symptoms ranged from abdominal pain, mass per abdomen, upper/lower gastrointestinal bleeding and few cases presented as small bowel obstruction and intestinal perforation. Surgery was the mainstay of the treatment. All were positive for tyrosine kinase. One case was non resectable and another showed metastasis to the mesenteric lymph nodes, which is uncommon. All received Imatinib post operatively. Recurrence was seen in one patient with small bowel Gastro - Intestinal Stromal Tumours at 2 years. Conclusions: Gastro - Intestinal Stromal Tumours are uncommon with varied presentations and may be aggressive and can recur. Gastro - Intestinal Stromal Tumourselaborate tyrosine kinase, hence KIT receptor inhibitor Imatinib was useful in all including nonresectable& recurrent tumours which drastically changed the diagnosis and management of these tumours.***

**Keywords:** Gastrointestinal Stromal Tumours, Small intestine, Perforation, Tyrosine Kinase, Imatinib

## 1. Introduction

Gastrointestinal stromal tumours (GIST) are mesenchymal tumours of the digestive tract that originate from interstitial Cajal cells, the pace makers of the gut that initiate peristalsis[1]. They account for 3% of all gastrointestinal tumors[2]. In frequency these tumours rank third after adenocarcinoma and lymphomas of gastrointestinal tract tumours histologically. Age incidence for Gastro - Intestinal Stromal Tumours is usually in adults between 40 and 70 years and can be benign or malignant. They are usually located in the stomach and small intestine, but they can be located anywhere in the gastrointestinal tract, including the omentum and peritoneum. Generally, Gastro - Intestinal Stromal Tumours have a silent behaviour and are diagnosed incidentally. The most common symptoms encountered are abdominal mass, weight loss, gastrointestinal bleeding and pain abdomen. Rarely do they present as small or large bowel obstruction and very rarely as bowel perforation. Expression of tumour marker receptor tyrosine kinase KIT by Gastro - Intestinal Stromal Tumour cells has revolutionized the diagnosis and management of Gastro - Intestinal Stromal Tumoursduring the last 15 years. Discovery of ImatinibMesylate, a specific tyrosine kinase inhibitor, resulted in significantly improved survival. We present a case series of 10 cases of Gastrointestinal Stromal Tumours managed in a tertiary care hospital attached with this medical college, over a period of 3 years (January 2016 to December 2018).

## 2. Materials and Methods

This is a retrospective observational study. Medical records of 10 cases of Gastro - Intestinal Stromal Tumoursmanaged during the period from January 2016 to December 2018 were reviewed for patient demographics, clinical presentation, investigation results (upper gastrointestinal endoscopy and colonoscopy, radiologic imaging). The tumour characteristics - locations of the tumours, type of surgical resections, histopathology, immunohistochemistry analysis, ImatinibMesylate therapy post operatively or as palliation (even where resectional surgery not contemplated), treatment outcome were noted and studied. Follow up for recurrence over a period ranging from 6 months to 4 years were also studied. The prognostic factors - size, mitotic index & metastasis were also observed.

Ethical clearance certificate was taken from institutional ethics committee, Kamineni institute of medical sciences, Telangana, India.

## 3. Results

Of the 10 patients, men accounted (n=7, 70%), women (n=3, 30%). Age range was 28 to 75 years, mean age 52.3 years, median age 72.5 years. Symptoms ranged from abdominal pain, epigastric discomfort, abdominal mass, upper /lower gastrointestinal bleeding, rectal bleeding, anaemia, weight loss and small bowel obstruction. Sites involved were small

bowel in (n=5, 50%), stomach in (n=2, 20%), mesentery in (n= 2, 20%), and rectum in (n=1, 10%).

Gastric wedge resection done in 2 cases, small bowel resection and anastomosis done in 5 cases, excision of mesenteric Gastro - Intestinal Stromal Tumour with adjacent jejunum in 1 case but postoperative histopathology reported metastasis to the mesenteric lymph nodes. Anterior resection in 1 case of rectal Gastro - Intestinal Stromal Tumour. One (n=1, 10%) case of mesenteric was non resectable. Recurrence seen in one patient (n=1, 10%) with small bowel Gastro - Intestinal Stromal Tumour at 1 year. The non resectable case of recurrent Gastro - Intestinal Stromal Tumour received Imatinib.

Tumour histology showed spindle shaped cells with necrosis and haemorrhage in all cases (Figure.3). Mitotic index varied from 0/50 HPF to >10/10 HPF.

One case (n=1, 10%) of jejunalmesenteric Gastro - Intestinal Stromal Tumour showed metastatic deposits in 12 out of 24 mesenteric lymph nodes. Immunohistochemistry (IHC) for CD117/C kit was positive (Figure.4) in all cases. Recurrence was seen in one case (n=1, 10%) of small bowel GIST at 2 years post treatment. One case (n=1, 10%) was lost to follow up and one case died of road traffic accident 7 months post treatment (Table 1).

**Table 1**

| S. No | Age/ Gender | Location of GIST | Primary symptom | Primary treatment | Histopathology | IHC analysis | Post op Imatinib | FU/recurrence & time period |
|---|---|---|---|---|---|---|---|---|
| 1 | 66/ M | Small gut | Small bowel obstruction | Surgery | Spindle cells 8 - 10/50 HPF | CD117/Ckit Positive | Yes | YES, 2 years post op |
| 2 | 75/ M | Body of stomach | Upper GI bleeding | Surgery | Spindle cells <5/50 HPF | CD117/Ckit Positive | Yes | No, at 2 years 10 Months |
| 3 | 42/ F | Small gut | Lower abdominal pain | Surgery | Spindle cells 9/50HPF | CD117/Ckit Positive | Yes | No, at 2 years 7 months |
| 4 | 61/ M | Rectum | Lower GI bleeding | Surgery | Spindle cells 5/50HPF | CD117/Ckit Positive | Yes | No, 3 years post Treatment |
| 5 | 38/ M | Jejunum | Abdominal pain | Surgery | Spindle cells <1/50 HPF | CD117/Ckit Positive | Yes | Lost to follow up |
| 6 | 40/ M | Stomach | Epigastric discomfort | Surgery | Severe nuclear atypia, 6/50 HPF | CD117/Ckit Positive | Yes | No, till 7 months post treatment, died of road traffic accident |
| 7 | 38/ F | Mesentery | Abdominal discomfort | Surgery | Spindle cells, twisted nuclei, 7/50 HPF | CD117/Ckit Positive | Yes | No, 3 years 6 months post treatment |
| 8 | 28/ F | Small gut | Abdominal pain | Surgery | Mixed spindle and epitheloid cells 5/50 HPF | CD117/Ckit Positive | Yes | No, 3 years 8 months post Treatment |
| 9 | 70/ M | Jejunum | RIF, Right lumbar mass | Surgery | Spindle cells, 7/50 HPF | CD117/Ckit Positive | Yes | No, 3 years 1 month post Treatment |
| 10 | 65/ M | Jejunal mesentery | Recurrent large abdominal mass | Imatinib | Spindle cells in whorls, >10/10 HPF mitotic index, malignant GIST, high grade | CD117/ Ckit Positive | Yes | Metastatic disease, surviving 2 years 4 months post Treatment |

## 4. Discussion

Gastro - Intestinal Stromal Tumours are the commonest mesenchymal tumours of the gastrointestinal tract. Apart from stomach, small gut, they may originate in the large gut, oesophagus, mesentery and omentum. The 8th American Joint Committee on Cancer (AJCC) Cancer Staging Manual lists the following approximate distributions - Stomach (60%), Small intestine (30%), Rectum (3%), Colon (1–2%), Oesophagus (<1%), Omentum / mesentery (rare) [3]. Infrequently, Gastro - Intestinal Stromal Tumours may arise in the appendix, gallbladder, pancreas, retro peritoneum, and tissues around pelvic organs. Gastro - Intestinal Stromal Tumours were found commonly in adult males, between ages 28 – 75 years and can be benign or malignant. Presenting complaints depended on the site of the tumour. Small gut Gastro - Intestinal Stromal Tumour presented with abdominal lump, obstruction and perforation (Figure.1). Gastric Gastro - Intestinal Stromal Tumour presented with epigastric discomfort, upper gastrointestinal bleeding. Rectal Gastro - Intestinal Stromal Tumour presented with rectal bleeding. Mesenteric Gastro - Intestinal Stromal Tumour reported with abdominal mass, anaemia. The abdominal radiograph (erect) showed features of small gut obstruction. Ultrasound, Computed Tomography scan (Figure.2), Magnetic Resonance Imaging showed the site, size of the tumours and the adjacent organs (liver, lymph nodes for involvement). Upper gastrointestinal endoscopy and colonoscopy showed wall irregularity and thickening in gastric and colonic / rectal Gastro - Intestinal Stromal Tumour respectively. All patients required surgery.20 to 25% of gastric and 40 to 50% of small gut Gastro - Intestinal Stromal Tumour exhibit aggressive behavior[5]. Metastatic Gastro - Intestinal Stromal Tumour is found in 10% to 25% of patients[5, 6].

Oncogenic mutations are detected in 95% of Gastro - Intestinal Stromal Tumour in either KIT or PDGFRA (platelet - derived growth factor receptor alpha) tyrosine kinase receptors[7]. Gastro - Intestinal Stromal Tumour pathogenesis is the result of activation of either of these

tyrosine kinase receptors[7, 2]. Histologically (Figure.3) Gastro - Intestinal Stromal Tumour is composed of the following[8] - Spindle cells (70%), epithelioid cells (20%), mixed spindle and epithelioid cells (10%) [7].

All received Imatinib post operatively. Imatinib Mesylate is tyrosine kinase receptor inhibitor and is the hallmark of treatment of GISTs. Imatinib has exhibited response rate in >80% cases and enhanced the survival to >5yrs in more than 50% of unresectable or metastatic Gastro - Intestinal Stromal Tumours. The dosage of Imatinib should be modified in hepatic or renal impairment. Common toxic effects of Imatinib are nausea, vomiting, skin rash, and bone marrow suppression and in some patients with tumour haemorrhage has been noted Predictors of aggressive behaviour in GISTs have been proposed as - Very low risk - size <2cm and mitotic index <5/50 HPF, low risk being 2 - 5 cm and mitotic index <5/50 HPF, intermediate risk being <5cm and 6 - 10 /50 HPF mitotic index or 5 - 10 cm and 6 - 10 /50 HPF, high risk being >5cm and >5/50 HPF or >10 cm & any mitotic rate or any size and >10 /50 HPF.

Predictors for recurrence are - tumour size >5cm, high grade, tumour rupture and small bowel origin[5, 8]. Every effort should be made to avoid tumour rupture during surgery as this drastically reduces survival[10].5 year survival was 42% when complete resection was done as compared to 9% if the excision was incomplete[8].

We had used Imatinib in the recurrent unresectable mesenteric and omental Gastro - Intestinal Stromal Tumour and all the operated cases postoperatively. Indications of preoperative Imatinib are: large localized, resectable tumours, impending haemorrhage or rupture, poorly localized small tumours that are difficult to resect, non - metastatic but unresectable localized Gastro - Intestinal Stromal Tumour and if tumour free resection margins not achievable. Preoperative Imatinib may be continued until maximal response is achieved.

Response should be assessed after 8 weeks of initiation[4]. In our series one case of recurrence of small bowel GIST and another case of unresectable recurrent mesenteric Gastro - Intestinal Stromal Tumour received Imatinib for 12 weeks and showed good palliation and regression of the tumours. A very peculiar feature of this series was that in one patient of jejunal mesenteric GIST whose tumour was resected but showed metastasis in the mesenteric lymph nodes (12 out of 24 lymph nodes were positive), a very unusual feature of metastatic Gastro - Intestinal Stromal Tumour.

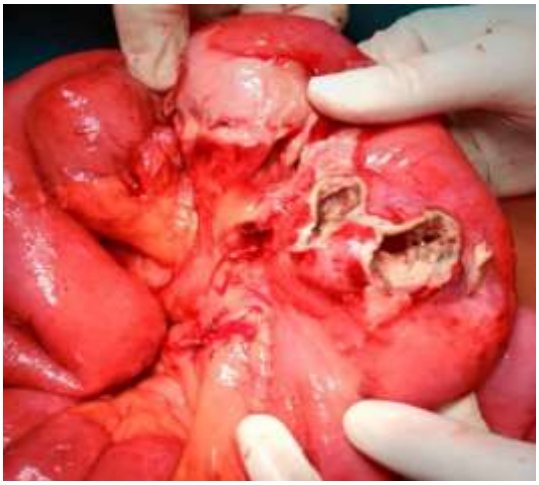

**Figure 1:** Perforated Gastro intestinal stromal tumour in jejunum

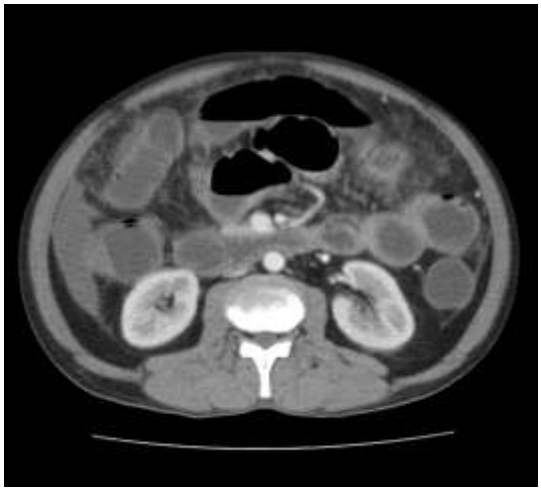

**Figure 2:** Axial CT image demonstrated a pneumoperitoneum and significant fat stranding surrounding a jujenal segment of small bowel, which shoes gas locules at its wall representing the site of perforation.

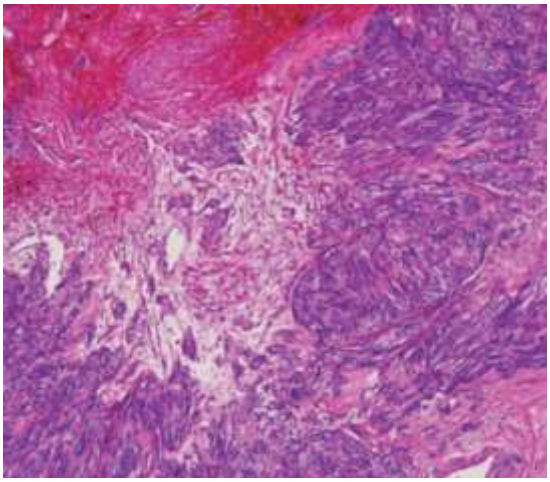

**Figure 3:** Histological staining H&E showing spindle shaped cells with necrosis and haemorrhage

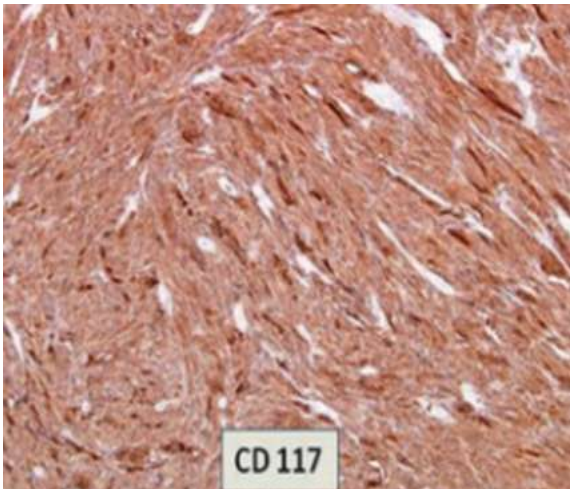


**Figure 4:** Immunohistochemistry (IHC) for CD117 was positive

## 5. Conclusion

Gastro - Intestinal Stromal Tumours are unpredictable mesenchymal tumours. Common sites are stomach and small gut. Mesenteric and omentalGastro - Intestinal Stromal Tumours are rare. Surgery and ImatinibMesylate therapy are the options available to the surgeon. Imatinib along with complete en bloc surgical excision with clear margins and unbreached pseudo capsule is the standard initial management for all localized resectableGastro - Intestinal Stromal Tumours &help in improving long term survival. For gastric Gastro - Intestinal Stromal Tumours, a wedge resection or resection anastomosis for intestine is adequate.

En - bloc resection should be considered if neighbouring structures are involved but are removable. NeoadjuvantImatinib can be considered for downsizing of initially unresectable tumour thus allowing adequate subsequent resection with reduced surgical morbidity. Adjuvant Imatinib is indicated in patients at higher risk of recurrence. In metastatic or recurrent GIST, the primary treatment would be Imatinib. Sunitinib can be used for resistant or intolerant cases.

A multidisciplinary approach and close collaboration between a medical oncologist, gastroenterologist, radiologist, oncopathologist and principally the surgeon are mandatory to provide Gastro - Intestinal Stromal Tumours patients with the best available treatment.

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## 7. Declarations

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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## Author Profile

**Dr. G. Harishwar Goud** is Final year Post Graduate student, Department of General Surgery, Kamineni institute of medical sciences, Narketpally, Nalgonda, Telangana. Dr. G. HarishwarGoud received M. B. B. S degree in 2018 from Prathima Institute of medical sciences, Karimnagar. He received best poster and paper awards in Telangana state ASICON 2020 and 2021 respectively.

**Dr. N. Shravan Kumar**is an Assistant Professor in Department of General surgery, KamineniInstitute of Medical Sciences, Narketpally, Telangana. Dr. N. Shravankumar received M. B. B. S and DNB (General Surgery) degrees in 2011 and 2018 respectively. He has a special interest in laparoscopic surgeries and other minimal invasive surgeries.